Summary of Product Characteristics

Index

Haloperidol

EMC

HALDOL Decanoate 50 mg/ml solution for injection

Summary of Product Characteristics Updated 09-Nov-2023 | Essential Pharma Ltd (Malta)

1. Name of the medicinal product

HALDOL Decanoate 50 mg/ml solution for injection

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2. Qualitative and quantitative composition

50 mg/ml solution:

Each ml of solution contains 70.52 mg of haloperidol decanoate, equivalent to 50 mg of haloperidol base.

100 mg/ml solution:

Each ml of solution contains 141.04 mg of haloperidol decanoate, equivalent to 100 mg of haloperidol base.

Excipients with known effect:

50 mg/ml and 100 mg/ml solution:

Each ml of solution contains 15 mg of benzyl alcohol and up to 1 ml of sesame oil.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for injection.

Slightly amber, slightly viscous solution, free from visible foreign material.

4. Clinical particulars

4.1 Therapeutic indications

HALDOL Decanoate is indicated for the maintenance treatment of schizophrenia and schizoaffective disorder in adult patients currently stabilised with oral haloperidol (see section 5.1).

4.2 Posology and method of administration

Treatment initiation and dose titration must be carried out under close clinical supervision.

Posology

The individual dose will depend on both the severity of the symptoms and the current oral haloperidol dose. Patients must always be maintained on the lowest effective dose.

As the initial dose of haloperidol decanoate is based on a multiple of the daily oral haloperidol dose, specific guidance on switching from other antipsychotics cannot be provided (see section 5.1).

Adults aged 18 years and above

Table 1: Haloperidol decanoate dose recommendations for adults aged 18 years and above

Transition from oral haloperidol • A haloperidol decanoate dose of 10 to 15 times the previous daily dose of oral haloperidol is recommended. • Based on this conversion, the haloperidol decanoate dose will be 25 to150 mg for most patients.
Continuation of treatment • It is recommended to adjust the haloperidol decanoate dose by up to 50 mg every 4 weeks (based on individual patient response) until an optimal therapeutic effect is obtained. • The most effective dose is expected to range between 50 and 200 mg. • It is recommended to assess the individual benefit-risk when considering doses above 200 mg every 4 weeks. • A maximum dose of 300 mg every 4 weeks must not be exceeded because the safety concerns outweigh the clinical benefits of treatment.
Dosing interval • Usually 4 weeks between injections. • Adjustment of the dosing interval may be required (based on individual patient response).

Supplementation with non-decanoate haloperidol • Supplementation with non-decanoate haloperidol may be considered during transition to HALDOL Decanoate, dose adjustment or episodes of exacerbation of psychotic symptoms (based on individual patient response). • The combined total dose of haloperidol from both formulations must not exceed the corresponding maximum oral haloperidol dose of 20 mg/day.

Special populations

Elderly

Table 2: Haloperidol decanoate dose recommendations for elderly patients

Transition from oral haloperidol • A low haloperidol decanoate dose of 12.5 to 25 mg is recommended.
Continuation of treatment • It is recommended only to adjust the haloperidol decanoate dose if required (based on individual patient response) until an optimal therapeutic effect is obtained. • The most effective dose is expected to range between 25 and 75 mg. • Doses above 75 mg every 4 weeks should only be considered in patients who have tolerated higher doses and after reassessment of the patient's individual benefit-risk profile.
Dosing interval • Usually 4 weeks between injections. • Adjustment of the dosing interval may be required (based on individual patient response).
Supplementation with non-decanoate haloperidol • Supplementation with non-decanoate haloperidol may be considered during transition to HALDOL Decanoate, dose adjustment or episodes of exacerbation of psychotic symptoms (based on individual patient response). • The combined total dose of haloperidol from both formulations must not exceed the corresponding maximum oral haloperidol dose of 5 mg/day or the previously administered oral haloperidol dose in patients who have received long-term treatment with oral haloperidol.

Renal impairment

The influence of renal impairment on the pharmacokinetics of haloperidol has not been evaluated. No dose adjustment is recommended, but caution is advised when treating patients with renal impairment. However, patients with severe renal impairment may require a lower initial dose, with subsequent adjustments at smaller increments and at longer intervals than in patients without renal impairment (see section 5.2).

Hepatic impairment

The influence of hepatic impairment on the pharmacokinetics of haloperidol has not been evaluated. Since haloperidol is extensively metabolised in the liver, it is recommended to halve the initial dose, and adjust the dose with smaller increments and at longer intervals than in patients without hepatic impairment (see sections 4.4 and 5.2).

Paediatric population

The safety and efficacy of HALDOL Decanoate in children and adolescents below 18 years of age have not been established. No data are available.

Method of administration

HALDOL Decanoate is for intramuscular use only and must not be administered intravenously. It is administered as a deep intramuscular injection in the gluteal region. It is recommended to alternate between the two gluteal muscles. As the administration of volumes greater than 3 ml is uncomfortable for the patient, such large volumes are not recommended. For instructions on handling HALDOL Decanoate, see section 6.6.

4.3 Contraindications

• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

• Comatose state.

• Central nervous system (CNS) depression.

• Parkinson's disease.

- Dementia with Lewy bodies.
- Progressive supranuclear palsy.
- Known QTc interval prolongation or congenital long QT syndrome.
- Recent acute myocardial infarction.
- Uncompensated heart failure.
- History of ventricular arrhythmia or torsades de pointes.
- Uncorrected hypokalaemia.
- Concomitant treatment with medicinal products that prolong the QT interval (see section 4.5).

4.4 Special warnings and precautions for use

Increased mortality in elderly people with dementia

Rare cases of sudden death have been reported in psychiatric patients receiving antipsychotics, including haloperidol (see section 4.8).

Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death. Analyses of seventeen placebo-controlled studies (modal duration of 10 weeks), largely in patients taking atypical antipsychotics, revealed a risk of death in treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10 week controlled study, the rate of death in patients treated with antipsychotics was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that treatment of elderly patients with haloperidol is also associated with increased mortality. This association may be stronger for haloperidol than for atypical antipsychotic medicinal products, is most pronounced in the first 30 days after the start of treatment, and persists for at least 6 months. The extent to which this association is attributable to the medicinal product, as opposed to being confounded by patient characteristics, has not yet been elucidated.

HALDOL Decanoate is not indicated for the treatment of dementia-related behavioural disturbances.

Cardiovascular effects

QTc prolongation and/or ventricular arrhythmias, in addition to sudden death, have been reported with haloperidol (see sections 4.3 and 4.8). The risk of these events appears to increase with high doses, high plasma concentrations, in predisposed patients or with parenteral use, particularly intravenous administration.

HALDOL Decanoate must not be administered intravenously.

Caution is advised in patients with bradycardia, cardiac disease, family history of QTc prolongation or history of heavy alcohol exposure. Caution is also required in patients with potentially high plasma concentrations (see section 4.4, Poor metabolisers of CYP2D6).

A baseline ECG is recommended before treatment. During therapy, the need for ECG monitoring for QTc interval prolongation and for ventricular arrhythmias must be assessed in all patients. Whilst on therapy, it is recommended to reduce the dose if QTc is prolonged, but haloperidol must be discontinued if the QTc exceeds 500 ms.

Electrolyte disturbances such as hypokalaemia and hypomagnesaemia increase the risk for ventricular arrhythmias and must be corrected before treatment with haloperidol is started. Therefore, baseline and periodic electrolyte monitoring is recommended.

Tachycardia and hypotension (including orthostatic hypotension) have also been reported (see section 4.8). Caution is recommended when haloperidol is administered to patients manifesting hypotension or orthostatic hypotension.

Cerebrovascular events

In randomised, placebo-controlled clinical studies in the dementia population, there was an approximately 3-fold increased risk of cerebrovascular adverse events with some atypical antipsychotics. Observational studies comparing the stroke rate in elderly patients exposed to any antipsychotic to the stroke rate in those not exposed to such medicinal products found an increased stroke rate among exposed patients. This increase may be higher with all butyrophenones, including haloperidol. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other patient populations. HALDOL Decanoate must be used with caution in patients with risk factors for stroke.

Neuroleptic malignant syndrome

Haloperidol has been associated with neuroleptic malignant syndrome: a rare idiosyncratic response characterized by hyperthermia, generalised muscle rigidity, autonomic instability, altered consciousness and increased serum creatine phosphokinase levels. Hyperthermia is often an early sign of this syndrome. Antipsychotic treatment must be withdrawn immediately and appropriate supportive therapy and careful monitoring instituted.

Tardive dyskinesia

Tardive dyskinesia may appear in some patients on long-term therapy or after discontinuation of the medicinal product. The syndrome is mainly characterized by rhythmic involuntary movements of the tongue, face, mouth or jaw. The manifestations may be permanent in some patients. The syndrome may be masked when treatment is reinstituted, when the dose is increased or when a switch is made to a different antipsychotic. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotics, including HALDOL Decanoate, must be considered.

Extrapyramidal symptoms

Extrapyramidal symptoms may occur (e.g. tremor, rigidity, hypersalivation, bradykinesia, akathisia, acute dystonia). The use of haloperidol has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move, often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Acute dystonia may occur during the first few days of treatment with haloperidol, but later onset as well as onset after dose increases has been reported. Dystonic symptoms can include, but are not limited to, torticollis, facial grimacing, trismus, tongue protrusion, and abnormal eye movements, including oculogyric crisis. Males and younger age groups are at higher risk of experiencing such reactions. Acute dystonia may necessitate stopping the medicinal product.

Antiparkinson medicinal products of the anticholinergic type may be prescribed as required to manage extrapyramidal symptoms, but it is recommended that they are not prescribed routinely as a preventive measure. If concomitant treatment with an antiparkinson medicinal product is required, it may have to be continued after stopping HALDOL Decanoate if its excretion is faster than that of haloperidol in order to avoid the development or aggravation of extrapyramidal symptoms. The possible increase in intraocular pressure must be considered when anticholinergic medicinal products, including antiparkinson medicinal products, are administered concomitantly with HALDOL Decanoate.

Seizures/convulsions

It has been reported that seizures can be triggered by haloperidol. Caution is advised in patients suffering from epilepsy and in conditions predisposing to seizures (e.g. alcohol withdrawal and brain damage).

Hepatobiliary concerns

As haloperidol is metabolised by the liver, dose adjustment and caution is advised in patients with hepatic impairment (see sections 4.2 and 5.2). Isolated cases of liver function abnormalities or hepatitis, most often cholestatic, have been reported (see section 4.8).

Endocrine system concerns

Thyroxin may facilitate haloperidol toxicity. Antipsychotic therapy in patients with hyperthyroidism must be used only with caution and must always be accompanied by therapy to achieve a euthyroid state.

Hormonal effects of antipsychotics include hyperprolactinaemia, which may cause galactorrhoea, gynaecomastia and oligomenorrhea or amenorrhoea (see section 4.8). Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics and human breast tumours has been demonstrated in clinical and epidemiological studies, caution is recommended in patients with relevant medical history. HALDOL Decanoate must be used with caution in patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumours (see section 5.3).

Hypoglycaemia and syndrome of inappropriate antidiuretic hormone secretion have been reported with haloperidol (see section 4.8).

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotics. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with HALDOL Decanoate and preventive measures undertaken.

Treatment initiation

Patients being considered for HALDOL Decanoate therapy must be initially treated with oral haloperidol to reduce the possibility of an unexpected adverse sensitivity to haloperidol.

Patients with depression

It is recommended that HALDOL Decanoate is not used alone in patients in whom depression is predominant. It may be combined with antidepressants to treat those conditions in which depression and psychosis coexist (see section 4.5).

Poor metabolisers of CYP2D6

HALDOL Decanoate should be used with caution in patients who are known poor metabolisers of cytochrome P450 (CYP) 2D6 and who are coadministered a CYP3A4 inhibitor.

Excipients of HALDOL Decanoate

HALDOL Decanoate contains benzyl alcohol, which may cause allergic reactions. HALDOL Decanoate must be used with caution in patients with renal or hepatic impairment, or in patients who are pregnant or breast-feeding, because of

the risk of accumulation and toxicity (metabolic acidosis).

HALDOL Decanoate contains sesame oil, which may rarely cause severe allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Cardiovascular effects

HALDOL Decanoate is contraindicated in combination with medicinal products known to prolong the QTc interval (see section 4.3). Examples include:

• Class IA antiarrhythmics (e.g. disopyramide, quinidine).

• Class III antiarrhythmics (e.g. amiodarone, dofetilide, dronedarone, ibutilide, sotalol).

• Certain antidepressants (e.g. citalopram, escitalopram).

• Certain antibiotics (e.g. azithromycin, clarithromycin, erythromycin, levofloxacin, moxifloxacin, telithromycin).

• Other antipsychotics (e.g. phenothiazine derivatives, sertindole, pimozide, ziprasidone)

• Certain antifungals (e.g. pentamidine).

• Certain antimalarials (e.g. halofantrine).

• Certain gastrointestinal medicinal products (e.g. dolasetron).

• Certain medicinal products used in cancer (e.g. toremifene, vandetanib).

• Certain other medicinal products (e.g. bepridil, methadone).

This list is not exhaustive.

Caution is advised when HALDOL Decanoate is used in combination with medicinal products known to cause electrolyte imbalance (see section 4.4).

Medicinal products that may increase haloperidol plasma concentrations

Haloperidol is metabolised by several routes (see section 5.2). The major pathways are glucuronidation and ketone reduction. The cytochrome P450 enzyme system is also involved, particularly CYP3A4 and, to a lesser extent, CYP2D6. Inhibition of these routes of metabolism by another medicinal product or a decrease in CYP2D6 enzyme activity may result in increased haloperidol concentrations. The effect of CYP3A4 inhibition and of decreased CYP2D6 enzyme activity may be additive (see section 5.2). Based on limited and sometimes conflicting information, the potential increase in haloperidol plasma concentrations when a CYP3A4 and/or CYP2D6 inhibitor is coadministered may range between 20 to 40%, although in some cases, increases of up to 100% have been reported. Examples of medicinal products that may increase haloperidol plasma concentrations (based on clinical experience or drug interaction mechanism) include:

• CYP3A4 inhibitors – alprazolam, fluvoxamine, indinavir, itraconazole, ketoconazole, nefazodone, posaconazole, saquinavir, verapamil, voriconazole.

• CYP2D6 inhibitors – bupropion, chlorpromazine, duloxetine, paroxetine, promethazine, sertraline, venlafaxine.

• Combined CYP3A4 and CYP2D6 inhibitors: fluoxetine, ritonavir.

• Uncertain mechanism – buspirone.

This list is not exhaustive.

Increased haloperidol plasma concentrations may result in an increased risk of adverse events, including QTc-prolongation (see section 4.4). Increases in QTc have been observed when haloperidol was given with a combination of the metabolic inhibitors ketoconazole (400 mg/day) and paroxetine (20 mg/day).

It is recommended that patients who take haloperidol concomitantly with such medicinal products be monitored for signs or symptoms of increased or prolonged pharmacologic effects of haloperidol, and the HALDOL Decanoate dose be decreased as deemed necessary.

Medicinal products that may decrease haloperidol plasma concentrations

Coadministration of haloperidol with potent enzyme inducers of CYP3A4 may gradually decrease the plasma concentrations of haloperidol to such an extent that efficacy may be reduced. Examples include:

• Carbamazepine, phenobarbital, phenytoin, rifampicin, St John's Wort (*Hypericum, perforatum*).

This list is not exhaustive.

Enzyme induction may be observed after a few days of treatment. Maximal enzyme induction is generally seen in about 2 weeks and may then be sustained for the same period of time after the cessation of therapy with the medicinal product. During combination treatment with inducers of CYP3A4, it is recommended that patients be monitored and the

HALDOL Decanoate dose increased as deemed necessary. After withdrawal of the CYP3A4 inducer, the concentration of haloperidol may gradually increase and therefore it may be necessary to reduce the HALDOL Decanoate dose.

Sodium valproate is known to inhibit glucuronidation, but does not affect haloperidol plasma concentrations.

Effect of haloperidol on other medicinal products

Haloperidol can increase the CNS depression produced by alcohol or CNS-depressant medicinal products, including hypnotics, sedatives or strong analgesics. An enhanced CNS effect, when combined with methyldopa, has also been reported.

Haloperidol may antagonise the action of adrenaline and other sympathomimetic medicinal products (e.g. stimulants like amphetamines) and reverse the blood pressure-lowering effects of adrenergic-blocking medicinal products such as guanethidine.

Haloperidol may antagonise the effect of levodopa and other dopamine agonists.

Haloperidol is an inhibitor of CYP2D6. Haloperidol inhibits the metabolism of tricyclic antidepressants (e.g. imipramine, desipramine), thereby increasing plasma concentrations of these medicinal products.

Other forms of interaction

In rare cases the following symptoms were reported during the concomitant use of lithium and haloperidol: encephalopathy, extrapyramidal symptoms, tardive dyskinesia, neuroleptic malignant syndrome, acute brain syndrome and coma. Most of these symptoms were reversible. It remains unclear whether this represents a distinct clinical entity.

Nonetheless, it is advised that in patients who are treated concomitantly with lithium and HALDOL Decanoate, therapy must be stopped immediately if such symptoms occur.

Antagonism of the effect of the anticoagulant phenindione has been reported.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women (more than 400 pregnancy outcomes) indicate no malformative or foeto/ neonatal toxicity of haloperidol. However, there have been isolated case reports of birth defects following foetal exposure to haloperidol in combination with other medicinal products. Animal studies have shown reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of HALDOL Decanoate during pregnancy.

Newborn infants exposed to antipsychotics (including haloperidol) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, it is recommended that newborn infants be monitored carefully.

Breastfeeding

Haloperidol is excreted in human milk. Small amounts of haloperidol have been detected in plasma and urine of breast-fed newborns of mothers treated with haloperidol. There is insufficient information on the effects of haloperidol in breast-fed infants. A decision must be made whether to discontinue breastfeeding or to discontinue HALDOL Decanoate therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

Haloperidol elevates prolactin level. Hyperprolactinaemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients (see section 4.4).

4.7 Effects on ability to drive and use machines

HALDOL Decanoate has a moderate influence on the ability to drive and use machines. Some degree of sedation or impairment of alertness may occur, particularly with higher doses and at the start of treatment and may be potentiated by alcohol. It is recommended that patients be advised not to drive or operate machines during treatment, until their susceptibility is known.

4.8 Undesirable effects

The safety of haloperidol decanoate was evaluated in 410 patients who participated in 3 comparator studies (1 comparing haloperidol decanoate versus fluphenazine and 2 comparing the decanoate formulation to oral haloperidol), 9 open label studies and 1 dose response study.

Based on pooled safety data from these clinical studies, the most commonly reported adverse reactions were: extrapyramidal disorder (14%), tremor (8%), parkinsonism (7%), muscle rigidity (6%) and somnolence (5%).

In addition, the safety of haloperidol was evaluated in 284 haloperidol-treated patients who participated in 3 placebo-controlled clinical studies and in 1295 haloperidol-treated patients who participated in 16 double-blind active comparator-controlled clinical studies.

Table 3 lists adverse reactions as follows:

• Reported in clinical studies with haloperidol decanoate.

• Reported in clinical studies with haloperidol (non-decanoate formulations) and relate to the active moiety.

• From postmarketing experience with haloperidol decanoate and haloperidol.

Adverse reaction frequencies are based on (or estimated from) clinical trials or epidemiology studies with haloperidol decanoate, and classified using the following convention:

Very common:	≥ 1/10
Common:	≥ 1/100 to <1/10
Uncommon:	≥ 1/1,000 to <1/100
Rare:	≥ 1/10,000 to <1/1,000
Very rare:	<1/10,000
Not known:	cannot be estimated from the available data.

The adverse reactions are presented by System Organ Class and in order of decreasing seriousness within each frequency category.

Table 3: Adverse reactions

System Organ Class	**Adverse Reaction**				
	Frequency				
	Very Common	**Common**	**Uncommon**	**Rare**	**Not known**
Blood and lymphatic system disorders					Pancytopenia Agranulocytosis Thrombocytopenia Leukopenia Neutropenia
Immune system disorders					Anaphylactic reaction Hypersensitivity
Endocrine disorders					Inappropriate antidiuretic hormone secretion Hyperprolactinaemia
Metabolic and nutritional disorders					Hypoglycaemia
Psychiatric disorders		Depression Insomnia			Psychotic disorder Agitation Confusional state Loss of libido Libido decreased Restlessness
Nervous system disorders	Extrapyramidal disorder	Akathisia Parkinsonism Masked facies Tremor Somnolence	Akinesia Dyskinesia Dystonia Cogwheel rigidity Hypertonia		Neuroleptic malignant syndrome Tardive dyskinesia Convulsion Bradykinesia

		Sedation	Headache		Hyperkinesia Hypokinesia Dizziness Muscle contractions involuntary Motor dysfunction Nystagmus
Eye disorders			Oculogyric crisis Vision blurred Visual disturbance		
Cardiac disorders			Tachycardia		Ventricular fibrillation Torsade de pointes Ventricular tachycardia Extrasystoles
Vascular disorders					Hypotension Orthostatic hypotension
Respiratory, thoracic and mediastinal disorders					Laryngeal oedema Bronchospasm Laryngospasm Dyspnoea
Gastrointestinal disorders		Constipation Dry mouth Salivary hypersecretion			Vomiting Nausea
Hepatobiliary disorders					Acute hepatic failure Hepatitis Cholestasis Jaundice Liver function test abnormal
Skin and subcutaneous tissue disorders					Angioedema Dermatitis exfoliative Leukocytoclastic vasculitis Photosensitivity reaction Urticaria Pruritus Rash Hyperhidrosis
Musculoskeletal and connective tissue disorders		Muscle rigidity			Rhabdomyolysis Torticollis Trismus Muscle spasms Muscle twitching Musculoskeletal stiffness

Renal and urinary disorders					Urinary retention
Pregnancy, puerperium and perinatal conditions					Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders		Sexual dysfunction			Priapism Amenorrhoea Galactorrhoea Dysmenorrhoea Menorrhagia Erectile dysfunction Gynaecomastia Menstrual disorder Breast pain Breast discomfort
General disorders and administration site conditions		Injection site reaction			Sudden death Face oedema Oedema Hyperthermia Hypothermia Gait disturbance Injection site abscess
Investigations		Weight increased			Electrocardiogram QT prolonged Weight decreased

Electrocardiogram QT prolonged, ventricular arrhythmias (ventricular fibrillation, ventricular tachycardia), torsade de pointes and sudden death have been reported with haloperidol.

Class effects of antipsychotics

Cardiac arrest has been reported with antipsychotics.

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis, have been reported with antipsychotics. The frequency is unknown.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

4.9 Overdose

While overdose is less likely to occur with parenteral than with oral medication, the following details are based on oral haloperidol, also taking into account the extended duration of action of HALDOL Decanoate.

Symptoms and signs

The manifestations of haloperidol overdose are an exaggeration of the known pharmacological effects and adverse reactions. The most prominent symptoms are severe extrapyramidal reactions, hypotension and sedation. An extrapyramidal reaction is manifest by muscular rigidity and a generalised or localised tremor. Hypertension rather than hypotension is also possible.

In extreme cases, the patient would appear comatose with respiratory depression and hypotension that could be severe enough to produce a shock-like state. The risk of ventricular arrhythmias, possibly associated with QTc prolongation, must be considered.

Treatment

There is no specific antidote. Treatment is supportive. Dialysis is not recommended in the treatment of overdose because it removes only very small amounts of haloperidol (see section 5.2).

For comatose patients, a patent airway must be established by use of an oropharyngeal airway or endotracheal tube. Respiratory depression may necessitate artificial respiration.

It is recommended that ECG and vital signs be monitored, and that monitoring continues until the ECG is normal. Treatment of severe arrhythmias with appropriate anti-arrhythmic measures is recommended.

Hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma or concentrated albumin and vasopressor agents, such as dopamine or noradrenaline. Adrenaline must not be used because it might cause profound hypotension in the presence of haloperidol.

In cases of severe extrapyramidal reactions, it is recommended that an antiparkinson medicinal product be administered, and continued for several weeks. Antiparkinson medicinal products must be withdrawn very cautiously as extrapyramidal symptoms may emerge.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics; antipsychotics; butyrophenone derivatives, ATC code: N05AD01.

Mechanism of action

Haloperidol decanoate is an ester of haloperidol and decanoic acid, and as such, a depot antipsychotic belonging to the butyrophenones group. After intramuscular injection, haloperidol decanoate is gradually released from muscle tissue and hydrolysed slowly into free haloperidol, which enters the systemic circulation.

Haloperidol is a potent central dopamine type 2 receptor antagonist, and at recommended doses, has low alpha-1 antiadrenergic activity and no antihistaminergic or anticholinergic activity.

Pharmacodynamic effects

Haloperidol suppresses delusions and hallucinations as a direct consequence of blocking dopaminergic signalling in the mesolimbic pathway. The central dopamine blocking effect has activity on the basal ganglia (nigrostriatal bundles). Haloperidol causes efficient psychomotor sedation, which explains the favourable effect on mania and other agitation syndromes.

The activity on the basal ganglia probably underlies the undesirable extrapyramidal motor effects (dystonia, akathisia and parkinsonism).

The antidopaminergic effects of haloperidol on lactotropes in the anterior pituitary explain hyperprolactinaemia due to inhibition of dopamine-mediated tonic inhibition of prolactin secretion.

Clinical studies

In clinical studies, patients were mostly reported to have received prior treatment with orally administered haloperidol before converting to haloperidol decanoate. Occasionally, patients had previously been treated orally with another antipsychotic medicinal product.

5.2 Pharmacokinetic properties

Absorption

Administration of haloperidol decanoate as a depot intramuscular injection results in a slow and sustained release of free haloperidol. The plasma concentrations rise gradually, usually peaking within 3 to 9 days after injection.

Steady state plasma levels are reached within 2 to 4 months in patients receiving monthly injections.

Distribution

Mean haloperidol plasma protein binding in adults is approximately 88 to 92%. There is a high inter-subject variability for plasma protein binding. Haloperidol is rapidly distributed to various tissues and organs, as indicated by the large volume of distribution (mean values 8 to 21 l/kg after intravenous dosing). Haloperidol crosses the blood-brain barrier easily. It also crosses the placenta and is excreted in breast milk.

Biotransformation

Haloperidol is extensively metabolised in the liver. The main metabolic pathways of haloperidol in humans include glucuronidation, ketone reduction, oxidative N-dealkylation and formation of pyridinium metabolites. The metabolites of haloperidol are not considered to make a significant contribution to its activity; however, the reduction pathway accounts approximately for 23% of the biotransformation, and back-conversion of the reduced metabolite of haloperidol to haloperidol cannot be fully ruled out. The cytochrome P450 enzymes CYP3A4 and CYP2D6 are involved in haloperidol metabolism. Inhibition or induction of CYP3A4, or inhibition of CYP2D6, may affect haloperidol metabolism. A decrease in CYP2D6 enzyme activity may result in increased haloperidol concentrations.

Elimination

The terminal elimination half-life of haloperidol after intramuscular injection with haloperidol decanoate is on average 3 weeks. This is longer than for the non-decanoate formulations, where the haloperidol terminal elimination half-life is on average 24 hours after oral administration and 21 hours after intramuscular administration.

Haloperidol apparent clearance after extravascular administration ranges from 0.9 to 1.5 l/h/kg and is reduced in poor metabolisers of CYP2D6. Reduced CYP2D6 enzyme activity may result in increased concentrations of haloperidol. The inter-subject variability (coefficient of variation, %) in haloperidol clearance was estimated to be 44% in a population pharmacokinetic analysis in patients with schizophrenia. After intravenous haloperidol administration, 21% of the dose was eliminated in the faeces and 33% in the urine. Less than 3% of the dose is excreted unchanged in the urine.

Linearity/non-linearity

The pharmacokinetics of haloperidol following intramuscular injections of haloperidol decanoate are dose-related. The relationship between dose and plasma haloperidol level is approximately linear for doses below 450 mg.

Special populations

Elderly

Haloperidol plasma concentrations in elderly patients were higher than in younger adults administered the same dose. Results from small clinical studies suggest a lower clearance and a longer elimination half-life of haloperidol in elderly patients. The results are within the observed variability in haloperidol pharmacokinetics. Dose adjustment is recommended in elderly patients (see section 4.2).

Renal impairment

The influence of renal impairment on the pharmacokinetics of haloperidol has not been evaluated. About one-third of a haloperidol dose is excreted in urine, mostly as metabolites. Less than 3% of administered haloperidol is eliminated unchanged in the urine. Haloperidol metabolites are not considered to make a significant contribution to its activity, although for the reduced metabolite of haloperidol, back-conversion to haloperidol cannot be fully ruled out. Even though impairment of renal function is not expected to affect haloperidol elimination to a clinically relevant extent, caution is advised in patients with renal impairment, and especially those with severe impairment, due to the long half-life of haloperidol and its reduced metabolite, and the possibility of accumulation (see section 4.2).

Because of the high haloperidol distribution volume and its high protein binding, only very small amounts are removed by dialysis.

Hepatic impairment

The influence of hepatic impairment on the pharmacokinetics of haloperidol has not been evaluated. However, hepatic impairment may have significant effects on the pharmacokinetics of haloperidol because it is extensively metabolised in the liver. Therefore, dose adjustment and caution is advised in patients with hepatic impairment (see sections 4.2 and 4.4).

Pharmacokinetic/pharmacodynamics relationships

Therapeutic concentrations

Based on published data from multiple clinical studies, therapeutic response is obtained in most patients with acute or chronic schizophrenia at plasma concentrations of 1 to 10 ng/ml. A subset of patients may require higher concentrations as a consequence of a high inter-subject variability in haloperidol pharmacokinetics.

In patients with first-episode schizophrenia treated with short-acting haloperidol formulations, therapeutic response may be obtained at concentrations as low as 0.6 to 3.2 ng/ml, as estimated based on measurements of D2 receptor occupancy and assuming that a D2 receptor occupancy level of 60 to 80% is most appropriate for obtaining therapeutic response and limiting extrapyramidal symptoms. On average, concentrations in this range would be obtained with doses of 1 to 4 mg daily.

Due to the high inter-subject variability in haloperidol pharmacokinetics and the concentration-effect relationship, it is recommended to adjust the individual haloperidol decanoate dose based on the patient's response. This must take into account the time after a change in dose to achieve a new steady state plasma concentration and the additional time to elicit a therapeutic response. Measurement of haloperidol blood concentrations may be considered in individual cases.

Cardiovascular effects

The risk of QTc prolongation increases with haloperidol dose and with haloperidol plasma concentrations.

Extrapyramidal symptoms

Extrapyramidal symptoms can occur within the therapeutic range, although the frequency is usually higher with doses producing higher than therapeutic concentrations.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of local tolerability, repeat dose toxicity and genotoxicity. In rodents, haloperidol administration showed a decrease in fertility, limited teratogenicity as

well as embryo-toxic effects.

In a carcinogenicity study of haloperidol, dose-dependent increases in pituitary gland adenomas and mammary gland carcinomas were seen in female mice. These tumours may be caused by prolonged dopamine D2 antagonism and hyperprolactinaemia. The relevance of these tumour findings in rodents in terms of human risk is unknown.

Haloperidol has been shown to block the cardiac hERG channel in several published studies *in vitro*. In a number of *in vivo* studies, intravenous administration of haloperidol in some animal models has caused significant QTc prolongation at doses around 0.3 mg/kg, producing C_{max} plasma levels at least 7 to 14 times higher than the therapeutic plasma concentrations of 1 to 10 ng/ml that were effective in the majority of patients in clinical studies. These intravenous doses, which prolonged QTc, did not cause arrhythmias. In some animal studies, higher intravenous haloperidol doses of 1 mg/kg or greater caused QTc prolongation and/or ventricular arrhythmias at C_{max} plasma levels at least 38 to 137 times higher than the therapeutic plasma concentrations that were effective in the majority of patients in clinical studies.

6. Pharmaceutical particulars

6.1 List of excipients

Benzyl alcohol, sesame oil.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years..

6.4 Special precautions for storage

Store in the original package to protect from light. This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

50 mg/ml solution:

1 ml or 3 ml of solution in an amber glass ampoule.

1 ml ampoules: Packs of 1, 3 or 5 ampoules.

3 ml ampoules: Packs of 1 or 5 ampoules; multipacks containing 50 (10 packs of 5) ampoules.

100 mg/ml solution:

1 ml of solution in an amber glass ampoule.

Packs of 1 or 5 ampoules.

Not all pack sizes may be marketed

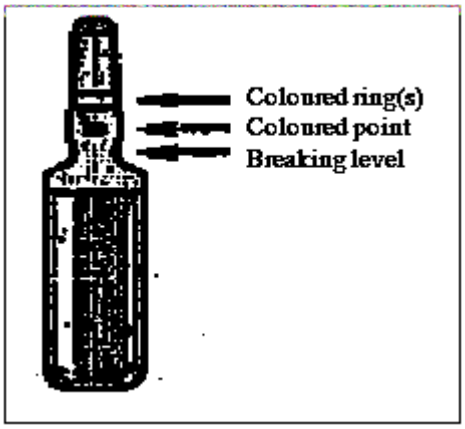
6.6 Special precautions for disposal and other handling

• Before using the ampoule, roll it briefly between both hand palms to warm up the product.

• Hold the ampoule between the thumb and index finger, leaving the tip of the ampoule free.

• With the other hand, hold the tip of ampoule putting the index finger against the neck of ampoule, and the thumb on the coloured point parallel to the identification coloured rings.

• Keeping the thumb on the point, sharply break the tip of ampoule while holding firmly the other part of the ampoule in the hand.



Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Marketing authorisation holder

Essential Pharma Limited,

Vision Exchange Building

Triq it-Territorjals, Zone 1,

Central Business District,

Birkirkara, CBD 1070,

Malta

8. Marketing authorisation number(s)

HALDOL Decanoate 50 mg/ml solution for injection

PL 50301/0008

HALDOL Decanoate 100 mg/ml solution for injection

PL 50301/0009

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 23 July 1982

Date of latest renewal: 07 January 2003

10. Date of revision of the text

12 September 2023

Company Contact Details

Essential Pharma Ltd (Malta)

Address

Vision Exchange Building, Triq it-Territorjals, Zone 1,
Central Business District, Birkirkara, CBD 1070, Malta

Medical Information Direct Line

01784 477167

Medical Information e-mail

medinfo@essentialpharmagroup.com

Stock Availability

info@essentialpharmagroup.com

Telephone

01784 477167

Drug Safety e-mail

drugsafety@essentialpharmagroup.com

Customer Care direct line

01784 477167

WWW

https://essentialpharmagroup.com/

Iloperidone

FDA

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use FANAPT safely and effectively. See full prescribing information for FANAPT.

FANAPT® (iloperidone) tablets, for oral use
Initial U.S. Approval: 2009

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. FANAPT is not approved for use in patients with dementia-related psychosis. (5.1)

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	4/2024
Dose and Administration (2.1, 2.2, 2.3, 2.4)	4/2024
Warnings and Precautions (5.6, 5.7, 5.11, 5.15, 5.16)	4/2024
Warnings and Precautions, (5.11)	1/2025
Warnings and Precautions, Suicide (5.14)	Removed 4/2024

----------INDICATIONS AND USAGE----------

FANAPT is an atypical antipsychotic indicated for:

- Treatment of schizophrenia in adults. (1, 14.1)
- Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults. (1, 14.2)

----------DOSAGE AND ADMINISTRATION----------

- Administer FANAPT orally twice daily without regard to meals. (2.1)
- Titrate the dosage of FANAPT to avoid orthostatic hypotension. See Full Prescribing Information for titration schedule. (2.1)
- Recommended Dosage:

Indication	Starting Dosage	Recommended Dosage
Schizophrenia (2.1)	1 mg twice daily	6 mg to 12 mg twice daily
Bipolar Mania (2.1)	1 mg twice daily	12 mg twice daily

- CYP2D6 Poor Metabolizers: See Full Prescribing Information for titration schedule and recommended dosage. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg tablets. (3)

----------CONTRAINDICATIONS----------

Known hypersensitivity to FANAPT or to any components in the formulation. (4, 6.2)

----------WARNINGS AND PRECAUTIONS----------

- Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis: Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack). (5.2)
- QT prolongation: Prolongs QT interval and may be associated with arrhythmia and sudden death. Avoid use of FANAPT in combination with other drugs that are known to prolong QTc; use caution and consider dose modification when prescribing FANAPT with other drugs that inhibit FANAPT metabolism. Monitor serum potassium and magnesium in patients at risk for electrolyte disturbances. (1, 5.3, 7.1, 7.2, 12.3)
- Neuroleptic Malignant Syndrome (NMS): Manage with immediate discontinuation of drug and close monitoring. (5.4)
- Tardive dyskinesia: Discontinue if clinically appropriate. (5.5)
- Metabolic Changes: Monitor for hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain. (5.6)
- Orthostatic hypotension and Syncope: Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope. (5.7)
- Seizures: Use cautiously in patients with a history of seizures or with conditions that lower seizure threshold. (5.9)
- Leukopenia, Neutropenia, and Agranulocytosis have been reported with antipsychotics. Perform complete blood counts (CBC) in patients with pre-existing low white blood cell count (WBC) or a history of leukopenia/neutropenia. Consider discontinuing FANAPT if clinically significant decline in WBC occurs in the absence of other causative factors. (5.10)
- Priapism: Cases have been reported in association with FANAPT treatment. Severe priapism may require surgical intervention. (5.14)
- Potential for cognitive and motor impairment: Use caution when operating machinery. (5.15)
- Intraoperative Floppy Iris Syndrome (IFIS): IFIS during cataract surgery may require modifications to the surgical technique. (5.16)

---------- ADVERSE REACTIONS----------

Commonly observed adverse reactions (incidence ≥5% and 2-fold greater than placebo) were (6.1):

- Schizophrenia: dizziness, dry mouth, fatigue, nasal congestion, orthostatic hypotension, somnolence, tachycardia, and weight increased.
- Bipolar mania: tachycardia, dizziness, dry mouth, hepatic enzymes increased, nasal congestion, weight increased, hypotension, and somnolence.

To report SUSPECTED ADVERSE REACTIONS, contact Vanda Pharmaceuticals Inc. at 1-844-GO-VANDA (1-844-468-2632) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

The dose of FANAPT should be reduced in patients co-administered a strong CYP2D6 or CYP3A4 inhibitor. (2.2, 7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)
- Lactation: Advise not to breast feed. (8.2)
- Pediatric Use: Safety and effectiveness not established in children and adolescents. (8.4)
- Hepatic Impairment: FANAPT is not recommended for patients with severe hepatic impairment. (2.3, 8.6)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 1/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. FANAPT is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

FANAPT® is indicated for:

- Treatment of schizophrenia in adults *[see Clinical Studies (14.1)]*.
- Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Titrate FANAPT to avoid orthostatic hypotension *[see Warnings and Precautions (5.7)]*.

Administer FANAPT orally with or without food.

Table 1 includes dosage recommendations for FANAPT for the treatment of schizophrenia and the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.

Table 1: Dosage Recommendations for FANAPT in Adults for the Treatment of Schizophrenia or Acute Treatment of Manic or Mixed Episodes Associated with Bipolar I Disorder

Indication and Population	Titration schedule							Recommended Dosage
	Day 1	*Day 2*	*Day 3*	*Day 4*	*Day 5*	*Day 6*	*Day 7*	
Schizophrenia	1mg twice daily	2 mg twice daily	4 mg twice daily	6 mg twice daily	8 mg twice daily	10 mg twice daily	12 mg twice daily	6 mg to 12 mg twice daily
Bipolar I Disorder Manic or Mixed Episodes	1 mg twice daily	3 mg twice daily	6 mg twice daily	9 mg twice daily	12 mg twice daily	Titration complete		12 mg twice daily

2.2 Dosage Recommendations for Use in Patients Who Are Known CYP2D6 Poor Metabolizers

Reduce the dose of FANAPT by one-half for CYP2D6 poor metabolizers *[see Clinical Pharmacology (12.3, 12.5)]*. Table 2 includes dosage recommendations for FANAPT in adults who are CYP2D6 poor metabolizers.

Table 2: Dosage Recommendations for FANAPT in Adults with Schizophrenia or Bipolar I Disorder Who are CYP2D6 Poor Metabolizers

Indication and Population	Titration schedule							Recommended Dosage
	Day 1	*Day 2*	*Day 3*	*Day 4*	*Day 5*	*Day 6*	*Day 7*	
Schizophrenia	1mg twice daily	2 mg twice daily	4 mg twice daily	6 mg twice daily	Titration complete			3 mg to 6 mg twice daily
Bipolar I Disorder Manic or Mixed Episodes	1 mg twice daily	3 mg twice daily	6 mg twice daily	Titration complete				6 mg twice daily

2.3 Dosage Recommendations in Patients with Hepatic Impairment

No dose adjustment for FANAPT is needed in patients with mild hepatic impairment. Patients with moderate hepatic impairment may require dose reduction, if clinically indicated. FANAPT is not recommended for patients with severe hepatic impairment *[see Use in Specific Populations (8.6)]*.

2.4 Dosage Modifications for Concomitant Use with Strong CYP2D6 Inhibitors and Strong CYP3A4 Inhibitors

Coadministration with Strong CYP2D6 Inhibitors

Reduce the dose of FANAPT one-half when administered concomitantly with strong CYP2D6 inhibitors such as fluoxetine or paroxetine. When the CYP2D6 inhibitor is withdrawn from the combination therapy, increase the dose of FANAPT to where it was before *[see Drug Interactions (7.1)]*.

Coadministration with Strong CYP3A4 Inhibitors

Reduce the dose of FANAPT by one-half when administered concomitantly with strong CYP3A4 inhibitors such as ketoconazole or clarithromycin. When the CYP3A4 inhibitor is withdrawn from the combination therapy, increase the dose of FANAPT to where it was before *[see Drug Interactions (7.1)]*.

Coadministration with Strong CYP2D6 and Strong CYP3A4 Inhibitors

Reduce the dose of FANAPT by about one-half if administered concomitantly with inhibitors of CYP2D6 and CYP3A4. When both CYP2D6 and CYP3A4 inhibitors are withdrawn from the combination therapy, increase the dose of FANAPT to where it was before *[see Drug Interactions (7.1)]*.

2.5 Reinitiation of Treatment in Patients Previously Discontinued

Although there are no data to specifically address reinitiation of treatment, it is recommended that the initiation titration schedule be followed whenever patients have had an interval off FANAPT of more than 3 days.

3 DOSAGE FORMS AND STRENGTHS

FANAPT tablets are available in the following strengths: 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg. The tablets are white, round, flat, beveled-edged, and identified with a logo "[redacted]" debossed on one side and tablet strength "1", "2", "4", "6", "8", "10", or "12" debossed on the other side.

4 CONTRAINDICATIONS

FANAPT is contraindicated in individuals with a known hypersensitivity reaction to the product. Anaphylaxis, angioedema, and other hypersensitivity reactions have been reported *[see Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 dementia-related psychosis placebo-controlled trials (modal duration of 10 weeks) largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in placebo-treated patients.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. FANAPT is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.2)]*.

5.2 Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials in elderly subjects with dementia, patients randomized to risperidone, aripiprazole, and olanzapine had a higher incidence of stroke and transient ischemic attack, including fatal stroke. FANAPT is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.1)]*.

5.3 QT Prolongation

In an open-label QTc study in patients with schizophrenia or schizoaffective disorder (n=160), FANAPT was associated with QTc prolongation of 9 msec at an iloperidone dose of 12 mg twice daily. The effect of FANAPT on the QT interval was augmented by the presence of CYP450 2D6 or 3A4 metabolic inhibition (paroxetine 20 mg once daily and ketoconazole 200 mg twice daily, respectively). Under conditions of metabolic inhibition for both 2D6 and 3A4, FANAPT 12 mg twice daily was associated with a mean QTcF increase from baseline of about 19 msec.

No cases of torsade de pointes or other severe cardiac arrhythmias were observed during the pre-marketing clinical program.

The use of FANAPT should be avoided in combination with other drugs that are known to prolong QTc including Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval (e.g., pentamidine, levomethadyl acetate, methadone). FANAPT should also be avoided in patients with a known genetic susceptibility to congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

Certain circumstances may increase the risk of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3)

concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval; (5) recent acute myocardial infarction; and/or (6) uncompensated heart failure.

Caution is warranted when prescribing FANAPT with drugs that inhibit FANAPT metabolism *[see Drug Interactions (7.1)]*, and in patients with reduced activity of CYP2D6 *[see Clinical Pharmacology (12.3, 12.5)]*.

It is recommended that patients being considered for FANAPT treatment who are at risk for significant electrolyte disturbances have baseline serum potassium and magnesium measurements with periodic monitoring. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. FANAPT should be avoided in patients with histories of significant cardiovascular illness, e.g., QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. FANAPT should be discontinued in patients who are found to have persistent QTc measurements >500 msec.

If patients taking FANAPT experience symptoms that could indicate the occurrence of cardiac arrhythmias, e.g., dizziness, palpitations, or syncope, the prescriber should initiate further evaluation, including cardiac monitoring.

5.4 Neuroleptic Malignant Syndrome (NMS)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with administration of antipsychotic drugs, including FANAPT. Clinical manifestations include hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs), and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

If NMS is suspected, immediately discontinue FANAPT and provide intensive symptomatic treatment and monitoring.

5.5 Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. The risk appears to be highest among the elderly, especially elderly women, but it is impossible to predict, which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible increase with the duration of treatment and cumulative dose. The syndrome can develop after relatively brief treatment periods at low doses. It may also occur after discontinuation of treatment.

Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment itself may suppress (or partially suppress) the signs and symptoms of the syndrome, possibly masking the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, FANAPT should be prescribed in a manner that is most likely to reduce the risk of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients: 1) who suffer from a chronic illness that is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment producing a satisfactory clinical response. Periodically reassess the need for continued treatment.

If signs and symptoms of tardive dyskinesia appear in a patient on FANAPT, drug discontinuation should be considered. However, some patients may require treatment with FANAPT despite the presence of the syndrome.

5.6 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all atypical antipsychotic drugs have been shown to produce some metabolic changes, each drug in the class has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including FANAPT. Assess fasting plasma glucose before or soon after initiation of antipsychotic medication and monitor periodically during long-term treatment.

Schizophrenia

In a 4-week fixed-dose placebo-controlled study of adults with schizophrenia, the mean change from baseline in serum glucose was 6.6 mg/dL and -0.5 mg/dL for FANAPT and placebo treated patients, respectively. The proportion of patients with shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) were 10.7% and 2.5% for FANAPT and placebo treated patients, respectively.

In pooled analyses from clinical studies, for adults with schizophrenia remaining on treatment with FANAPT 10-16 mg/day glucose increased, on average, from baseline by 1.8 mg/dL at 3-6 months (N=773) and by 5.4 mg/dL at 6-12 months (N=723) and at >12 months (N=425) of treatment. In a smaller group of patients remaining on treatment with FANAPT 20-24 mg/day, glucose decreased by 3.6 mg/dL at 3-6 months (N=34); by 9 mg/dL at 6-12 months (N=31), and by 18 mg/dL at > 12 months (N=20) of treatment.

Bipolar Mania

In a 4-week fixed dose study of adults with bipolar mania, mean changes from baseline in serum glucose and the proportion of patients with shifts in fasting glucose from Normal (<100 mg/dL) to High (≥126 mg/dL) for patients receiving FANAPT were similar to those for patients receiving placebo.

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. Before or soon after initiation of antipsychotic medications, obtain a fasting lipid profile at baseline and monitor periodically during treatment.

Schizophrenia

In a 4-week fixed dose study of adults with schizophrenia, the mean change from baseline in fasted total cholesterol was 8.2 mg/dL and -2.2 mg/dL for FANAPT and placebo treated patients, respectively. The effects on LDL were similar to those on total cholesterol (changes of 9 mg/dL and -1.4 mg/dL for FANAPT and placebo treated patients, respectively). Mean changes from baseline in fasted triglycerides were -0.8 mg/dL and 16.5 mg/dL for FANAPT and placebo treated patients, respectively.

The proportion of patients with shifts from normal to high fasted total cholesterol, LDL, and triglycerides were similar for FANAPT and placebo-treated patients. The proportion of patients with shifts in fasted HDL from normal (≥40 mg/dL) to low (<40 mg/dL) was greater for placebo patients (23.8%) compared to patients treated with FANAPT (12.1%).

In pooled analysis from clinical studies, for adults with schizophrenia remaining on treatment with FANAPT, on average, both cholesterol and triglycerides decreased from baseline for adults with schizophrenia remaining on treatment at 3-6 months, 6-12 months, and >12-month time points in both 10-16 mg/day and 20-24 mg/day dose groups.

Bipolar Mania

In a 4-week fixed dose study of adults with bipolar mania, the mean changes from baseline for fasted total cholesterol, LDL, HDL, and triglycerides for FANAPT were similar to those for placebo-treated patients. The proportion of patients with shifts in fasted total cholesterol from normal (<200 mg/dL) to high (≥240 mg/dL) was greater for FANAPT treated patients (10.7%) than placebo-treated patients (7.2%). Shifts from normal to high LDL and triglycerides and from normal to low HDL occurred at rates for FANAPT similar to those for placebo treated patients.

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Monitor weight at baseline and frequently thereafter.

Schizophrenia

Across all short- and long-term studies of adults with schizophrenia, the overall mean change from baseline at endpoint was 2.1 kg.

In 4 placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies in adults with schizophrenia the mean change in weight (kg) was -0.1, 2, and 2.7 for placebo, FANAPT 10-16 mg/day, and FANAPT 20-24 mg/day groups, respectively. The proportion of patients with weight gain >7% increase from baseline was 4%, 12%, and 18% for placebo, FANAPT 10-16 mg/day, and FANAPT 20-24 mg/day groups, respectively.

Bipolar Mania

In a 4-week fixed dose study of adults with bipolar mania the mean change in weight (kg) was 1.6 and 4.6 kg for placebo and FANAPT 24 mg/day groups, respectively. The proportion of patients with weight gain ≥7% increase from baseline was 14% and 35%, for placebo and FANAPT 24 mg/day groups, respectively.

5.7 Orthostatic Hypotension and Syncope

FANAPT can induce orthostatic hypotension associated with dizziness, tachycardia, and syncope. This reflects its alpha1-adrenergic antagonist properties. In double-blind placebo-controlled short-term studies in patients with schizophrenia, where the dose was increased slowly, as recommended above, syncope was reported in 0.4% (5/1,344) of patients treated with FANAPT, compared with 0.2% (1/587) on placebo. Orthostatic hypotension was reported in 5% of patients given 20 mg to 24 mg/day, 3% of patients given 10 mg to 16 mg/day, and 1% of patients given placebo.

In a double-blind placebo-controlled short-term study in patients with bipolar mania, syncope was reported in 0.5% (1/206) of patients treated with FANAPT, compared with 0% (0/208) on placebo. In this study, orthostatic hypotension was reported in 4% (9/206) of patients treated with FANAPT and 2% (5/208) of patients given placebo.

More rapid titration would be expected to increase the rate of orthostatic hypotension and syncope.

Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension (e.g., elderly patients, patients with dehydration, hypovolemia, and concomitant treatment with antihypertensive medications), patients with known cardiovascular disease (history of myocardial infarction, ischemic heart disease, heart failure, or conduction abnormalities), and patients with cerebrovascular disease.

5.8 Falls

Antipsychotics, including FANAPT, may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

5.9 Seizures

Like other antipsychotic drugs, FANAPT may cause seizures. The risk is greatest in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in older patients.

5.10 Leukopenia, Neutropenia and Agranulocytosis

In clinical trial and postmarketing experience, leukopenia and neutropenia have been reported temporally related to antipsychotic agents. Agranulocytosis (including fatal cases) has also been reported.

Possible risk factors for leukopenia/neutropenia include preexisting low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and should discontinue FANAPT at the first sign of a decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue FANAPT in patients with absolute neutrophil count $<1000/mm^3$ and follow their WBC until recovery.

5.11 Hyperprolactinemia

As with other drugs that antagonize dopamine D2 receptors, FANAPT elevates prolactin levels.

Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male patients.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Mammary gland proliferative changes and increases in serum prolactin were seen in mice and rats treated with FANAPT *[see Nonclinical Toxicology (13)]*. Published epidemiologic studies have shown inconsistent results when exploring the potential association between hyperprolactinemia and breast cancer.

In a short-term placebo-controlled trial (4-weeks) in patients with schizophrenia, the mean change from baseline to endpoint in plasma prolactin levels for the FANAPT 24 mg/day-treated group was an increase of 2.6 ng/mL compared to a decrease of 6.3 ng/mL in the placebo-group. In placebo-controlled trials in patients with schizophrenia, elevated plasma prolactin levels (≥1.15xULN) were observed in 26% of adults treated with FANAPT compared to 12% in the placebo group. In the short-term trials, FANAPT was associated with modest levels of prolactin elevation compared to greater prolactin elevations observed with some other antipsychotic

agents. In pooled analysis from clinical studies including longer term trials, in 3210 adults treated with iloperidone, gynecomastia was reported in 2 male subjects (0.1%) compared to 0% in placebo-treated patients, and galactorrhea was reported in 8 female subjects (0.2%) compared to 3 female subjects (0.5%) in placebo-treated patients.

In a short-term, placebo-controlled trial (4-weeks) in patients with bipolar mania, the mean change from baseline to endpoint in plasma prolactin levels for the FANAPT group was an increase of 15.66 ng/mL compared to a decrease of 0.58 ng/mL for the placebo group. In this trial, elevated plasma prolactin levels (≥1.15xULN) were observed in 35% of adults treated with FANAPT compared to 1% of the placebo group.

5.12 Body Temperature Regulation

Atypical antipsychotics may disrupt the body's ability to reduce core body temperature. Strenuous exercise, exposure to extreme heat, dehydration, and anticholinergic medications may contribute to an elevation in core body temperature; use FANAPT with caution in patients who may experience these conditions.

5.13 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients. Antipsychotic drugs, including FANAPT, should be used cautiously in patients at risk for aspiration.

5.14 Priapism

Four cases of priapism were reported in the pre-marketing FANAPT program (3 in the clinical studies for schizophrenia and 1 in the clinical study for manic and mixed episodes associated with bipolar I disorder). Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. FANAPT shares this pharmacologic activity. Severe priapism may require surgical intervention.

5.15 Potential for Cognitive and Motor Impairment

FANAPT, like other antipsychotics, may cause somnolence and has the potential to impair judgment, thinking or motor skills. In short-term, placebo-controlled trials of schizophrenia, somnolence (including sedation) was reported in 12% (104/874) of adult patients treated with FANAPT at doses of 10 mg/day or greater versus 5.3% (31/587) treated with placebo. In a short-term, placebo-controlled trial of bipolar mania, somnolence (including sedation) was reported in 8% (16/206) of adult patients treated with FANAPT versus 3% (6/208) treated with placebo.

Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with FANAPT does not affect them adversely.

5.16 Intraoperative Floppy Iris Syndrome (IFIS)

IFIS has been observed during cataract surgery in some patients on or previously treated with alpha-1 adrenergic blockers. This variant of small pupil syndrome is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigation currents, progressive intraoperative miosis despite preoperative dilation with standard mydriatic drugs, and potential prolapse of the iris toward the phacoemulsification incisions. The patient's surgeon should be prepared for possible modifications to their surgical technique, such as the utilization of iris hooks, iris dilator rings, or viscoelastic substances. There does

not appear to be a benefit of stopping alpha1 blocker therapy prior to cataract surgery. The initiation of therapy with FANAPT in patients for whom cataract or glaucoma surgery is scheduled is not recommended.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see Warnings and Precautions (5.1)]*
- Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis [*see Warnings and Precautions (5.2)]*
- QT Prolongation *[see Warnings and Precautions (5.3)]*
- Neuroleptic Malignant Syndrome (NMS) *[see Warnings and Precautions (5.4)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.5)]*
- Metabolic Changes *[see Warnings and Precautions (5.6)]*
- Orthostatic Hypotension and Syncope *[see Warnings and Precautions (5.7)]*
- Falls *[see Warnings and Precautions (5.8)]*
- Seizures *[see Warnings and Precautions (5.9)]*
- Leukopenia, Neutropenia and Agranulocytosis *[see Warnings and Precautions (5.10)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.11)]*
- Body Temperature Regulation *[see Warnings and Precautions (5.12)]*
- Dysphagia *[see Warnings and Precautions (5.13)]*
- Priapism *[see Warnings and Precautions (5.14)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.15)]*
- Intraoperative Floppy Iris Syndrome *[see Warnings and Precautions (5.16)]*

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trial of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The information below is derived from a clinical trial database for FANAPT consisting of 3,229 patients exposed to FANAPT at doses of 10 mg/day or greater, for the treatment of schizophrenia and from a clinical trial database for FANAPT consisting of 312 patients exposed to FANAPT at doses of 24 mg/day, for the treatment of bipolar mania *[see Clinical Studies (14.2)]*. Of these, 999 received FANAPT for at least 6 months, with 657 exposed to FANAPT for at least 12 months for the treatment of schizophrenia and 69 received FANAPT for at least 6 months, with 28 exposed to FANAPT for at least 12 months for the treatment of bipolar mania. All of these patients who received FANAPT were participating in multiple-dose clinical trials. The conditions and duration of treatment with FANAPT varied greatly and included (in overlapping categories), open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and flexible-dose studies, and short-term and longer-term exposure.

Schizophrenia

The information presented in this section was derived from pooled data from 4 placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies in patients who received FANAPT at daily doses within a range of 10 to 24 mg (n=874).

Adverse Reactions Occurring at an Incidence of 2% or More among FANAPT-Treated Patients and More Frequent than Placebo

Table 3 enumerates the pooled incidences of adverse reactions that were spontaneously reported in four placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, listing those reactions that occurred in 2% or more of patients treated with FANAPT in any of the dose groups, and for which the incidence in FANAPT-treated patients in any dose group was greater than the incidence in patients treated with placebo.

Table 3: Percentage of Adverse Reactions in Short-Term, Fixed- or Flexible-Dose, Placebo-Controlled Schizophrenia Trials in Adult Patients*

Body System or Organ Class Dictionary-derived Term	Placebo % (N=587)	FANAPT 10-16 mg/day % (N=483)	FANAPT 20-24 mg/day % (N=391)
Body as a Whole			
Arthralgia	2	3	3
Fatigue	3	4	6
Musculoskeletal Stiffness	1	1	3
Weight Increased	1	1	9
Cardiac Disorders			
Tachycardia	1	3	12
Eye Disorders			
Vision Blurred	2	3	1
Gastrointestinal Disorders			
Nausea	8	7	10
Dry Mouth	1	8	10
Diarrhea	4	5	7
Abdominal Discomfort	1	1	3
Infections			
Nasopharyngitis	3	4	3
Upper Respiratory Tract Infection	1	2	3
Nervous System Disorders			
Dizziness	7	10	20
Somnolence	5	9	15
Extrapyramidal Disorder	4	5	4
Tremor	2	3	3
Lethargy	1	3	1
Reproductive System			
Ejaculation Failure	<1	2	2
Respiratory			
Nasal Congestion	2	5	8
Dyspnea	<1	2	2
Skin			
Rash	2	3	2
Vascular Disorders			
Orthostatic Hypotension	1	3	5

Body System or Organ Class	Placebo	FANAPT 10-16 mg/day	FANAPT 20-24 mg/day
	%	%	%
Dictionary-derived Term	(N=587)	(N=483)	(N=391)
Hypotension	<1	<1	3

* Table includes adverse reactions that were reported in 2% or more of patients in any of the FANAPT dose groups and which occurred at greater incidence than in the placebo group. Figures rounded to the nearest integer.

Bipolar Mania

Table 4 enumerates the adverse reactions that occurred at an incidence of ≥2% and greater than placebo in a placebo-controlled, 4-week bipolar mania trial with FANAPT.

Table 4: Adverse Reactions Occurring in ≥2% of Adult Patients Treated with FANAPT and > Placebo in a Short-Term, Fixed-Dose, Placebo-Controlled Bipolar Mania Trial

System Organ Class	Placebo	FANAPT 24 mg/day**
Preferred Terms	N=208	N=206
	%	%
Cardiac disorders		
Tachycardia*	5	23
Gastrointestinal disorders		
Dry mouth	2	9
Nausea*	3	4
Investigations		
Hepatic enzyme increased*	1	8
Weight increased*	1	6
Nervous system disorders		
Dizziness*	1	12
Headache*	4	5
Somnolence*	3	8
Akathisia	0	4
Renal and urinary disorders		
Urinary urgency and Polyuria*	0	3
Reproductive system and breast disorders		
Sexual Dysfunction*	0.5	4
Respiratory, thoracic, and mediastinal disorders		
Nasal congestion	1	6
Vascular disorders		
Hypotension*	3	6
General disorders and administration site conditions		
Fatigue*	1	3

*The following terms were combined:
Tachycardia includes: heart rate increased, sinus tachycardia, postural orthostatic tachycardia syndrome, and tachycardia
Nausea includes: nausea and vomiting
Hepatic enzyme increased includes: predominantly alanine aminotransferase increased and including aspartate aminotransferase increased, hepatic enzyme increased, and transaminase increased)
Weight increased includes: weight increased and BMI increased
Dizziness includes: dizziness and postural dizziness

Headache includes: Headache and Tension headache
Somnolence includes: predominantly sedation and including sedation complication and somnolence
Urinary urgency and Polyuria includes: hypertonic bladder, micturition urgency, polyuria, and urinary incontinence
Sexual Dysfunction includes: ejaculation failure, erectile dysfunction, retrograde ejaculation, and ejaculation delayed
Hypotension includes: orthostatic hypotension
Fatigue includes: lethargy
**Patients with poor CYP2D6 metabolizer status received 12 mg/day.

Dose-Related Adverse Reactions in Clinical Trials

Based on the pooled data from 4 placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies, adverse reactions in patients with schizophrenia that occurred with a greater than 2% incidence in the patients treated with FANAPT, and for which the incidence in patients treated with FANAPT 20-24 mg/day were twice than the incidence in patients treated with FANAPT 10-16 mg/day were: abdominal discomfort, dizziness, hypotension, musculoskeletal stiffness, tachycardia, and weight increased.

Common and Drug-Related Adverse Reactions in Clinical Trials

Based on the pooled data from 4 placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies of patients with schizophrenia, the following adverse reactions occurred in ≥5% incidence in the patients treated with FANAPT and at least twice the placebo rate for at least 1 dose: dizziness, dry mouth, fatigue, nasal congestion, somnolence, tachycardia, orthostatic hypotension, and weight increased. Dizziness, tachycardia, and weight increased were at least twice as common on 20-24 mg/day as on 10-16 mg/day.

In a short-term, placebo-controlled trial in patients with bipolar mania the following adverse reactions occurred in ≥5% incidence in the patients treated with FANAPT and at least twice the placebo rate: tachycardia, dizziness, dry mouth, hepatic enzymes increased, nasal congestion, weight increased, hypotension, and somnolence.

Extrapyramidal Symptoms (EPS) in Clinical Trials

Pooled data from the 4 placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies of patients with schizophrenia provided information regarding EPS. Adverse event data collected from those trials showed the following rates of EPS-related adverse events as shown in Table 5.

Table 5: Percentage of EPS Compared to Placebo in 4- or 6-week Schizophrenia Trials

Preferred Term	Placebo (%) (N=587)	FANAPT 10-16 mg/day (%) (N=483)	FANAPT 20-24 mg/day (%) (N=391)
All EPS events	**11.6**	**13.5**	**15.1**
Tremor	1.9	2.5	3.1
Akathisia	2.7	1.7	2.3
Dyskinesia	1.5	1.7	1
Dystonia	0.7	1	0.8
Bradykinesia	0	0.6	0.5
Parkinsonism	0	0.2	0.3

Table 6 shows the rates of EPS-related events in a 4-week bipolar mania trial.

Table 6: Percentage of EPS Compared to Placebo in a 4-week Bipolar Mania Trial

Preferred Term	Placebo (%)	FANAPT 24 mg/day* (%)

	N = 208	N = 206
All EPS events	0	8.3
Akathisia	0	4.4
Extrapyramidal Disorder	0	1
Blepharospasm	0	0.5
Dystonia	0	0.5
Muscle Spasm	0	0.5
Restlessness	0	0.5
Torticollis	0	0.5
Tremor	0	0.5

*Patients with poor CYP2D6 metabolizer status received 12 mg/day.

Adverse Reactions Associated with Discontinuation of Treatment in Clinical Trials

Based on the pooled data from 4 placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies in patients with schizophrenia, there was no difference in the incidence of discontinuation due to adverse reactions between FANAPT-treated (5%) and placebo-treated (5%) patients. The types of adverse reactions that led to discontinuation were similar for the FANAPT- and placebo-treated patients.

In a 4-week, placebo-controlled study in patients with bipolar mania, the incidence of discontinuation due to adverse reactions was higher in FANAPT-treated (8.7%) patients than placebo-treated (5.3%) patients. Adverse reactions that led to discontinuation in more than one FANAPT-treated subject were liver enzyme elevations, nausea and vomiting, dizziness and hypotension.

Demographic Differences in Adverse Reactions in Clinical Trials

An examination of population subgroups in the 4 placebo-controlled, 4- or 6-week, fixed- or flexible-dose studies of patients with schizophrenia did not reveal any evidence of differences in safety on the basis of age, sex or race.

Laboratory Test Abnormalities in Clinical Trials

There were no differences between FANAPT and placebo in the incidence of discontinuation due to changes in hematology, or urinalysis.

Serum Transaminases

In a short-term placebo-controlled trial, asymptomatic alanine aminotransferase (ALT) elevations ≥3x ULN occurred in 9.2% of FANAPT-treated patients with acute mania compared to 1.5% of placebo treated subjects. AST elevations were less common.

Hematocrit

In short-term placebo-controlled trials (4- to 6-weeks) in patients with schizophrenia, there were 1.0% (13/1342) FANAPT-treated patients with hematocrit at least one time below the extended normal range during post-randomization treatment, compared to 0.3% (2/585) on placebo. The extended normal range for lowered hematocrit was defined in each of these trials as the value 15% below the normal range for the centralized laboratory that was used in the trial.

In a short-term placebo-controlled trial (4 weeks) in patients with bipolar mania, there were 3.5% (7/200) FANAPT-treated patients with hematocrit at least one time below the extended normal range (<0.85xLLN) during post-randomization treatment, compared to 0.5% (1/196) on placebo.

Analysis of clinical laboratory data following administration of FANAPT suggested the mechanism of hemodilution based on consistent decreases in hematocrit, hemoglobin, white blood cells, total protein, and

albumin. Decreases in hematocrit and total protein have been observed with other alpha receptor antagonists and are attributed to hemodilution *[see Clinical Pharmacology (12.2)]*.

Serum Urate Levels

In a 4-week placebo-controlled trial in patients with bipolar mania, treatment with FANAPT 12 mg twice a day resulted in an increase of serum urate levels of approximately 27.2 umol/L (0.457 mg/dL) compared to 0.1 umol/L (0.002 mg/dL) in placebo group.

Other Reactions During the Pre-marketing Evaluation of FANAPT

Patients with Schizophrenia

The following is a list of MedDRA terms that reflect adverse reactions in patients treated with FANAPT at multiple doses ≥ 4 mg/day during any phase of a trial with the database of 3,210 FANAPT-treated patients with schizophrenia. All reported reactions are included except those already listed in Table 3, or other parts of the *Adverse Reactions (6)*, those considered in the *Warnings and Precautions (5)*, those reaction terms which were so general as to be uninformative, reactions reported in fewer than 3 patients and which were neither serious nor life-threatening, reactions that are otherwise common as background reactions, and reactions considered unlikely to be drug related.

Reactions are further categorized by MedDRA system organ class and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not listed in Table 3 appear in this listing); infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Blood and Lymphatic Disorders: Infrequent – anemia, iron deficiency anemia; *Rare* – leukopenia

Cardiac Disorders: Frequent – palpitations; *Rare* – arrhythmia, atrioventricular block first degree, cardiac failure (including congestive and acute)

Ear and Labyrinth Disorders: Infrequent – vertigo, tinnitus

Endocrine Disorders: Infrequent – hypothyroidism

Eye Disorders: Frequent – conjunctivitis (including allergic); *Infrequent* – dry eye, blepharitis, eyelid edema, eye swelling, lenticular opacities, cataract, hyperemia (including conjunctival)

Gastrointestinal Disorders: Infrequent – gastritis, salivary hypersecretion, fecal incontinence, mouth ulceration; *Rare* – aphthous stomatitis, duodenal ulcer, hiatus hernia, hyperchlorhydria, lip ulceration, reflux esophagitis, stomatitis

General Disorders and Administrative Site Conditions: Infrequent – edema (general, pitting, due to cardiac disease), difficulty in walking, thirst; *Rare* – hyperthermia

Hepatobiliary Disorders: Infrequent – cholelithiasis

Investigations: Frequent: weight decreased; *Infrequent* – hemoglobin decreased, neutrophil count increased, hematocrit decreased

Metabolism and Nutrition Disorders: Infrequent – increased appetite, dehydration, hypokalemia, fluid retention

Musculoskeletal and Connective Tissue Disorders: *Frequent* – myalgia, muscle spasms; *Rare* – torticollis

Nervous System Disorders: Infrequent – paresthesia, psychomotor hyperactivity, restlessness, amnesia, nystagmus; *Rare* – restless legs syndrome

Psychiatric Disorders: Frequent – restlessness, aggression, delusion; *Infrequent* – hostility, libido decreased, paranoia, anorgasmia, confusional state, mania, catatonia, mood swings, panic attack, obsessive-compulsive disorder, bulimia nervosa, delirium, polydipsia psychogenic, impulse-control disorder, major depression

Renal and Urinary Disorders: Frequent – urinary incontinence; *Infrequent* – dysuria, pollakiuria, enuresis, nephrolithiasis; *Rare* – urinary retention, renal failure acute

Reproductive System and Breast Disorders: Frequent – erectile dysfunction; *Infrequent* – testicular pain, amenorrhea, breast pain; *Rare* – menstruation irregular, gynecomastia, menorrhagia, metrorrhagia, postmenopausal hemorrhage, prostatitis

Respiratory, Thoracic and Mediastinal Disorders: Infrequent – epistaxis, asthma, rhinorrhea, sinus congestion, nasal dryness; *Rare* – dry throat, sleep apnea syndrome, dyspnea exertional

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of FANAPT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure: retrograde ejaculation and hypersensitivity reactions (including anaphylaxis; angioedema; throat tightness; oropharyngeal swelling; swelling of the face, lips, mouth, and tongue; urticaria; rash; and pruritus).

7 DRUG INTERACTIONS

7.1 Clinically Important Drug Interactions with FANAPT

Table 7 presents clinically important drug interactions with FANAPT.

Table 7: Clinically Important Drug Interactions with FANAPT

Strong CYP2D6 Inhibitors	
Clinical Impact	Coadministration of fluoxetine with iloperidone increased exposure (area under curve, [AUC]) of iloperidone and its metabolite P88, by about 2- to 3- fold, and decreased the AUC of its metabolite P95 by one-half *[see Clinical Pharmacology (12.3, 12.5)]*. Coadministration of paroxetine with iloperidone resulted in increased mean steady-state peak concentrations of iloperidone and its metabolite P88, by about 1.6- fold, and decreased mean steady-state peak concentrations of its metabolite P95 by one-half *[see Clinical Pharmacology (12.3, 12.5)]*.
Intervention	Reduce the dose of FANAPT by one-half when administered with strong CYP2D6 inhibitors. When a strong CYP2D6 inhibitor is withdrawn from the combination therapy, the iloperidone dose should be returned to the previous level *[see Dosage and Administration (2.4)]*.
Strong CYP3A4 Inhibitors	
Clinical Impact	Co-administration of ketoconazole with iloperidone, increased the AUC of iloperidone and its metabolites P88 and P95 by 57%, 55%, and 35%, respectively *[see Clinical Pharmacology (12.3)]*.
Intervention	Reduce the dose of FANAPT by one-half when administered with strong CYP3A4 inhibitors. When the CYP3A4 inhibitor is withdrawn from the combination therapy,

	the FANAPT dose should be returned to the previous level *[see Dosage and Administration (2.4)]*.
Concomitant use of Strong CYP2D6 and Strong CYP3A4 Inhibitors	
Clinical Impact	Coadministration of iloperidone with paroxetine and ketoconazole resulted in a 1.4-fold increase in steady-state concentrations of iloperidone and its metabolite P88 and a 1.4- fold decrease in the P95 in the presence of paroxetine *[see Clinical Pharmacology (12.3)]*.
Intervention	Coadministration of FANAPT with inhibitors of both CYP2D6 and CYP3A4 did not add to the effect of either inhibitor given alone. Reduce the dose of FANAPT by about one-half if administered concomitantly with both a CYP2D6 and CYP3A4 inhibitor same as if it is coadministered with only one inhibitor. When the inhibitors of CYP2D6 and CYP3A4 are withdrawn from the combination therapy, the FANAPT dose should be returned to the previous level *[see Dosage and Administration (2.4)]*.

7.2 Drugs that Prolong the QT Interval

Concomitant use of drugs that prolong the QT interval may add to the QT effects of FANAPT and increase the risk of cardiac arrhythmia. Avoid the use of FANAPT in combination with any other drugs that prolong the QT interval *[see Warnings and Precautions (5.3)]*.

7.3 Drugs that Lower Blood Pressure

Concomitant use of FANAPT with medications that lower blood pressure could potentially cause symptomatic hypotension. Avoid coadministration of FANAPT with alpha-adrenergic blocking agents and adjust medications that affect blood pressure as needed *[see Warnings and Precautions (5.7)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to FANAPT during pregnancy. For more information contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

Risk Summary

Neonates whose mothers are exposed to antipsychotic drugs, including FANAPT, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery *[see Clinical Considerations]*. The limited available data with FANAPT in pregnant women are not sufficient to inform a drug-associated risk for major birth defects and miscarriage. Iloperidone was not teratogenic when administered orally to pregnant rats during organogenesis at doses up to 26 times the maximum recommended human dose of 24 mg/day on mg/m^2 basis. However, it prolonged the duration of pregnancy and parturition, increased still births, early intrauterine deaths, increased incidence of developmental delays, and decreased post-partum pup survival. Iloperidone was not teratogenic when administered orally to pregnant rabbits during organogenesis at doses up to 20-times the MRHD on mg/m^2 basis. However, it increased early intrauterine deaths and decreased fetal viability at term at the highest dose which was also a maternally toxic dose *[see Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates whose mothers were exposed to antipsychotic drugs during the third trimester of pregnancy. These symptoms have varied in severity. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately.

Data

Animal Data

In an embryo-fetal development study, pregnant rats were given 4, 16, or 64 mg/kg/day (1.6, 6.5, and 26 times the maximum recommended human dose (MRHD) of 24 mg/day on a mg/m^2 basis) of iloperidone orally during the period of organogenesis. The highest dose caused increased early intrauterine deaths, decreased fetal weight and length, decreased fetal skeletal ossification, and an increased incidence of minor fetal skeletal anomalies and variations; this dose also caused decreased maternal food consumption and weight gain.

In an embryo-fetal development study, pregnant rabbits were given 4, 10, or 25 mg/kg/day (3, 8, and 20 times the MRHD on a mg/m^2 basis) of iloperidone during the period of organogenesis. The highest dose caused increased early intrauterine deaths and decreased fetal viability at term; this dose also caused maternal toxicity.

In additional studies in which rats were given iloperidone at doses similar to the above beginning from either pre-conception or from day 17 of gestation and continuing through weaning, adverse reproductive effects included prolonged pregnancy and parturition, increased stillbirth rates, increased incidence of fetal visceral variations, decreased fetal and pup weights, and decreased post-partum pup survival. There were no drug effects on the neurobehavioral or reproductive development of the surviving pups. No-effect doses ranged from 4 to 12 mg/kg except for the increase in stillbirth rates which occurred at the lowest dose tested of 4 mg/kg, which is 1.6 times the MRHD on a mg/m^2 basis. Maternal toxicity was seen at the higher doses in these studies.

The iloperidone metabolite P95, which is a major circulating metabolite of iloperidone in humans but is not present in significant amounts in rats, was given to pregnant rats during the period of organogenesis at oral doses of 20, 80, or 200 mg/kg/day. No teratogenic effects were seen. Delayed skeletal ossification occurred at all doses. No significant maternal toxicity was produced. Plasma levels of P95 (AUC) at the highest dose tested were 2 times those in humans receiving the MRHD of iloperidone.

8.2 Lactation

Risk Summary

There is no information regarding the presence of iloperidone or its metabolites in human milk, the effects of iloperidone on a breastfed child, nor the effects of iloperidone on human milk production. Iloperidone is present in rat milk [see *Data*]. Because of the potential for serious adverse reactions in breastfed infants, advise a woman not to breastfeed during treatment with FANAPT.

Data

The transfer of radioactivity into the milk of lactating rats was investigated following a single dose of [14C] iloperidone at 5 mg/kg. The concentration of radioactivity in milk at 4 hours post-dose was near 10-fold greater than that in plasma at the same time. However, by 24 hours after dosing, concentrations of radioactivity in milk had fallen to values slightly lower than plasma. The metabolic profile in milk was qualitatively similar to that in plasma.

8.4 Pediatric Use

Safety and effectiveness of FANAPT have not been established in pediatric patients.

8.5 Geriatric Use

Clinical Studies of FANAPT in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 years and over to determine whether or not they respond differently than younger adult patients. Of the 3,210 patients with schizophrenia treated with FANAPT in clinical trials, 25 (0.5%) were ≥65 years old and there were no patients ≥75 years old. Of the 206 patients with bipolar mania treated with FANAPT in a clinical trial, 2 (0.1%) were 65 years old and there were no patients were >65 years old.

Elderly patients with dementia-related psychosis treated with FANAPT are at an increased risk of death compared to placebo. FANAPT is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions (5.1, 5.2)]*.

8.6 Hepatic Impairment

No dose adjustment to FANAPT is needed in patients with mild hepatic impairment (Child-Pugh class A). Patients with moderate hepatic impairment (Child-Pugh class B) may require dose reduction. FANAPT is not recommended for patients with severe hepatic impairment (Child-Pugh class C) *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

FANAPT is not a controlled substance.

9.2 Abuse

FANAPT has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. While the clinical trials did not reveal any tendency for drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this experience the extent to which a CNS active drug, FANAPT, will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of FANAPT misuse or abuse (e.g. development of tolerance, increases in dose, drug-seeking behavior).

10 OVERDOSAGE

10.1 Human Experience

In pre-marketing trials involving over 3,522 patients, accidental or intentional overdose of FANAPT was documented in 8 patients ranging from 48 mg to 576 mg taken at once and 292 mg taken over a 3-day period. No fatalities were reported from these cases. The largest confirmed single ingestion of FANAPT was 576 mg; no adverse physical effects were noted for this patient. The next largest confirmed ingestion of FANAPT was 438 mg over a 4-day period; extrapyramidal symptoms and a QTc interval of 507 msec were reported for this patient with no cardiac sequelae. This patient resumed FANAPT treatment for an additional 11 months. In general, reported signs and symptoms were those resulting from an exaggeration of the known pharmacological effects (e.g., drowsiness and sedation, tachycardia, and hypotension) of FANAPT.

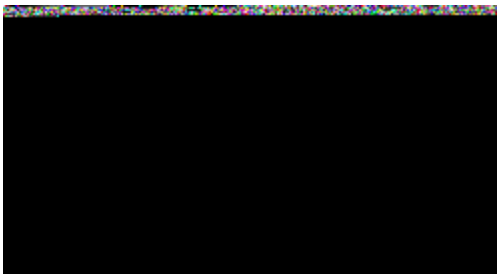
10.2 Management of Overdose

There is no specific antidote for FANAPT. Therefore, appropriate supportive measures should be instituted. In case of acute overdose, the healthcare provider should establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous ECG monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine should not be used, as they have the potential for QT-prolonging effects that might be additive to those of FANAPT. Similarly, it is reasonable to expect that the alpha-blocking properties of bretylium might be additive to those of FANAPT, resulting in problematic hypotension. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of FANAPT-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision should continue until the patient recovers.

Consider contacting the Poison Help Line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

11 DESCRIPTION

FANAPT is an atypical antipsychotic belonging to the chemical class of piperidinyl-benzisoxazole derivatives. Its chemical name is 4'-[3-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino]propoxy]-3'-methoxyacetophenone. Its molecular formula is $C_{24}H_{27}FN_2O_4$ and its molecular weight is 426.48. The structural formula is:



Iloperidone is a white to off-white finely crystalline powder. It is practically insoluble in water, very slightly soluble in 0.1 N HCl and freely soluble in chloroform, ethanol, methanol, and acetonitrile.

FANAPT tablets are intended for oral administration only. Each round, uncoated tablet contains 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, or 12 mg of iloperidone. Inactive ingredients are: lactose monohydrate, microcrystalline cellulose, hydroxypropylmethylcellulose, crospovidone, magnesium stearate, colloidal silicon dioxide, and purified water (removed during processing). The tablets are white, round, flat, beveled-edged, and identified with a logo "[redacted]" debossed on one side and tablet strength "1", "2", "4", "6", "8", "10", or "12" debossed on the other side.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of iloperidone in schizophrenia and bipolar I disorder is unknown. However, the efficacy of iloperidone could be mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5\text{-}HT_2$) antagonism. Iloperidone forms an active metabolite, P88, that has an in vitro receptor binding profile similar to the parent drug.

12.2 Pharmacodynamics

Iloperidone acts as an antagonist with high (nM) affinity binding to serotonin $5\text{-}HT_{2A}$, dopamine D_2 and D_3 receptors, and norepinephrine NEα1 receptors (K_i values of 5.6, 6.3, 7.1, and 0.36 nM, respectively). Iloperidone has moderate affinity for dopamine D_4, and serotonin $5\text{-}HT_6$ and $5\text{-}HT_7$ receptors (K_i values of 25, 43, and 22, nM respectively), and low affinity for the serotonin $5\text{-}HT_{1A}$, dopamine D_1, and histamine H_1 receptors (K_i values of 168, 216, and 437 nM, respectively). Iloperidone has no appreciable affinity (K_i>1000 nM) for cholinergic muscarinic receptors. The affinity of iloperidone metabolite P88 is generally equal to or less than that of the parent compound, while the metabolite P95 only shows affinity for $5\text{-}HT_{2A}$ (K_i value of 3.91) and the $NE_{α1A}$, $NE_{α1B}$, $NE_{α1D}$, and $NE_{α2C}$ receptors (K_i values of 4.7, 2.7, 8.8, and 4.7 nM respectively).

12.3 Pharmacokinetics

The pharmacokinetics of iloperidone is more than dose proportional. Steady-state concentrations are attained within 3 to 4 days of dosing. Iloperidone accumulation is predictable from single-dose pharmacokinetics.

Absorption

Iloperidone is well absorbed after administration of the tablet with time to peak plasma concentrations (T_{max}) occurring within 2 to 4 hours. The relative bioavailability of the tablet formulation compared to oral solution is 96%.

Effect of Food

Administration of iloperidone with a standard high-fat meal did not significantly affect the C_{max} or AUC of iloperidone, P88, or P95, but delayed T_{max} by 1 hour for iloperidone, 2 hours for P88 and 6 hours for P95. FANAPT can be administered without regard to meals.

Distribution

Iloperidone has an apparent volume of distribution of 1340-2800 L. At therapeutic concentrations, the unbound fraction of iloperidone in plasma is ~3% and of each metabolite (P88 and P95) it is ~8%.

Elimination

The observed mean elimination half-lives for iloperidone, P88, and P95 in CYP2D6 extensive metabolizers (EM) are 18, 26, and 23 hours, respectively, and in poor metabolizers (PM) are 33, 37, and 31 hours, respectively.

Iloperidone has an apparent clearance (clearance / bioavailability) of 47 to 102 L/h.

Metabolism

Elimination of iloperidone is mainly through hepatic metabolism. Iloperidone is metabolized primarily by 3 biotransformation pathways: carbonyl reduction, hydroxylation (mediated by CYP2D6) and *O*-demethylation (mediated by CYP3A4). There are 2 predominant iloperidone metabolites, P95 and P88. The iloperidone metabolite P95 represents 47.9% of the AUC of iloperidone and its metabolites in plasma at steady-state for extensive metabolizers (EM) and 25% for poor metabolizers (PM). The active metabolite P88 accounts for 19.5% and 34.0% of total plasma exposure in EM and PM, respectively.

Approximately 7% - 10% of Caucasians and 3% - 8% of black/African Americans lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas the rest are intermediate, extensive, or ultrarapid metabolizers.

Excretion

The bulk of the radioactive materials were recovered in the urine (mean 58.2% and 45.1% in EM and PM, respectively), with feces accounting for 19.9% (EM) to 22.1% (PM) of the dosed radioactivity.

Specific Populations

Patients with Renal Impairment

Renal impairment (creatinine clearance <30 mL/min) had minimal effect on C_{max} of iloperidone (given in a single dose of 3 mg) and its metabolites P88 and P95 in any of the 3 analytes measured. $AUC_{0-\infty}$ was increased by 24%, decreased by 6%, and increased by 52% for iloperidone, P88 and P95, respectively, in subjects with renal impairment.

Patients with Hepatic Impairment

In adult subjects with mild hepatic impairment, no relevant difference in pharmacokinetics of iloperidone, P88 or P95 (total or unbound) was observed compared to healthy adult controls. In subjects with moderate hepatic impairment a higher (2-fold) and more variable free exposure to the active metabolites P88 was observed compared to healthy controls, whereas exposure to iloperidone and P95 was generally similar (less than 50% change compared to control). Studies with severe liver impaired subjects have not been conducted *[see Dosage and Administration (2.3), Use in Specific Populations (8.6)]*.

Effect of Smoking

Based on *in vitro* studies utilizing human liver enzymes, FANAPT is not a substrate for CYP1A2; smoking should therefore not have an effect on the pharmacokinetics of FANAPT.

Drug Interactions Studies

CYP2D6 and CYP3A4 Inhibitors

The effects of fluoxetine and ketoconazole on the exposures of FANAPT, P88, and P95 are summarized in Figure 1.

Figure 1: Effect of CYP3A4 and CYP2D6 Inhibitors on the Pharmacokinetics of FANAPT and its Metabolites

Ketoconazole: Co-administration of ketoconazole (200 mg twice daily for 4 days), a potent inhibitor of CYP3A4, with a 3 mg single dose of iloperidone to 19 healthy volunteers, ages 18-45 years, increased the area under the curve (AUC) of iloperidone and its metabolites P88 and P95 by 57%, 55% and 35%, respectively. Weaker inhibitors (e.g., erythromycin, grapefruit juice) have not been studied.

Fluoxetine: Coadministration of fluoxetine (20 mg twice daily for 21 days), a potent inhibitor of CYP2D6, with a single 3 mg dose of iloperidone to 23 healthy volunteers, ages 29-44 years, who were classified as CYP2D6 extensive metabolizers, increased the AUC of iloperidone and its metabolite P88, by about 2- to 3- fold, and decreased the AUC of its metabolite P95 by one-half.

Paroxetine: Coadministration of paroxetine (20 mg/day for 5-8 days), a potent inhibitor of CYP2D6, with multiple doses of iloperidone (8 or 12 mg twice daily) to patients with schizophrenia ages 18-65 years resulted in increased mean steady-state peak concentrations of iloperidone and its metabolite P88, by about 1.6 fold, and decreased mean steady-state peak concentrations of its metabolite P95 by one-half.

Paroxetine and Ketoconazole: Coadministration of paroxetine (20 mg once daily for 10 days), a CYP2D6 inhibitor, and ketoconazole (200 mg twice daily) with multiple doses of iloperidone (8 or 12 mg twice daily) to patients with schizophrenia ages 18-65 years resulted in a 1.4 fold increase in steady-state concentrations of iloperidone and its metabolite P88 and a 1.4 fold decrease in the P95 in the presence of paroxetine.

Dextromethorphan: A study in healthy volunteers showed that changes in the pharmacokinetics of dextromethorphan (80 mg dose) when a 3 mg dose of iloperidone was co-administered resulted in a 17% increase in total exposure and a 26% increase in the maximum plasma concentrations C_{max} of dextromethorphan. Thus, an interaction between iloperidone and other CYP2D6 substrates is unlikely.

Fluoxetine: A single 3 mg dose of iloperidone had no effect on the pharmacokinetics of fluoxetine (20 mg twice daily).

Midazolam (a sensitive CYP 3A4 substrate): A study in patients with schizophrenia showed a less than 50% increase in midazolam total exposure at iloperidone steady state (14 days of oral dosing at up to 10 mg iloperidone twice daily) and no effect on midazolam C_{max}. Thus, an interaction between iloperidone and other CYP3A4 substrates is unlikely.

In Vitro Studies

Based on the *in vitro* data, iloperidone is not a substrate for CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. This suggests that an interaction of iloperidone with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

In vitro studies in human liver microsomes showed that iloperidone does not substantially inhibit the metabolism of drugs metabolized by the following cytochrome P450 isozymes: CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, or CYP2E1. Furthermore, *in vitro* studies in human liver microsomes showed that iloperidone does not have enzyme inducing properties, specifically for the following cytochrome P450 isozymes: CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4 and CYP3A5.

Transporter Interaction: Iloperidone and P88 are not substrates of P-gp and iloperidone is a weak P-gp inhibitor.

12.5 Pharmacogenomics

CYP2D6 Poor Metabolizer (PM): The gene encoding CYP2D6 has polymorphisms that impact protein function. CYP2D6 poor metabolizers are individuals with two non-functioning alleles, resulting in no enzyme activity.

Pharmacokinetic data from CYP2D6 poor metabolizers (n=8) treated with iloperidone demonstrated an increase in the AUC of iloperidone and its metabolite P88 by 47% and 85%, respectively and decrease the AUC of metabolite P95 by 85% compared to normal metabolizers (n=18) *[see Dosage and Administration (2.2)]*.

Approximately 7% of White populations, 2% of Asian populations, and 2% of African-American populations are poor metabolizers.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Lifetime carcinogenicity studies were conducted in CD-1 mice and Sprague Dawley rats. Iloperidone was administered orally at doses of 2.5, 5.0, and 10 mg/kg/day to CD-1 mice and 4, 8, and 16

mg/kg/day to Sprague Dawley rats (0.5, 1.0, and 2.0 times and 1.6, 3.2, and 6.5 times, respectively, the MRHD of 24 mg/day on a mg/m^2 basis). There was an increased incidence of malignant mammary gland tumors in female mice treated with the lowest dose (2.5 mg/kg/day) only. There were no treatment-related increases in neoplasia in rats.

The carcinogenic potential of the iloperidone metabolite P95, which is a major circulating metabolite of iloperidone in humans but is not present at significant amounts in mice or rats, was assessed in a lifetime carcinogenicity study in Wistar rats at oral doses of 25, 75, and 200 mg/kg/day in males and 50, 150, and 250 (reduced from 400) mg/kg/day in females. Drug-related neoplastic changes occurred in males, in the pituitary gland (pars distalis adenoma) at all doses and in the pancreas (islet cell adenoma) at the high dose. Plasma levels of P95 (AUC) in males at the tested doses (25, 75, and 200 mg/kg/day) were approximately 0.4, 3, and 23 times, respectively, the human exposure to P95 at the MRHD of iloperidone.

Mutagenesis: Iloperidone was negative in the Ames test and in the *in vivo* mouse bone marrow and rat liver micronucleus tests. Iloperidone induced chromosomal aberrations in Chinese Hamster Ovary (CHO) cells *in vitro* at concentrations which also caused some cytotoxicity.

The iloperidone metabolite P95 was negative in the Ames test, the V79 chromosome aberration test, and an *in vivo* mouse bone marrow micronucleus test.

Impairment of Fertility: Iloperidone decreased fertility at 12 and 36 mg/kg in a study in which both male and female rats were treated. The no-effect dose was 4 mg/kg, which is 1.6 times the MRHD of 24 mg/day on a mg/m^2 basis.

14 CLINICAL STUDIES

14.1 Schizophrenia

The efficacy of FANAPT in the treatment of schizophrenia was supported by 2 placebo- and active-controlled short-term (4- and 6-week) trials and one long-term placebo-controlled randomized withdrawal trial. All trials enrolled patients who met the DSM-III/IV criteria for schizophrenia.

Three instruments were used for assessing psychiatric signs and symptoms in these studies. The Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) are both multi-item inventories of general psychopathology usually used to evaluate the effects of drug treatment in schizophrenia. The Clinical Global Impression (CGI) assessment reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient.

Study 1, a 6-week, placebo-controlled trial (n=706), involved 2 flexible dose ranges of FANAPT (12 mg to 16 mg/day or 20 mg to 24 mg/day) compared to placebo and an active control (risperidone). For the 12 mg to 16 mg/day group, the titration schedule of FANAPT was 1 mg twice daily on Days 1 and 2, 2 mg twice daily on Days 3 and 4, 4 mg twice daily on Days 5 and 6, and 6 mg twice daily on Day 7. For the 20 mg to 24 mg/day group, the titration schedule of FANAPT was 1 mg twice daily on Day 1, 2 mg twice daily on Day 2, 4 mg twice daily on Day 3, 6 mg twice daily on Days 4 and 5, 8 mg twice daily on Day 6, and 10 mg twice daily on Day 7. The primary endpoint was change from baseline on the BPRS total score at the end of treatment (Day 42). Both the 12 mg to 16 mg/day and the 20 mg to 24 mg/day dose ranges of FANAPT were superior to placebo on the BPRS total score. The active control antipsychotic drug appeared to be superior to FANAPT in this trial within the first 2 weeks, a finding that may in part be explained by the more rapid titration that was

possible for that drug. In patients in this study who remained on treatment for at least 2 weeks, iloperidone appeared to have had comparable efficacy to the active control.

Study 2 (NCT00254202), a 4-week, placebo-controlled trial (n=604), involved one fixed-dose of FANAPT (24 mg/day) compared to placebo and an active control (ziprasidone). The titration schedule for this study was similar to that for the 6-week study. This study involved titration of FANAPT starting at 1 mg twice daily on Day 1 and increasing to 2, 4, 6, 8, 10, and 12 mg twice daily on Days 2, 3, 4, 5, 6, and 7. The primary endpoint was change from baseline on the PANSS total score at the end of treatment (Day 28). The 24 mg/day FANAPT dose was superior to placebo in the PANSS total score. FANAPT appeared to have similar efficacy to the active control drug which also needed a slow titration to the target dose.

In a longer-term trial (Study 3; NCT01291511), clinically stable adult outpatients (n=303) meeting DSM-IV criteria for schizophrenia who remained stable following 12 weeks of open-label treatment with flexible doses of FANAPT (8 mg to 24 mg/day administered as twice daily doses) were randomized to placebo or to continue on their current FANAPT dose (8 mg to 24 mg/day administered as twice daily doses) for observation for possible relapse during the double-blind relapse prevention phase. Stabilization during the open-label phase was defined as being on an established dose of FANAPT that was unchanged due to efficacy in the 4 weeks prior to randomization, having CGI-Severity score of ≤4 and PANSS total score ≤70, a score of ≤4 on each of the following individual PANSS items (P1-delusions, P2-conceptual disorganization, P3-hallucinatory behavior, P6-suspiciousness/persecution, P7-hostility, or G8-uncooperativeness), and no hospitalization or increase in level of care to treat exacerbations. Relapse or impending relapse during the double-blind relapse prevention phase was defined as any of the following: hospitalization due to worsening of schizophrenia, increase (worsening) of the PANSS total score ≥30%, CGI-Improvement score ≥6, patient had suicidal, homicidal, or aggressive behavior, or need for any other antipsychotic medication.

Figure 2: Kaplan Meier Estimation of Percent Relapse/Impending Relapse (Study 3)

Based on the interim analysis, an independent data monitoring committee decided the study should be discontinued early due to evidence of efficacy. Based on results from the interim analysis, which were confirmed by the final analysis dataset, patients treated with FANAPT experienced a statistically significant longer time to relapse or impending relapse than patients who received placebo. Figure 2 displays the estimated cumulative proportion of patients with relapse or impending relapse based on the final data set.

14.2 Manic or Mixed Episodes Associated with Bipolar I Disorder

The efficacy of FANAPT in the acute treatment of manic or mixed episodes associated with bipolar I disorder in adults was supported by one multicenter, randomized, double-blind, placebo-controlled study that enrolled patients who met the DSM-5 criteria for bipolar I disorder, manic or mixed type (Study 1; NCT04819776). Demographic and baseline characteristics were similar for the FANAPT and placebo groups. Median age was 46 (range 18 to 65). 45% were female, 64% were White, and 28% were Black or African-American.

Manic symptoms were assessed with the Young Mania Rating Scale (YMRS). The YMRS is an 11-item clinician rated scale traditionally used to assess the degree of manic symptomatology. YMRS total scores may range from 0 to 60 with a higher score reflecting greater severity.

A 4-week, placebo-controlled trial (n=392) involved one fixed-dose of FANAPT (24 mg/day) compared to placebo. The primary endpoint was change in YMRS total score from baseline to Day 28. The 24 mg/day dose

of FANAPT was superior to placebo on the primary endpoint. Examination of subgroups did not reveal clear evidence of differential responsiveness on the basis of age, sex, or race.

The results of the study are shown in Table 8. The LS mean changes from baseline in YMRS total score are shown in Figure 3.

Table 8: Primary Efficacy Results for Change from Baseline in YMRS Total Score in the Acute Treatment of Manic or Mixed Episodes Associated with Bipolar I Disorder in Adults (Study 1)

Study Number	Treatment Group (# ITT patients)	Primary Efficacy Endpoint: Change from Baseline to Day 28 in YMRS Total Score		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
1	FANAPT (24 mg/day)* (n=198)	29.2 (5.27)	-14.0 (0.64)	-4.0 (-5.70, -2.25)
	Placebo (n=194)	28.8 (4.64)	-10.0 (0.63)	

ITT = intent-to-treat, YMRS = Young Mania Rating Scale, LS mean = least Squares mean, SD = standard deviation, SE = standard error
[a] Difference (drug minus placebo) in least-squares mean change from baseline
*Dose was superior to placebo

Figure 3: Change from Baseline in YMRS Total Score by Study Visit (Study 1)

16 HOW SUPPLIED/STORAGE AND HANDLING

FANAPT tablets are white, round and identified with a logo "  " debossed on one side and tablet strength "1", "2", "4", "6", "8", "10", or "12" debossed on the other side. Tablets are supplied in the following strengths and package configurations:

Package Configuration	Tablet Strength (mg)	NDC Code
Bottles of 60	1 mg	43068-101-02
Bottles of 60	2 mg	43068-102-02
Bottles of 60	4 mg	43068-104-02
Bottles of 60	6 mg	43068-106-02
Bottles of 60	8 mg	43068-108-02
Bottles of 60	10 mg	43068-110-02
Bottles of 60	12 mg	43068-112-02
Titration Pack	2x1 mg, 2x2 mg, 2x4 mg, 2x6 mg (Total of 8 tablets)	43068-113-04

Storage

Store FANAPT tablets at controlled room temperature, 25°C (77°F); excursions permitted to 15° to 30 °C (59° to 86°F) [See USP Controlled Room Temperature]. Protect FANAPT tablets from exposure to light and moisture.

17 PATIENT COUNSELING INFORMATION

QT Interval Prolongation

Patients should be advised to consult their healthcare provider immediately if they feel faint, lose consciousness, or have heart palpitations. Patients should be counseled not to take FANAPT with other drugs that cause QT interval prolongation *[see Warnings and Precautions (5.3)]*. Patients should be told to inform their healthcare provider that they are taking FANAPT before any new drug is taken.

Neuroleptic Malignant Syndrome (NMS)

Counsel patients and caregivers about a potentially fatal adverse reaction, NMS, that has been reported with administration of antipsychotic drugs, including FANAPT. Advise patients and caregivers to contact the healthcare provider or to report to the emergency room if they experience signs and symptoms of NMS *[see Warnings and Precautions (5.4)]*.

Tardive Dyskinesia

Counsel patients on the signs and symptoms of tardive dyskinesia and to contact their healthcare provider if these abnormal movements occur *[see Warnings and Precautions (5.5)]*.

Metabolic Changes

Educate patients of metabolic changes, how to recognize symptoms of hyperglycemia and diabetes mellitus, and the need for specific monitoring, including blood glucose, lipids, and weight. Patients should be counseled that weight gain has occurred during treatment with FANAPT *[see Warnings and Precautions (5.6)]*.

Orthostatic Hypotension and Syncope

Educate patients about the risk of orthostatic hypotension and syncope, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose *[see Warnings and Precautions (*5.7*)]*.

Leukopenia/Neutropenia

Advise patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia that they should have their CBC monitored while taking FANAPT *[see Warnings and Precautions (5.10)]*.

Heat Exposure and Dehydration

Educate patients regarding appropriate care in avoiding overheating and dehydration *[see Warnings and Precautions (5.12)]*.

Interference with Cognitive and Motor Performance

Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that FANAPT therapy does not affect them adversely *[see Warnings and Precautions (5.15)]*.

Intraoperative Floppy Iris Syndrome

Instruct patients to tell their ophthalmologist about their use of FANAPT before cataract surgery or other procedures involving the eyes, even if the patient is no longer taking FANAPT *[see Warnings and Precautions (5.16)]*.

Pregnancy

Advise patients that third trimester use of FANAPT may cause extrapyramidal and/or withdrawal symptoms in a neonate. Advise patients to notify their healthcare provider with known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

Pregnancy Registry

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to FANAPT during pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

Advise women not to breastfeed during treatment with FANAPT *[see Use in Specific Populations (8.2)]*.

Concomitant Medication

Advise patients to inform their healthcare provider if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions *[see Drug Interactions (7)]*.

Alcohol

Patients should be advised to avoid alcohol while taking FANAPT.

Distributed by:

Vanda Pharmaceuticals Inc.

Washington, D.C. 20037 USA

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Lumateperone

FDA

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CAPLYTA safely and effectively. See full prescribing information for CAPLYTA.

CAPLYTA® (lumateperone) capsules, for oral use
Initial U.S. Approval: 2019

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS
See full prescribing information for complete boxed warning.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis. (5.1)**
- **Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adult patients. Closely monitor all antidepressant-treated patients for worsening and emergence of suicidal thoughts and behaviors. Safety and effectiveness of CAPLYTA have not been established in pediatric patients. (5.2, 8.4)**

----------INDICATIONS AND USAGE----------

CAPLYTA is an atypical antipsychotic indicated for the treatment of:

- Schizophrenia in adults. (1)
- Depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate. (1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended dosage of CAPLYTA is 42 mg once daily with or without food. (2.1)
- Dose titration is not required. (2.1)
- Moderate or severe hepatic impairment: Recommended dosage is 21 mg once daily. (2.3, 8.6)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules: 42 mg, 21 mg, 10.5 mg (3)

----------CONTRAINDICATIONS----------

Known hypersensitivity to lumateperone or any components of CAPLYTA. (4)

----------WARNINGS AND PRECAUTIONS----------

- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g., stroke and transient ischemic attack). (5.3)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring. (5.4)
- *Tardive Dyskinesia:* Discontinue treatment if clinically appropriate. (5.5)
- *Metabolic Changes:* Monitor for hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain. (5.6)
- *Leukopenia, Neutropenia, and Agranulocytosis*: Perform complete blood counts (CBC) in patients with pre-existing low white blood cell count (WBC) or history of leukopenia or neutropenia. Consider discontinuing CAPLYTA if clinically significant decline in WBC occurs in absence of other causative factors. (5.7)
- *Orthostatic Hypotension and Syncope:* Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope. (5.8)
- *Seizures:* Use cautiously in patients with a history of seizure or with conditions that lower seizure threshold. (5.10)
- *Potential for Cognitive and Motor Impairment:* Use caution when operating machinery. (5.11)

----------ADVERSE REACTIONS----------

Most common adverse reactions in clinical trials (incidence ≥ 5% and greater than twice placebo) were (6.1):

- Schizophrenia: somnolence/sedation and dry mouth.
- Bipolar depression: somnolence/sedation, dizziness, nausea, dry mouth.

To report SUSPECTED ADVERSE REACTIONS, contact Intra-Cellular Therapies, Inc. at 1-888-611-4824 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- CYP3A4 inducers: Avoid concomitant use. (7.1)
- Strong CYP3A4 inhibitors: Recommended dosage is 10.5 mg once daily. (2.2, 7.1)
- Moderate CYP3A4 inhibitors: Recommended dosage is 21 mg once daily. (2.2, 7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the Full Prescribing Information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; and SUICIDAL THOUGHTS AND BEHAVIORS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1)].*

Suicidal Thoughts and Behaviors
Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric and young adults in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors *[see Warnings and Precautions (5.2)].* The safety and effectiveness of CAPLYTA have not been established in pediatric patients *[see Use in Specific Populations (8.4)].*

1 INDICATIONS AND USAGE

CAPLYTA is indicated for the treatment of:

- Schizophrenia in adults *[see Clinical Studies (14.1)]*.
- Depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate *[see Clinical Studies (14.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of CAPLYTA is 42 mg administered orally once daily with or without food. Dose titration is not required.

2.2 Dosage Recommendations for Concomitant Use with Moderate or Strong CYP3A4 Inhibitors

Coadministration with Strong CYP3A4 Inhibitors
The recommended dosage for patients receiving strong CYP3A4 inhibitors is CAPLYTA 10.5 mg once daily *[see Drug Interactions (7.1)]*.

Coadministration with Moderate CYP3A4 Inhibitors
The recommended dosage for patients receiving moderate CYP3A4 inhibitors is CAPLYTA 21 mg once daily *[see Drug Interactions (7.1)]*.

2.3 Dosage Recommendations for Patients with Hepatic Impairment

For patients with moderate or severe hepatic impairment (Child-Pugh class B or C), the recommended dosage of CAPLYTA is 21 mg once daily *[see Use in Specific Populations (8.6)]*.

3 DOSAGE FORMS AND STRENGTHS

CAPLYTA capsules are available in three strengths:

- 42 mg: Blue cap and opaque white body imprinted with “ITI-007 42 mg”
- 21 mg: Opaque white cap and body imprinted with “ITI-007 21 mg”
- 10.5 mg: Opaque light pink cap and body imprinted with “ITI-007 10.5 mg”

4 CONTRAINDICATIONS

CAPLYTA is contraindicated in patients with history of hypersensitivity reaction to lumateperone. Reactions have included pruritus, rash (e.g. allergic dermatitis, papular rash, and generalized rash), and urticaria.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in placebo-treated patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.3)]*.

5.2 Suicidal Thoughts and Behaviors in Children, Adolescents and Young Adults

In pooled analyses of placebo-controlled trials of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

Table 1: Risk Differences of the Number of Patients of Suicidal Thoughts and Behavior in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric* and Adult Patients

Age Range	Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviors per 1000 Patients Treated
	Increases Compared to Placebo
<18 years old	14 additional patients
18-24 years old	5 additional patients
	Decreases Compared to Placebo
25-64 years old	1 fewer patient
≥65 years old	6 fewer patients

*CAPLYTA is not approved for use in pediatric patients.

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for any indication for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing CAPLYTA, in patients whose depression is persistently worse, or who are experiencing suicidal thoughts or behaviors.

5.3 Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials in elderly subjects with dementia, patients randomized to risperidone, aripiprazole, and olanzapine had a higher incidence of stroke and transient ischemic attack, including fatal stroke. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1)]*.

5.4 Neuroleptic Malignant Syndrome

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with administration of antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, delirium, and autonomic instability. Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If NMS is suspected, immediately discontinue CAPLYTA and provide intensive symptomatic treatment and monitoring.

5.5 Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs. The risk appears to be highest among the elderly, especially elderly women, but it is not possible to predict which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of tardive dyskinesia and the likelihood that it will become irreversible increase with the duration of treatment and the cumulative dose. The syndrome can develop after a relatively brief treatment period, even at low doses. It may also occur after discontinuation of treatment.

Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, possibly masking the underlying process. The effect that symptomatic suppression has upon the long-term course of tardive dyskinesia is unknown.

Given these considerations, CAPLYTA should be prescribed in a manner most likely to reduce the risk of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients: 1) who suffer from a chronic illness that is known to respond to antipsychotic drugs; and 2) for whom alternative, effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment producing a satisfactory clinical response. Periodically reassess the need for continued treatment.

If signs and symptoms of tardive dyskinesia appear in a patient on CAPLYTA, drug discontinuation should be considered. However, some patients may require treatment with CAPLYTA despite the presence of the syndrome.

5.6 Metabolic Changes

Antipsychotic drugs have caused metabolic changes, including hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain. Although all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma or death, has been reported in patients treated with antipsychotics. There have been reports of hyperglycemia in patients treated with CAPLYTA. Assess fasting plasma glucose before or soon after initiation of antipsychotic medication and monitor periodically during long-term treatment.

Schizophrenia

In pooled data from short-term (4- to 6-week), placebo-controlled trials of adult patients with schizophrenia, mean changes from baseline and the proportion of patients with shifts from normal to greater than normal levels of fasting glucose in patients treated with CAPLYTA were similar to those in patients treated with placebo.

In an uncontrolled open-label trial of CAPLYTA for up to 1 year in patients with stable schizophrenia, the percentages of patients with shifts in fasting glucose and insulin values from normal to high were 8% and 12%, respectively. 4.7% of patients with normal hemoglobin A1c (<6.5%) at baseline developed elevated levels (≥6.5%) post-baseline.

Bipolar Depression

In data from short-term (6-week), placebo-controlled monotherapy and adjunctive therapy bipolar depression trials, mean changes from baseline and the proportion of patients with shifts from normal to greater than normal levels of fasting glucose and insulin in patients treated with CAPLYTA were similar to those in patients treated with placebo.

Dyslipidemia

Antipsychotics have caused adverse alterations in lipids. Before or soon after initiation of antipsychotic medications, obtain a fasting lipid profile at baseline and monitor periodically during treatment.

Schizophrenia

In pooled data from short-term (4- to 6-week), placebo-controlled trials of adult patients with schizophrenia, mean changes from baseline and the proportion of patients with shifts to higher levels of fasting total cholesterol and triglycerides were similar in patients treated with CAPLYTA and placebo.

In an uncontrolled open-label trial of CAPLYTA for up to 1 year in patients with stable schizophrenia, the percentages of patients with a shift from normal to high were 8%, 5%, and 4% for total cholesterol, triglycerides, and LDL cholesterol, respectively.

Bipolar Depression

In data from short-term (6-week), placebo-controlled monotherapy and adjunctive therapy bipolar depression trials, mean changes from baseline and the proportion of patients with shifts to higher levels of fasting total cholesterol and triglycerides were similar in patients treated with CAPLYTA and placebo.

In an uncontrolled open-label trial of CAPLYTA for up to 6 months in patients with bipolar depression, the proportion of patients with a shift from normal to high were 10%, 5%, and 2% for total cholesterol, triglycerides, and LDL cholesterol, respectively.

Weight Gain

Weight gain has been observed with use of antipsychotics. Monitor weight at baseline and frequently thereafter.

Schizophrenia

In pooled data from placebo-controlled trials of adult patients with schizophrenia, mean changes from baseline and the proportion of patients with an increase in weight ≥7% from baseline to end of study was similar in patients treated with CAPLYTA and placebo.

In an uncontrolled open-label trial of CAPLYTA for up to 1 year in patients with stable schizophrenia, the mean change in body weight was approximately -2 kg (SD 5.6) at Day 175 and approximately - 3.2 kg (SD 7.4) at Day 350.

Bipolar Depression

In data from short-term (6-week), placebo-controlled monotherapy and adjunctive therapy bipolar depression trials, mean changes from baseline and the proportion of patients with an increase in weight ≥7% from baseline to end of study were similar in patients treated with CAPLYTA and placebo.

In an uncontrolled open-label trial of CAPLYTA for up to 6 months in patients with bipolar depression, the mean change in body weight was -0.01 kg (SD 3.1) at Day 175.

5.7 Leukopenia, Neutropenia, and Agranulocytosis

Leukopenia and neutropenia have been reported during treatment with antipsychotic agents, including CAPLYTA. Agranulocytosis (including fatal cases) has been reported with other agents in the class.

Possible risk factors for leukopenia and neutropenia include pre-existing low white blood cell count (WBC) or absolute neutrophil count (ANC) and history of drug-induced leukopenia or neutropenia. In patients with a pre-existing low WBC or ANC or a history of drug-induced leukopenia or neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of CAPLYTA at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue CAPLYTA in patients with absolute neutrophil count $< 1000/mm^3$ and follow their WBC until recovery.

5.8 Orthostatic Hypotension and Syncope

Atypical antipsychotics cause orthostatic hypotension and syncope. Generally, the risk is greatest during initial dose administration. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension (e.g., elderly patients, patients with dehydration, hypovolemia, and concomitant treatment with antihypertensive medications), patients with known cardiovascular disease (history of myocardial infarction, ischemic heart disease, heart failure, or conduction abnormalities), and patients with cerebrovascular disease. CAPLYTA has not been

evaluated in patients with a recent history of myocardial infarction or unstable cardiovascular disease. Such patients were excluded from pre-marketing clinical trials.

Schizophrenia

In pooled data from short-term (4- to 6-week), placebo-controlled schizophrenia trials, the frequencies of orthostatic hypotension for CAPLYTA and placebo were 0.7% and 0%, respectively. The rates of syncope for CAPLYTA and placebo were 0.2% and 0.2%.

Bipolar Depression

In data from short-term (6-week), placebo-controlled monotherapy and adjunctive therapy bipolar depression trials, the frequencies of orthostatic hypotension for CAPLYTA and placebo were both 0%. The rates of syncope for CAPLYTA and placebo were 0.3% and 0.5%, respectively in the monotherapy trials, and there were no reports for CAPLYTA or placebo in the adjunctive therapy trial.

5.9 Falls

Antipsychotics, including CAPLYTA, may cause somnolence, postural hypotension, and motor and sensory instability, which may lead to falls and, consequently, fractures and other injuries. For patients with diseases, conditions or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and periodically during long-term treatment.

5.10 Seizures

Like other antipsychotic drugs, CAPLYTA may cause seizures. The risk is greatest in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in older patients.

5.11 Potential for Cognitive and Motor Impairment

CAPLYTA, like other antipsychotics, may cause somnolence and has the potential to impair judgment, thinking, and motor skills. Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with CAPLYTA does not affect them adversely.

Schizophrenia

In short-term (i.e., 4- to 6-week), placebo-controlled clinical trials of patients with schizophrenia, somnolence and sedation were reported in 24% of CAPLYTA-treated patients, compared to 10% of placebo-treated patients.

Bipolar Depression

In short term (6-week), placebo-controlled monotherapy and adjunctive therapy bipolar depression clinical trials, somnolence and sedation were reported in 13% of CAPLYTA-treated patients, compared to 3% of placebo-treated patients.

5.12 Body Temperature Dysregulation

Atypical antipsychotics may disrupt the body's ability to reduce core body temperature. Strenuous exercise, exposure to extreme heat, dehydration, and anticholinergic medications may contribute to an elevation in core body temperature; use CAPLYTA with caution in patients who may experience these conditions.

5.13 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Antipsychotic drugs, including CAPLYTA, should be used cautiously in patients at risk for aspiration.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in detail in other sections of the labeling:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Suicidal Thoughts and Behaviors *[see Boxed Warning, Warnings and Precautions (5.2)]*
- Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-related Psychosis *[see Warnings and Precautions (5.3)]*
- Neuroleptic Malignant Syndrome *[see Warnings and Precautions (5.4)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.5)]*

- Metabolic Changes *[see Warnings and Precautions (5.6)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.7)]*
- Orthostatic Hypotension and Syncope *[see Warnings and Precautions (5.8)]*
- Falls *[see Warnings and Precautions (5.9)]*
- Seizures *[see Warnings and Precautions (5.10)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.11)]*
- Body Temperature Dysregulation *[see Warnings and Precautions (5.12)]*
- Dysphagia *[see Warnings and Precautions (5.13)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of CAPLYTA has been evaluated in placebo-controlled clinical trials in 2664 adult patients with schizophrenia and bipolar depression exposed to one or more doses. A total of 402 CAPLYTA-exposed patients had at least 6 months of exposure and 108 had at least 1 year of exposure to the 42-mg dose of CAPLYTA.

Schizophrenia

The following findings are based on the pooled short-term (4- to 6-week), placebo-controlled studies in adult patients with schizophrenia in which CAPLYTA was administered at a daily dose of 42 mg (N=406).

There was no single adverse reaction leading to discontinuation that occurred at a rate of >2% in CAPLYTA-treated patients.

The most common adverse reactions (incidence of at least 5% of patients exposed to CAPLYTA and greater than twice the rate of placebo) are somnolence/sedation and dry mouth.

Adverse reactions associated with CAPLYTA (incidence of at least 2% in patients exposed to CAPLYTA and greater than placebo) are shown in Table 2.

Table 2: Adverse Reactions Reported in ≥2% of CAPLYTA-Treated Patients and Occurred at a Greater Incidence than in Placebo-Treated Patients in 4- to 6-week Schizophrenia Trials

	CAPLYTA 42 mg (N=406)	Placebo (N=412)
Somnolence/Sedation	24%	10%
Nausea	9%	5%
Dry Mouth	6%	2%
Dizziness[1]	5%	3%
Creatine Phosphokinase Increased	4%	1%
Fatigue	3%	1%
Vomiting	3%	2%
Hepatic Transaminases Increased[2]	2%	1%
Decreased Appetite	2%	1%

[1] Dizziness, dizziness postural
[2] ALT, AST, “hepatic enzymes” increased, or liver function test abnormal

Bipolar Depression – Monotherapy

The following findings are based on the pooled short-term (6-week), placebo-controlled monotherapy bipolar depression studies in adult patients treated with CAPLYTA administered at a daily dose of 42 mg (N=372).

There was no single adverse reaction leading to discontinuation that occurred at a rate of >2% in CAPLYTA-treated patients.

The most common adverse reactions (incidence of at least 5% of patients exposed to CAPLYTA and greater than twice the rate of placebo) are somnolence/sedation, dizziness, nausea, and dry mouth.

Adverse reactions associated with CAPLYTA (incidence of at least 2% in patients exposed to CAPLYTA and greater than placebo) are shown in Table 3.

Table 3: Adverse Reactions Reported in ≥2% of CAPLYTA-Treated Patients and that Occurred at Greater Incidence than in the Placebo-Treated Patients in Pooled 6-week Monotherapy Bipolar Depression Trials

	CAPLYTA 42 mg (N=372)	Placebo (N=374)
Headache	14%	8%
Somnolence/Sedation	13%	3%
Dizziness[1]	8%	4%
Nausea	8%	3%
Dry mouth	5%	1%
Diarrhea	4%	2%
Vomiting	4%	0%
Abdominal pain[2]	2%	1%
Upper respiratory tract infection	2%	1%

[1] Dizziness, dizziness postural
[2] Abdominal discomfort, abdominal pain, abdominal pain upper and lower

Bipolar Depression - Adjunctive Therapy with Lithium or Valproate

The following findings are based on a 6-week, placebo-controlled adjunctive therapy bipolar depression study in adult patients treated with CAPLYTA administered at a daily dose of 42 mg (N=177).

There was no single adverse reaction leading to discontinuation that occurred at a rate of >2% in CAPLYTA-treated patients.

The most common adverse reactions (incidence of at least 5% of patients exposed to CAPLYTA and greater than twice the rate of placebo) are somnolence/sedation, dizziness, nausea, and dry mouth.

Adverse reactions associated with CAPLYTA (incidence of at least 2% in patients exposed to CAPLYTA and greater than placebo) are shown in Table 4.

Table 4: Adverse Reactions Reported in ≥2% of CAPLYTA-Treated Patients and that Occurred at Greater Incidence than in the Placebo-Treated Patients in a 6-Week Adjunctive Therapy Bipolar Depression Trial

	CAPLYTA 42 mg (N=177)	Placebo (N=175)
Somnolence/Sedation	13%	3%
Dizziness[1]	11%	2%
Nausea	9%	4%
Dry mouth	5%	1%
Vomiting	4%	0%
Diarrhea	3%	2%
Upper respiratory tract infection	3%	1%
Blurred vision	3%	1%
Increased blood prolactin	2%	0%

[1] Dizziness, dizziness postural

Dystonia

Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. Although these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Extrapyramidal Symptoms (EPS)

In the short-term, placebo-controlled schizophrenia and bipolar depression studies, data was objectively collected on the Simpson-Angus Scale (SAS) for EPS (total score ranges from 0 to 40), the Barnes Akathisia Rating Scale (BARS) for akathisia (total score ranges from 0 to 14) and the Abnormal Involuntary Movement Scale (AIMS) for dyskinesia (total score ranges from 0 to 28).

Schizophrenia

In the 4- to 6-week, placebo-controlled schizophrenia trials, the frequency of reported events related to extrapyramidal symptoms (EPS), including akathisia, extrapyramidal disorder, muscle spasms, restlessness, musculoskeletal stiffness, dyskinesia, dystonia, muscle twitching, tardive dyskinesia, tremor, drooling, and involuntary muscle contractions was 6.7% for CAPLYTA and 6.3% for placebo.

In the 4- to 6-week schizophrenia trials, the mean changes from baseline for CAPLYTA-treated patients and placebo-treated patients were 0.1 and 0 for the SAS, -0.1 and 0 for the BARS, and 0.1 and 0 for the AIMS, respectively.

Bipolar Depression

In the 6-week, monotherapy bipolar depression trials, the frequency of reported reactions related to EPS, including muscle spasms, dyskinesia, extrapyramidal disorder, movement disorder, tremor, restlessness, and akathisia was 1.3% for CAPLYTA and 1.1% for placebo.

In a 6-week, adjunctive therapy bipolar depression trial, the frequency of reported reactions related to EPS, including tremor, muscle spasms, akathisia, extrapyramidal disorder, gait disturbance, and restlessness was 4.0% for CAPLYTA and 2.3% for placebo.

In the 6-week, monotherapy bipolar depression trials, the mean changes from baseline for CAPLYTA-treated patients and placebo-treated patients were 0 and 0 for the SAS, -0.1 and -0.1 for the BARS, and 0 and 0 for the AIMS, respectively. In the 6-week adjunctive therapy bipolar depression trial, the mean changes from baseline for CAPLYTA-treated patients and placebo-treated patients were 0 and 0 for the SAS, 0 and -0.1 for the BARS, and 0 and 0 for the AIMS, respectively.

6.2 Postmarketing Experience

The following adverse reaction has been identified during post-approval use of CAPLYTA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure.

Central and Peripheral Nervous System Disorders: burning sensation, including skin burning sensation

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with CAPLYTA

Table 5: Clinically Important Drug Interactions with CAPLYTA

CYP3A4 Inducers	
Clinical Impact	Concomitant use of CAPLYTA with CYP3A4 inducers decreases the exposure of lumateperone *[see Clinical Pharmacology (12.3)]*.
Intervention	Avoid concomitant use of CAPLYTA with CYP3A4 inducers.
Moderate or Strong CYP3A4 Inhibitors	
Clinical Impact	Concomitant use of CAPLYTA with moderate or strong CYP3A4 inhibitors increases lumateperone exposure *[see Clinical Pharmacology (12.3)]*, which may increase the risk of adverse reactions.
Intervention	Reduce CAPLYTA dose when used concomitantly with moderate or strong CYP3A4 inhibitors *[see Dosage and Administration (2.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including CAPLYTA, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or online at http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

Risk Summary

Neonates exposed to antipsychotic drugs during the third trimester are at risk for extrapyramidal and/or withdrawal symptoms following delivery *(see Clinical Considerations)*. Available data from case reports on CAPLYTA use in pregnant women are insufficient to establish any drug associated risks for birth defects, miscarriage, or adverse maternal or fetal outcomes. There are risks to the mother associated with untreated schizophrenia and with exposure to antipsychotics, including CAPLYTA, during pregnancy *(see Clinical Considerations)*. In animal reproduction studies, no malformations were observed with oral administration of lumateperone to pregnant rats and rabbits during organogenesis at doses up to 2.4 and 9.7 times, respectively, the maximum recommended human dose (MRHD) of 42 mg/day on a mg/m^2 basis. When pregnant rats were administered lumateperone during the period of organogenesis through lactation, the number of perinatal deaths of pups was increased at 4.9 times the MRHD, with no adverse effects on pups at 2.4 times the MRHD *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease associated maternal and/or embryo/fetal risk

There is risk to the mother from untreated schizophrenia, including increased risk of relapse, hospitalization, and suicide. Schizophrenia is associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.

Fetal/neonatal adverse reactions
Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.

Data

Animal Data
Pregnant rats were treated with oral doses of 3.5, 10.5, 21, and 63 mg/kg/day lumateperone (0.8, 2.4, 4.9, and 14.6 times the MRHD on a mg/m^2 basis) during the period of organogenesis. No malformations were observed with lumateperone at doses up to 2.4 times the MRHD. Findings of decreased body weight were observed in fetuses at 4.9 and 14.6 times the MRHD. Findings of incomplete ossification and increased incidences of visceral and skeletal variations were recorded in fetuses at 14.6 times the MRHD, a dose that induced maternal toxicity.

Pregnant rabbits were treated with oral doses of 2.1, 7, and 21 mg/kg/day lumateperone (1.0, 3.2, and 9.7 times the MRHD on a mg/m^2 basis) during the period of organogenesis. Lumateperone did not cause adverse developmental effects at doses up to 9.7 times the MRHD.

In a study in which pregnant rats were administered oral doses of 3.5, 10.5, and 21 mg/kg/day lumateperone (0.8, 2.4, and 4.9 times the MRHD on a mg/m^2 basis) during the period of organogenesis and through lactation, the number of live-born pups was decreased at 2.4 and 4.9 times the MRHD, and early postnatal deaths increased at a dose 4.9 times the MRHD. Impaired nursing and decreased body weight gain in pups were observed at 4.9 times, but not at 2.4 times, the MRHD.

Pregnant rats were treated with a human metabolite of lumateperone (reduced ketone metabolite) at oral doses of 15, 60, and 100 mg/kg/day (1.2, 19, and 27 times the exposure to this metabolite at the MRHD of lumateperone based on AUC plasma exposure) during the period of organogenesis. This metabolite did not cause adverse developmental effects at a dose 1.2 times the exposure at the MRHD of lumateperone; however, it caused an increase in visceral malformations (cleft palate) at 27 times and skeletal malformations at 19 times the exposure at the MRHD of lumateperone, a dose that induced maternal toxicity.

8.2 Lactation

Risk Summary

Lumateperone and its metabolites are present in human breast milk in low amounts. In a clinical lactation study, lumateperone was detected in human milk at an estimated daily infant dose 0.0004 mg/kg, with a relative infant dose (RID) of 0.06% the maternal weight-adjusted dosage. Several major circulating metabolites were similarly detected in breast milk in low amounts; however, aniline metabolites were not present in milk or maternal plasma at quantifiable levels *(see Data)*. There are no data on the effects of lumateperone on the breastfed infant or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CAPLYTA and any potential adverse effects on the breastfed child from CAPLYTA or from the underlying maternal condition.

Data

A lactation study in 17 lactating women evaluated the concentrations of lumateperone and its metabolites in plasma and mature breast milk following a single dose of 42 mg CAPLYTA. The estimated daily infant dose of lumateperone in human milk was 0.0004 mg/kg/day (with assumed average milk consumption of 200 ml/kg/day). The mean relative infant dose (RID) (with assumed mean milk consumption of 200 mL/kg/day and average maternal weight of 71 kg) was 0.06% of the maternal weight-adjusted dosage. Several major circulating metabolites were also present in breastmilk at estimated daily infant dose of 0.0004 mg/kg/day. Aniline metabolites were not present in milk or maternal plasma at quantifiable levels.

8.3 Females and Males of Reproductive Potential

Infertility

Based on findings from animal studies, lumateperone may impair male and female fertility *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness of CAPLYTA have not been established in pediatric patients.

Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric patients *[see Boxed Warning, Warnings and Precautions (5.2)]*.

8.5 Geriatric Use

Controlled clinical studies of CAPLYTA in the treatment of schizophrenia did not include any patients aged 65 or older to determine whether or not they respond differently from younger patients. Controlled clinical studies of CAPLYTA in the treatment of bipolar depression included patients aged 65 or older; the number of patients was not sufficient to determine whether or not they respond differently from younger patients.

Antipsychotic drugs increase the risk of death in elderly patients with dementia-related psychosis. CAPLYTA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.1) and (5.3)]*.

8.6 Hepatic Impairment

Patients with moderate (Child-Pugh class B) and severe (Child-Pugh class C) hepatic impairment generally had higher exposure to lumateperone than patients with normal hepatic function; therefore, a dosage reduction of CAPLYTA is recommended in patients with moderate or severe hepatic impairment *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

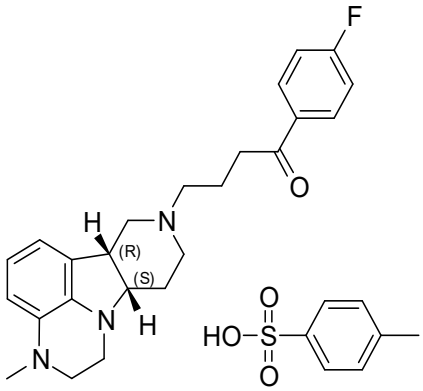
No dosage adjustment is recommended for patients with mild hepatic impairment (Child-Pugh class A).

10 OVERDOSAGE

No specific antidotes for CAPLYTA are known. In managing overdose, provide supportive care, including close medical supervision and monitoring and consider the possibility of multiple drug involvement. In case of overdose, consult a Certified Poison Control Center (1-800-222-1222 or www.poison.org).

11 DESCRIPTION

CAPLYTA capsules contains lumateperone, an atypical antipsychotic, present as lumateperone tosylate salt with the chemical name 4-((6b*R*,10a*S*)-3-methyl-2,3,6b,9,10,10*a*-hexahydro-1*H*,7*H*-pyrido[3',4':4,5]pyrrolo[1,2,3-*de*]quinoxalin-8-yl)-1-(4-fluoro-phenyl)-butan-1-one 4-methylbenzenesulfonate. Its molecular formula is $C_{31}H_{36}FN_3O_4S$, and its molecular weight is 565.71 g/mol with the following structure:



CAPLYTA capsules are intended for oral administration. Each CAPLYTA capsule contains lumateperone and are available in 42 mg (equivalent to 60 mg of lumateperone tosylate), 21 mg (equivalent to 30 mg of lumateperone tosylate), and 10.5 mg (equivalent to 15 mg of lumateperone tosylate) strengths. Capsules include the following inactive ingredients: croscarmellose sodium, gelatin, magnesium stearate, mannitol, and talc. Colorants include

FD&C blue #1 and red #3 (42 mg), FDA/E172 black iron oxide, FDA/E172 red iron oxide and FD&C red #3 (10.5 mg), and titanium dioxide (42 mg, 21 mg and 10.5 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of lumateperone in the treatment of schizophrenia and depressive episodes associated with bipolar I or II disorder is unknown. However, the efficacy of lumateperone could be mediated through a combination of antagonist activity at central serotonin 5-HT_{2A} receptors and postsynaptic antagonist activity at central dopamine D_2 receptors.

12.2 Pharmacodynamics

Lumateperone has high binding affinity for serotonin 5-HT_{2A} receptors (K_i = 0.54 nM) and moderate binding affinity for dopamine D_2 (K_i = 32 nM) receptors. Lumateperone has moderate binding affinity for serotonin transporters (K_i = 33 nM). Lumateperone also has moderate binding affinity for dopamine D_1 (41 nM) and D_4 and adrenergic $alpha_{1A}$ and $alpha_{1B}$ receptors (K_i projected at < 100 nM) but has low binding affinity (less than 50% inhibition at 100 nM) for muscarinic and histaminergic receptors.

Cardiac Electrophysiology

QTcF interval was evaluated in a randomized, placebo- and active- (moxifloxacin 400 mg) controlled, four-arm crossover study utilizing concentration-QTc effect modeling in 33 patients with schizophrenia. The placebo-corrected change from baseline QTcF (90% two-sided upper confidence interval) values of 4.9 (8.9) and 15.8 (19.8) ms for the 42 mg and the supratherapeutic dose of 126 mg (three times the recommended daily dosage) CAPLYTA, respectively, administered orally once daily for 5 days.

12.3 Pharmacokinetics

Following once daily oral administration of CAPLYTA, lumateperone steady state is reached in about 5 days. Lumateperone steady-state exposure is approximately dose-proportional in the range of 3.5 mg to 56 mg (0.08 to 1.3 times the approved recommended daily dosage). A large inter-subject variability in lumateperone PK parameters was observed, with coefficients of variation for C_{max} (peak plasma concentration) and AUC (area under the concentration vs time curve) ranging from 68% to 97% at steady state.

Absorption

The absolute bioavailability of lumateperone capsules is about 4.4%. C_{max} of lumateperone is reached approximately 1-2 hours after CAPLYTA dosing.

Effect of Food

Ingestion of a high-fat meal with CAPLYTA lowers lumateperone mean C_{max} by 33% and increases mean AUC by 9%. Median T_{max} was delayed about 1 hour (from 1 hour at fasted state to 2 hours in the presence of food).

Distribution

Protein binding of lumateperone is 97.4% at 5 µM (about 70-fold higher than therapeutic concentrations) in human plasma. The volume of distribution of lumateperone following intravenous administration is about 4.1 L/kg.

Elimination

The clearance of lumateperone is approximately 27.9 L/hour and the terminal half-life is about 18 hours after intravenous administration.

Metabolism

Lumateperone is extensively metabolized with more than twenty metabolites identified *in vivo*. After a single ^{14}C-labeled oral dose, lumateperone and glucuronidated metabolites represent about 2.8% and 51% of the total plasma radioactivity, respectively. *In vitro* studies show that multiple enzymes, including but not limited to uridine 5'-diphospho-glucuronosyltransferases (UDP-glucuronosyltransferase, UGT) 1A1, 1A4, and 2B15, aldoketoreductase (AKR)1C1, 1B10, and 1C4, and cytochrome P450 (CYP) 3A4, 2C8, and 1A2, are involved in the metabolism of lumateperone.

Excretion

In a human mass-balance study, 58% and 29% of the radioactive dose was recovered in the urine and feces, respectively. Less than 1% of the dose was excreted as unchanged lumateperone in the urine.

Specific Populations

Effects of hepatic or renal impairment on lumateperone exposure are presented in Figure 1. No clinically significant differences in the pharmacokinetics of lumateperone were observed based on age, sex, or race.

Figure 1: Effects of Intrinsic Factors on Lumateperone Pharmacokinetics

Drug Interaction Studies

Clinical Studies
The effects of other drugs on the exposures of lumateperone are presented in Figure 2.

Figure 2: Effects of Other Drugs on Lumateperone Pharmacokinetics

CYP3A4 substrates: No clinically significant differences in the pharmacokinetics of midazolam (CYP3A4 substrate) or its metabolite 1-hydroxymidazolam were observed when used concomitantly with single or multiple doses of lumateperone in patients with schizophrenia.

In Vitro Studies

Lumateperone showed little to no inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP3A4/5. It showed no induction of CYP1A2, CYP2B6, or CYP3A4.

Lumateperone did not appear to be a P-gp or BCRP substrate. It showed little to no inhibition of OCT2, OAT1, OAT3, OATP1B3, or OATP1B1.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies were conducted in rats and mice, and results showed no carcinogenic potential in either species.

In Sprague-Dawley rats, males were administered lumateperone (free base) at oral doses of 3.5, 7 or 14 mg/kg/day and females were administered lumateperone at oral doses of 3.5, 10.5, or 21 mg/kg/day for the first 385 days, then doses were reduced for the two higher dose groups so that the females were administered 3.5, 7 or 14 mg/kg/day, respectively, for the duration of the study. In this study the no adverse effect level for neoplastic lesions was determined to be 14 mg/kg/day (84 mg/m^2/day) for males and 10.5/7 mg/kg/day (42 mg/m^2/day) for females, which are 1.6 times (females) to 3.2 times (males) the MRHD on a mg/m^2 basis.

Male and female CD-1 mice were administered lumateperone at oral doses of 3.5, 10.5 or 21 mg/kg/day for the first 35 days, then doses were reduced to 1.4, 4.9, and 14 mg/kg/day, respectively, for the duration of the study. In this study, the no adverse effect level for neoplastic lesions was determined to be 10.5/4.9 mg/kg/day (15 mg/m^2/day) for each sex which is 0.6 times the MRHD on a mg/m^2 basis.

Mutagenesis

No evidence of mutagenic potential was found in the *in vitro* bacterial reverse mutation assay (Ames test) and the mouse lymphoma test without metabolic activation. Lumateperone was positive in the Ames test only in the presence of metabolic activation and only in the TA1537 strain and was positive in the mouse lymphoma test only in the presence of metabolic activation and only at high concentrations that inhibited cell growth; together these results were thought to be related to solubility limits and/or nonspecific effects on cellular function. Lumateperone was negative for clastogenic activity in the *in vivo* micronucleus assay in rats and was not genotoxic in the *in vivo* Comet assay in rats.

Impairment of Fertility

Female rats were treated with oral doses of 3.5, 10.5, 21 or 42 mg/kg/day lumateperone (free base) (0.8, 2.4, 4.9, and 9.7 times the MRHD on a mg/m^2 basis) prior to mating and continuing through conception and implantation. Estrus cycle irregularities were observed at doses ≥10.5 mg/kg/day. Decreases in the median number of corpora lutea and implantation sites, and increases in the number of non-gravid uteruses, were recorded at 42 mg/kg/day. Decreased gestation body weight and body weight gain, and increases in time to mating, were observed at 21 and 42 mg/kg/day.

Male rats were treated with oral doses of 3.5, 10.5, 21 or 42 mg/kg/day lumateperone (0.8, 2.4, 4.9, and 9.7 times the MRHD on a mg/m^2 basis) for 9 weeks prior to mating and throughout 14 days of mating. Decreased sperm motility, changes in sperm morphology, reduced epididymal counts, and adverse histopathology changes in testes and epididymides were observed at 21 and 42 mg/kg/day.

13.2 Animal Toxicology and/or Pharmacology

Oral administration of lumateperone caused systemic intracytoplasmic accumulation of pigmented material in dogs, rats, and mice at clinically relevant exposures (AUC). Intracytoplasmic pigmentation appeared to be localized in lysosomes. Accumulation of pigmented material persisted without reversal at the end of 1- to 2-month drug-free periods. Pigmented material was observed in the brain and spinal cord of all three species, and in the heart and eye of rats. Although the composition of the pigmented material was not established, the material is likely polymers or protein adducts formed from aniline metabolites of lumateperone.

In the dog, accumulation of pigmented material in the brain and spinal cord was associated with neuronal degeneration and necrosis, followed by axonal degeneration and histiocytic inflammation after oral administration of lumateperone for up to 9 months. In the rat, accumulation of pigmented material was associated with degenerative changes and signs of an inflammatory response in the spinal cord, peripheral nervous system, eye, and heart after oral administration of lumateperone for up to 2 years. Although overt degenerative changes were not observed in the rat brain, the presence of pigment-containing infiltrating macrophages is consistent with an inflammatory response.

The role of intracytoplasmic pigmented material in causing these lesions was not definitively established; however, the colocalization of pigmented material in tissues with degenerative changes and signs of inflammation is supportive. Alternatively, the aniline metabolites of lumateperone may undergo metabolic activation forming reactive metabolites that contribute to the observed toxicities. The role of intracellular accumulation of lumateperone or its non-aniline metabolites in these toxicities could not be ruled out.

The aniline metabolites thought to be responsible for these toxicities were detected in dogs and rats but were not present in humans at quantifiable levels. Based on all the available evidence, these toxicities do not appear to be relevant to humans.

14 CLINICAL STUDIES

14.1 Schizophrenia

CAPLYTA was evaluated for the treatment of schizophrenia in two placebo-controlled trials.

Study 1 (NCT01499563) was a four-week, randomized, double-blind, placebo-controlled, multi-center study in adult patients with a diagnosis of schizophrenia according to the DSM-IV-TR criteria. The primary efficacy measure was change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score at Week 4. The PANSS is a 30-item scale used to measure symptoms of schizophrenia. Each item is rated by a clinician on a seven-point scale. A score of 1 indicates the absence of symptoms, and a score of 7 indicates extremely severe symptoms. The PANSS total score may range from 30 to 210 with higher scores reflecting greater overall symptom severity.

A total of 335 patients were randomized to receive CAPLYTA 42 mg, CAPLYTA 84 mg (two times the recommended daily dose), an active comparator, or placebo. The study was not designed to allow for efficacy comparison of CAPLYTA and the active comparator. Demographic and baseline disease characteristics were similar for the CAPLYTA, active comparator, and placebo groups. Median age was 42 years (range 20 to 55 years). 17% were female, 19% were Caucasian, and 78% were African American.

Compared to the placebo group, patients randomized to CAPLYTA 42 mg showed a statistically significant reduction from baseline to Day 28 in the PANSS total score. The treatment effect in the CAPLYTA 84 mg group (vs. placebo) was not statistically significant. The results of Study 1 are shown in Table 6.

Study 2 (NCT02282761) was a four-week, randomized, double-blind, placebo-controlled, multi-center study in adult patients with a diagnosis of schizophrenia according to the DSM-5 criteria. The primary efficacy measure was change from baseline in the PANSS total score at Week 4.

A total of 450 patients were randomized to receive CAPLYTA 28 mg (two-thirds the recommended daily dose), CAPLYTA 42 mg, or placebo. Demographic and baseline disease characteristics were similar for the CAPLYTA and placebo groups. Median age was 44 years (range 19 to 60 years); 23% were female, 26% were Caucasian and 66% were African American.

Compared to the placebo group, patients randomized to CAPLYTA 42 mg showed a statistically significant reduction from baseline to Day 28 in the PANSS total score. The treatment effect in the CAPLYTA 28 mg group (vs. placebo) was not statistically significant. The results of Study 2 are shown in Table 6.

Studies 1 and 2 did not include any patients aged 65 or older. Examination of subgroups by sex and race did not suggest differences in response in either study.

Table 6: Primary Efficacy Results for Change from Baseline in PANSS Total Score in Patients with Schizophrenia (Studies 1 and 2)

			Primary Efficacy Endpoint: PANSS Total Score		
Study Number	**Treatment Group**	**N**	**Mean Baseline Score (SD)**	**LS Mean Change from Baseline (SE)**	**Placebo-subtracted Difference (95% CI)**
1	CAPLYTA (42 mg)*	84	88.1 (11.0)	-13.2 (1.7)	-5.8 (-10.5, -1.1) [a]
	Placebo	85	86.3 (13.1)	-7.4 (1.7)	--
2	CAPLYTA (42 mg)*	150	90.0 (9.6)	-14.5 (1.3)	-4.2 (-7.8, -0.6)
	Placebo	150	89.0 (10.3)	-10.3 (1.3)	--

The PANSS total score may range from 30 to 210; higher scores reflect greater symptom severity.
SD: standard deviation; SE: standard error; LS Mean: least squares mean; CI: unadjusted confidence interval.
[a] Difference (drug minus placebo) in LS mean change from baseline not adjusted for sample size increase after unblinded interim analysis.
*Statistically significantly superior to placebo.

Figure 3: Change from Baseline in PANSS Total Score by Time (Weeks) in Patients with Schizophrenia in Study 2.

14.2 Depressive Episodes Associated with Bipolar I or II Disorder (Bipolar Depression)

Monotherapy

The efficacy of CAPLYTA, as monotherapy, was established in a 6-week, randomized, double-blind, placebo-controlled, multi-center study in adult patients who met DSM-5 criteria for depressive episodes associated with bipolar I or bipolar II disorder (Study 3; NCT03249376). The primary efficacy measure was the change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score at Week 6. The MADRS is a 10-item clinician-rated scale with total scores ranging from 0 (no depressive features) to 60 (maximum score). The secondary endpoint was the change from baseline in Clinical Global Impression-Bipolar-Severity of Illness scale (CGI-BP-S) total score at Week 6. The CGI-BP-S total score is a clinician-rated scale that measures the patient's current illness state on a 21-point scale that assesses depression, mania, and overall illness, where a higher score is associated with greater illness severity.

A total of 381 patients were randomized to receive CAPLYTA 42 mg or placebo. Demographic and baseline characteristics were similar for the CAPLYTA and placebo groups. Median age was 45 (range 18 to 72). 58% were female, 91% were Caucasian, and 8% were African-American.

Compared to the placebo group, patients randomized to CAPLYTA 42 mg showed a statistically significant improvement from baseline to Day 43 in the MADRS total score and CGI-BP-S total score. The results of Study 3 are shown in Table 7.

Examination of subgroups by age, sex, and race did not suggest differences in response in the study.

Adjunctive Therapy with Lithium or Valproate

The efficacy of CAPLYTA, as adjunctive therapy with lithium or valproate, was established in a 6-week, randomized, double-blind, placebo-controlled, multi-center study in adult patients who met DSM-5 criteria for depressive episodes associated with bipolar I or bipolar II disorder (Study 4; NCT02600507). The primary efficacy measure was the change from baseline in MADRS total score at Week 6. The secondary endpoint was the change from baseline in CGI-BP-S

depression score at Week 6. The CGI-BP-S depression score is a clinician-rated scale that measures the patient's current illness state on a 7-point scale, where a higher score is associated with greater illness severity.

A total of 529 patients were randomized to receive CAPLYTA 28 mg (two-thirds the recommended daily dose), CAPLYTA 42 mg, or placebo. Demographic and baseline characteristics were similar for the CAPLYTA and placebo groups. Median age was 46 (range 18 to 74). 58% were female, 88% were Caucasian, and 11% were African-American.

Compared to the placebo group, patients randomized to CAPLYTA 42 mg showed a statistically significant improvement from baseline to Day 43 in the MADRS total score and CGI-BP-S depression score. The treatment effect in the CAPLYTA 28 mg group (vs. placebo) was not statistically significant. The results of Study 4 are shown in Table 7.

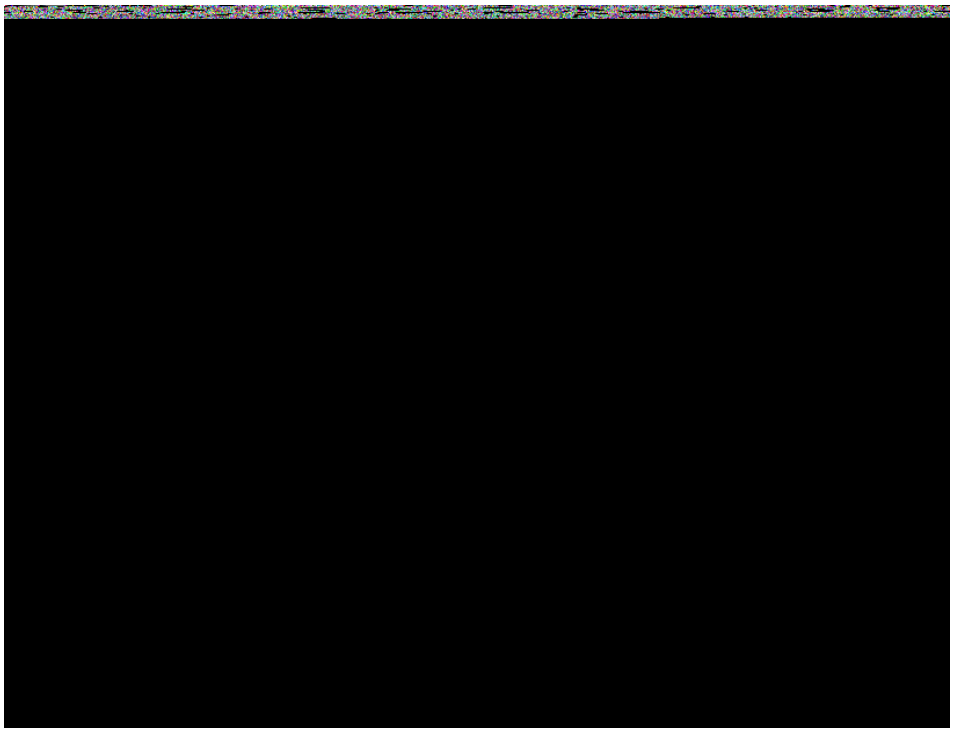
Examination of subgroups by age, sex, and race did not suggest differences in response in the study.

Table 7: Primary Efficacy Results from Bipolar Depression Trials (Studies 3 and 4)

			Primary Efficacy Endpoint: MADRS Total Score		
Study Number	**Treatment Group**	**N**	**Mean Baseline Score (SD)**	**LS Mean Change from Baseline (SE)**	**Placebo-subtracted Difference[a] (95% CI)**
Monotherapy					
3	CAPLYTA (42 mg)*	188	30.8 (4.9)	-16.7 (0.7)	-4.6 (-6.3, -2.8)
	Placebo	188	30.3 (4.6)	-12.1 (0.7)	
Adjunctive Therapy					
4	CAPLYTA (42 mg)* + lithium or valproate	174	32.2 (5.0)	-16.9 (0.8)	-2.4 (-4.4, -0.4)
	Placebo + lithium or valproate	174	32.1 (5.2)	-14.5 (0.8)	

The MADRS total score ranges from 0 to 60; higher scores reflect greater symptom severity
SD: standard deviation; SE: standard error; LS Mean: least squares mean; CI: confidence interval
[a] Difference (drug minus placebo) in LS mean change from baseline
*Statistically significantly superior to placebo.

Figure 4. Change from Baseline in MADRS Total Score by Visits (Study 3) in Patients With Depressive Episodes Associated with Bipolar I or II Disorder (Monotherapy)



16 HOW SUPPLIED/ STORAGE AND HANDLING

CAPLYTA (lumateperone) capsules are supplied as follows:

Capsule Strength	Capsule Color	Imprint Codes	Package Configuration	NDC Code
42 mg	Blue cap and opaque white body	ITI-007 42 mg	Box of 30 (3 Blister Packs of 10 capsules)	72060-142-30
42 mg	Blue cap and opaque white body	ITI-007 42 mg	Bottle of 30	72060-142-40
21 mg	Opaque white cap and body	ITI-007 21 mg	Bottle of 30	72060-121-40
10.5 mg	Opaque light pink cap and body	ITI-007 10.5 mg	Bottle of 30	72060-110-40

Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

Advise the patient or caregiver to read the FDA-approved patient labeling (Medication Guide).

Suicidal Thoughts and Behavior
Advise patients and caregivers to look for the emergence of suicidality, especially early during treatment and instruct them to report such symptoms to their healthcare provider *[see Boxed Warning, Warnings and Precautions (5.2)]*.

Neuroleptic Malignant Syndrome
Counsel patients about a potentially fatal adverse reaction, Neuroleptic Malignant Syndrome (NMS), that has been reported with administration of antipsychotic drugs. Advise patients, family members, or caregivers to contact the healthcare provider or to report to the emergency room if they experience signs and symptoms of NMS *[see Warnings and Precautions (5.4)]*.

Tardive Dyskinesia
Counsel patients on the signs and symptoms of tardive dyskinesia and to contact their healthcare provider if these abnormal movements occur *[see Warnings and Precautions (5.5)]*.

Metabolic Changes
Educate patients about the risk of metabolic changes, how to recognize symptoms of hyperglycemia and diabetes mellitus, and the need for specific monitoring, including blood glucose, lipids, and weight *[see Warnings and Precautions (5.6)]*.

Leukopenia/Neutropenia
Advise patients with a pre-existing low WBC or a history of drug induced leukopenia/ neutropenia that they should have their CBC monitored while taking CAPLYTA *[see Warnings and Precautions (5.7)]*.

Orthostatic Hypotension and Syncope
Educate patients about the risk of orthostatic hypotension and syncope, especially early in treatment, and also at times of re-initiating treatment *[see Warnings and Precautions (5.8)]*.

Interference with Cognitive and Motor Performance
Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that CAPLYTA therapy does not affect them adversely *[see Warnings and Precautions (5.11)]*.

Heat Exposure and Dehydration
Educate patients regarding appropriate care in avoiding overheating and dehydration *[see Warnings and Precautions (5.12)]*.

Concomitant Medications
Advise patients to inform their health care providers of any changes to their current prescription or over-the-counter medications because there is a potential for interactions *[see Drug Interactions (7.1)]*.

Pregnancy
Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with CAPLYTA. Advise patients that CAPLYTA used during the third trimester may cause extrapyramidal and/or withdrawal symptoms (agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder) in the neonate. Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to CAPLYTA during pregnancy *[see Use in Specific Populations (8.1)]*.

Infertility
Advise males and females of reproductive potential that CAPLYTA may impair fertility *[see Use in Specific Populations (8.3)]*.

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New York, NY 10016

MEDICATION GUIDE

CAPLYTA (kap-LITE-ah)
(lumateperone)
capsules

What is the most important information I should know about CAPLYTA?

CAPLYTA may cause serious side effects, including:

- **Increased risk of death in elderly people with dementia related psychosis.** Medicines like CAPLYTA can raise the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). CAPLYTA is not approved for the treatment of people with dementia-related psychosis.
- **Increased risk of suicidal thoughts and actions.** CAPLYTA and antidepressant medicines may increase suicidal thoughts and actions in some children, adolescents, and young adults **especially within the first few months of treatment or when the dose is changed.**
  - Depression and other mental illnesses are the most important causes of suicidal thoughts and actions.

  How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?
  - Pay close attention to any changes, especially sudden changes in mood, behaviors, thoughts, or feelings. This is very important when CAPLYTA or the antidepressant medicine is started or when the dose is changed.
  - Call your healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings, or if you develop suicidal thoughts or actions.
  - Keep all follow-up visits with your healthcare provider as scheduled. Call your healthcare provider between visits as needed, especially if you have concerns about symptoms.

  Call a healthcare provider right away if you or your family member have any of the following symptoms, especially if they are new, worse, or worry you:
  - thoughts about suicide or dying
  - new or worse depression
  - feeling very agitated or restless
  - trouble sleeping (insomnia)
  - acting aggressive, being angry, or violent
  - an extreme increase in activity and talking (mania)
  - attempts to commit suicide
  - new or worse anxiety
  - panic attacks
  - new or worse irritability
  - acting on dangerous impulses
  - other unusual changes in behavior or mood

What is CAPLYTA?

CAPLYTA is a prescription medicine used in adults:

- to treat schizophrenia
- alone to treat depressive episodes that happen with bipolar I or bipolar II disorder (bipolar depression)
- with the medicine lithium or valproate to treat depressive episodes that happen with bipolar I or bipolar II disorder (bipolar depression)

It is not known if CAPLYTA is safe and effective in children.

Do not take CAPLYTA if you are allergic to lumateperone or any of the ingredients in CAPLYTA. See the end of this Medication Guide for a complete list of ingredients in CAPLYTA.

Before taking CAPLYTA, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had heart problems or a stroke
- have or have had low or high blood pressure
- have or have had diabetes or high blood sugar, or a family history of diabetes or high blood sugar. Your healthcare provider should check your blood sugar before you start and during treatment with CAPLYTA.
- have or have had high levels of total cholesterol, LDL cholesterol, or triglycerides or low levels of HDL cholesterol
- have or have had seizures (convulsions)
- have or have had kidney or liver problems
- have or have had a low white blood cell count
- are pregnant or plan to become pregnant. CAPLYTA may harm your unborn baby. Taking CAPLYTA during your third trimester of pregnancy may cause your baby to have abnormal muscle movements or withdrawal symptoms after birth. Talk to your healthcare provider about the risk to your unborn baby if you take CAPLYTA during pregnancy.
  - Tell your healthcare provider if you become pregnant or think you are pregnant during treatment with CAPLYTA.
  - If you become pregnant during treatment with CAPLYTA, talk to your healthcare provider about registering with the National Pregnancy Registry for Atypical Antipsychotics. You can register by calling 1-866-961-2388 or go to http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.
- are breastfeeding or plan to breastfeed. CAPLYTA passes into your breastmilk. Talk to your healthcare provider about the risks and benefits of breastfeeding and the best way to feed your baby during treatment with CAPLYTA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

CAPLYTA and other medicines may affect each other causing possible serious side effects. CAPLYTA may affect the way other medicines work, and other medicines may affect how CAPLYTA works.

Your healthcare provider can tell you if it is safe to take CAPLYTA with your other medicines. Do not start or stop any medicines during treatment with CAPLYTA without first talking to your healthcare provider.

Know the medicines you take. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine.

How should I take CAPLYTA?

- Take CAPLYTA exactly as your healthcare provider tells you to take it. Do not change the dose or stop taking CAPLYTA without first talking to your healthcare provider.
- Take CAPLYTA 1 time each day with or without food.
- If you take too much CAPLYTA, call your healthcare provider or Poison Control Center at 1-800-222-1222 or go to the nearest hospital emergency room right away.

What should I avoid while taking CAPLYTA?

- Do not drive, operate machinery, or do other dangerous activities until you know how CAPLYTA affects you. CAPLYTA may make you drowsy.
- Do not become too hot or dehydrated during treatment with CAPLYTA.
  - Do not exercise too much.
  - In hot weather, stay inside in a cool place if possible.
  - Stay out of the sun.
  - Do not wear too much clothing or heavy clothing.
  - Drink plenty of water.

What are the possible side effects of CAPLYTA?

CAPLYTA may cause serious side effects, including:

- **See "What is the most important information I should know about CAPLYTA?"**
- **Stroke (cerebrovascular problems) in elderly people with dementia-related psychosis that can lead to death.**
- **Neuroleptic malignant syndrome (NMS) is a serious condition that can lead to death.** Call your healthcare provider or go to the nearest hospital emergency room right away if you have some or all of the following signs and symptoms of NMS:
  - high fever
  - changes in your breathing, heart rate, and blood pressure
  - increased sweating
  - confusion
  - stiff muscles
- **Uncontrolled body movements (tardive dyskinesia).** CAPLYTA may cause movements that you cannot control in your face, tongue, or other body parts. Tardive dyskinesia may not go away, even if you stop taking CAPLYTA. Tardive dyskinesia may also start after you stop taking CAPLYTA.
- **Problems with your metabolism such as:**
  - **high blood sugar (hyperglycemia) and diabetes.** Increases in blood sugar can happen in some people who take CAPLYTA. Extremely high blood sugar can lead to coma or death. Your healthcare provider should check your blood sugar before you start, or soon after you start CAPLYTA, and then regularly during long term treatment with CAPLYTA.

    Call your healthcare provider if you have any of these symptoms of high blood sugar during treatment with CAPLYTA:
    - feel very thirsty
    - feel very hungry
    - feel sick to your stomach
    - need to urinate more than usual
    - feel weak or tired
    - feel confused, or your breath smells fruity
  - **increased fat levels (cholesterol and triglycerides) in your blood.** Your healthcare provider should check the fat levels in your blood before you start, or soon after you start CAPLYTA, and then periodically during treatment with CAPLYTA.
  - w**eight gain.** You and your healthcare provider should check your weight before you start and often during treatment with CAPLYTA.

- **Low white blood cell count**. Your healthcare provider may do blood tests during the first few months of treatment with CAPLYTA.
- **Decreased blood pressure (orthostatic hypotension).** You may feel lightheaded or faint when you rise too quickly from a sitting or lying position.
- **Falls.** CAPLYTA may make you sleepy or dizzy, may cause a decrease in your blood pressure when changing position (orthostatic hypotension), and can slow your thinking and motor skills which may lead to falls that can cause fractures or other injuries.
- **Seizures (convulsions).**
- **Sleepiness, drowsiness, feeling tired, difficulty thinking and doing normal activities.** See "What should I avoid while taking CAPLYTA?"
- **Problems controlling your body temperature so that you feel too warm.** See "What should I avoid while taking CAPLYTA?"
- **Difficulty swallowing** that can cause food or liquid to get into your lungs.

The most common side effects of CAPLYTA include sleepiness, dizziness, nausea, and dry mouth.

CAPLYTA may cause fertility problems in females and males. Talk to your healthcare provider if this is a concern for you.

These are not all the possible side effects of CAPLYTA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store CAPLYTA?

- Store CAPLYTA at room temperature between 68°F to 77°F (20°C to 25°C).

Keep CAPLYTA and all medicines out of the reach of children.

General information about the safe and effective use of CAPLYTA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use CAPLYTA for a condition for which it was not prescribed. Do not give CAPLYTA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about CAPLYTA that is written for healthcare professionals.

What are the ingredients in CAPLYTA?

Active ingredient: lumateperone

Inactive ingredients: croscarmellose sodium, gelatin, magnesium stearate, mannitol, and talc. Colorants include FD&C blue #1 and red #3 (42 mg), FDA/E172 black iron oxide, FDA/E172 red iron oxide and FD&C red #3 (10.5 mg), and titanium dioxide (42 mg, 21 mg and 10.5 mg).

Distributed by: Intra-Cellular Therapies, Inc., New York, NY 10016

For more information, go to www.CAPLYTA.com or call (888) 252-4824

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: 6/2023

Lurasidone

EMA

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Latuda 18.5 mg film-coated tablets
Latuda 37 mg film-coated tablets
Latuda 74 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Latuda 18.5 mg film-coated tablets
Each film-coated tablet contains lurasidone hydrochloride equivalent to18.6 mg lurasidone.

Latuda 37 mg film-coated tablets
Each film-coated tablet contains lurasidone hydrochloride equivalent to 37.2 mg lurasidone.

Latuda 74 mg film-coated tablets
Each film-coated tablet contains lurasidone hydrochloride equivalent to 74.5 mg lurasidone.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Latuda 18.5 mg film-coated tablets
White to off-white, film-coated round tablets of 6 mm debossed with 'LA'

Latuda 37 mg film-coated tablets
White to off-white, film-coated round tablets of 8 mm debossed with 'LB'

Latuda 74 mg film-coated tablets
Pale green, film-coated oval tablets of 12 mm x 7 mm debossed with 'LD'

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Latuda is indicated for the treatment of schizophrenia in adults and adolescent aged 13 years and over.

4.2 Posology and method of administration

Posology

Adult population
The recommended starting dose is 37 mg of lurasidone once daily. No initial dose titration is required. It is effective in a dose range of 37 to 148 mg once daily. Dose increase should be based on physician judgement and observed clinical response. The maximum daily dose should not exceed 148 mg.

Patients on doses higher than 111 mg once daily who discontinue their treatment for longer than 3 days should be restarted on 111 mg once daily and up-titrated to their optimal dose. For all other doses patients can be restarted on their previous dose without need for up-titration.

Paediatric population
The recommended starting dose is 37 mg of lurasidone once daily. No initial dose titration is required. It is effective in a dose range of 37 to 74 mg once daily. Dose increase should be based on physician

judgement and observed clinical response. The maximum daily dose should not exceed 74 mg. In children, lurasidone should be prescribed by an expert in paediatric psychiatry.

Dose adjustment due to interactions
A starting dose of 18.5 mg is recommended and the maximum dose of lurasidone should not exceed 74 mg once daily in combination with moderate CYP3A4 inhibitors. Dose adjustment of lurasidone may be necessary in combination with mild and moderate CYP3A4 inducers (see section 4.5). For strong CYP3A4 inhibitors and inducers see section 4.3.

Switching between antipsychotic medicinal products
Due to different pharmacodynamic and pharmacokinetic profiles among antipsychotic medicinal products, supervision by a clinician is needed when switching to another antipsychotic product is considered medically appropriate.

Elderly people
Dosing recommendations for elderly patients with normal renal function (CrCl ≥ 80 ml/min) are the same as for adults with normal renal function. However, because elderly patients may have diminished renal function, dose adjustments may be required according to their renal function status (see "Renal impairment" below).

Limited data are available in elderly people treated with higher doses of lurasidone. No data are available in elderly people treated with 148 mg of lurasidone. Caution should be exercised when treating patients ≥65 years of age with higher doses of lurasidone.

Renal impairment
No dose adjustment of lurasidone is required in patients with mild renal impairment.
In patients with moderate (Creatinine Clearance (CrCl) ≥ 30 and < 50 ml/min), severe renal impairment (CrCL >15 and < 30 ml/min) and End Stage Renal Disease (ESRD) patients (CrCl < 15 ml/min), the recommended starting dose is 18.5 mg and the maximum dose should not exceed 74 mg once daily. Lurasidone should not be used in patients with ESRD unless the potential benefits outweigh the potential risks. If used in ESRD, clinical monitoring is advised.

Hepatic impairment
No dose adjustment of lurasidone is required in patients with mild hepatic impairment.
Dose adjustment is recommended in moderate (Child-Pugh Class B) and severe hepatic impairment (Child-Pugh Class C) patients. The recommended starting dose is 18.5 mg. The maximum daily dose in moderate hepatic impairment patients should not exceed 74 mg and in severe hepatic impairment patients should not exceed 37 mg once daily.

Method of administration

Latuda film-coated tablets are for oral use, to be taken once daily together with a meal.
If taken without food, it is anticipated that lurasidone exposure will be significantly lower as compared to when taken with food (see section 5.2).

Latuda tablets should be swallowed whole, in order to mask the bitter taste. Latuda tablets should be taken at the same time every day to aid compliance.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Concomitant administration of strong CYP3A4 inhibitors (e.g. boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) and strong CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin, St John's wort (*Hypericum perforatum*) (see section 4.5).

4.4 Special warnings and precautions for use

During antipsychotic treatment, improvement in the patient's clinical condition may take a few days to some weeks. Patients should be closely monitored during this period.

Suicidality
The occurrence of suicidal behaviour is inherent in psychotic illnesses and in some cases has been reported early after initiation or switch of antipsychotic therapy. Close supervision of high-risk patients should accompany antipsychotic therapy.

Parkinson's disease
If prescribed to patients with Parkinson's disease, antipsychotic medicinal products may exacerbate the underlying parkinsonism symptoms. Physicians should therefore weigh the risks versus the benefits when prescribing lurasidone to patients with Parkinson's disease.

Extrapyramidal symptoms (EPS)
Medicinal products with dopamine receptor antagonistic properties have been associated with extrapyramidal adverse reactions including rigidity, tremors, mask-like face, dystonias, drooling of saliva, drooped posture and abnormal gait. In placebo controlled clinical studies in adult patients with schizophrenia there was an increased occurrence of EPS following treatment with lurasidone compared to placebo.

Tardive dyskinesia
Medicinal products with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterised by rhythmical involuntary movements, predominantly of the tongue and/or face. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotics, including lurasidone, should be considered.

Cardiovascular disorders/QT prolongation
Caution should be exercised when lurasidone is prescribed in patients with known cardiovascular disease or family history of QT prolongation, hypokalaemia, and in concomitant use with other medicinal products thought to prolong the QT interval.

Seizures
Lurasidone should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Neuroleptic malignant syndrome (NMS)
Neuroleptic Malignant Syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels, has been reported to occur with lurasidone. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, lurasidone should be discontinued.

Elderly patients with dementia
Lurasidone has not been studied in elderly patients with dementia.

Overall mortality
In a meta-analysis of 17 controlled clinical trials, elderly patients with dementia treated with other atypical antipsychotics, including risperidone, aripiprazole, olanzapine, and quetiapine had an increased risk of mortality compared to placebo.

Cerebrovascular accident
An approximately 3-fold increased risk of cerebrovascular adverse reactions has been seen in randomised placebo-controlled clinical trials in the dementia population with some atypical antipsychotics, including risperidone, aripiprazole and olanzapine. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient

populations. Lurasidone should be used with caution in elderly patients with dementia who have risk factors for stroke.

Venous thromboembolism
Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with lurasidone and preventive measures undertaken.

Hyperprolactinaemia
Lurasidone elevates prolactin levels due to antagonism of dopamine D2 receptors. Patients should be counseled on signs and symptoms of elevated prolactin, such as gynecomastia, galactorrhea, amenorrhea and erectile dysfunction. Patient should be advised to seek medical attention if they experience any signs and symptoms.

Weight gain
Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Hyperglycaemia
Rare cases of glucose related adverse reactions, e.g. increase in blood glucose, have been reported in clinical trials with lurasidone. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Orthostatic hypotension/syncope
Lurasidone may cause orthostatic hypotension, perhaps due to its α1-adrenergic receptor antagonism. Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

Interaction with grapefruit juice
Grapefruit juice should be avoided during treatment with lurasidone (see section 4.5).

Serotonin syndrome
Concomitant administration of Latuda and other serotonergic agents, such as buprenorphine/opioids, MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).
If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.
Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms. If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

This medicine contains less than 1 mmol sodium (23 mg) per one tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions
Given the primary central nervous system effects of lurasidone, lurasidone should be used with caution in combination with other centrally acting medicinal products and alcohol.

Caution is advised when prescribing lurasidone with medicinal products known to prolong the QT interval, e.g. class IA antiarrhythmics (e.g. quinidine, disopyramide) and class III antiarrhythmics (e.g. amiodarone, sotalol), some antihistaminics, some other antipsychotics and some antimalarials (e.g. mefloquine).

Latuda should be used cautiously when co-administered with other serotonergic agents, such as buprenorphine/opioids, MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

Pharmacokinetic interactions
The concomitant administration of lurasidone and grapefruit juice has not been assessed. Grapefruit juice inhibits CYP3A4 and may increase the serum concentration of lurasidone. Grapefruit juice should be avoided during treatment with lurasidone.

Potential for other medicinal products to affect lurasidone
Lurasidone and its active metabolite ID-14283 both contribute to the pharmacodynamic effect at the dopaminergic and serotonergic receptors. Lurasidone and its active metabolite ID-14283 are primarily metabolised by CYP3A4.

CYP3A4 inhibitors
Lurasidone is contraindicated with strong CYP3A4 inhibitors (e.g. boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) (see section 4.3).

Coadministration of lurasidone with the strong CYP3A4 inhibitor ketoconazole resulted in a 9- and 6-fold increase in exposure of lurasidone and its active metabolite ID-14283 respectively.

Co-administration of lurasidone and posaconazole (strong CYP3A4 inhibitor) resulted in an approximate 4-5 fold increase in lurasidone exposure. A persistent effect of posaconazole on lurasidone exposure was observed up to 2-3 weeks after stop of posaconazole co-administration.

Coadministration of lurasidone with medicinal products that moderately inhibit CYP3A4 (e.g. diltiazem, erythromycin, fluconazole verapamil) may increase exposure to lurasidone. Moderate CYP3A4 inhibitors are estimated to result in a 2-5 fold increase in exposure of CYP3A4 substrates.

Coadministration of lurasidone with diltiazem (slow-release formulation), a moderate CYP3A4 inhibitor, resulted in a 2.2 and 2.4-fold increase in exposure of lurasidone and ID-14283 respectively (see section 4.2). The use of an immediate release formulation of diltiazem could result in a larger increase in lurasidone exposure.

CYP3A4 inducers
Lurasidone is contraindicated with strong CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifampicin, St John's wort (Hypericum perforatum)) (see section 4.3).

Coadministration of lurasidone with the strong CYP3A4 inducer rifampicin resulted in a 6-fold decrease in exposure of lurasidone.

Coadministration of lurasidone with mild (e.g. armodafinil, amprenavir, aprepitant, prednisone, rufinamide) or moderate (e.g. bosentan, efavirenz, etravirine, modafinil, nafcillin) inducers of CYP3A4 would be expected to give a <2-fold reduction in lurasidone exposure during co-administration and for up to 2 weeks after discontinuation of mild or moderate CYP3A4 inducers.

When lurasidone is coadministered with mild or moderate CYP3A4 inducers, the efficacy of lurasidone needs to be carefully monitored and a dose adjustment may be needed.

Transporters
Lurasidone is a substrate of P-gp and BCRP in vitro and the in vivo relevance of this is unclear. Coadministration of lurasidone with P-gp and BCRP inhibitors may increase exposure to lurasidone.

Potential for lurasidone to affect other medicinal products
Coadministration of lurasidone with midazolam, a sensitive CYP3A4 substrate, resulted in a < 1.5-fold increase in midazolam exposure. Monitoring is recommended when lurasidone and CYP3A4 substrates known to have a narrow therapeutic index (e.g. astemizole, terfenadine, cisapride, pimozide, quinidine, bepridil or ergot alkaloids [ergotamine, dihydroergotamine]) are coadministered.

Coadministration of lurasidone with digoxin (a P-gp substrate) did not increase the exposure to digoxin and only slightly increased Cmax (1.3 –fold) and therefore, it is considered that lurasidone can be coadministered with digoxin. Lurasidone is an *in vitro* inhibitor of the efflux transporter P-gp and the clinical relevance of intestinal P-gp inhibition cannot be excluded. Concomitant administration of the P-gp substrate dabigatran etexilate may result in increased dabigatran plasma concentrations.

Lurasidone is an *in vitro* inhibitor of the efflux transporter BCRP and the clinical relevance of intestinal BCRP inhibition cannot be excluded. Concomitant administration of BCRP substrates may result in increases in the plasma concentrations of these substrates.

Coadministration of lurasidone with lithium indicated that lithium had clinically negligible effects on the pharmacokinetics of lurasidone, therefore no dose adjustment of lurasidone is required when coadministered with lithium. Lurasidone does not impact concentrations of lithium.

A clinical drug interaction study investigating the effect of coadministration of lurasidone on patients taking oral combination contraceptives including norgestimate and ethinyl estradiol, indicated that lurasidone had no clinically or statistically meaningful effects on the pharmacokinetics of the contraceptive or sex hormone binding globulin (SHBG) levels. Therefore, lurasidone can be coadministered with oral contraceptives.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data (less than 300 pregnancy outcomes) from the use of lurasidone in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryonal/foetal development, parturition and postnatal development (see section 5.3). The potential risk for humans is unknown. Lurasidone should not be used during pregnancy unless clearly necessary.

Neonates exposed to antipsychotics (including lurasidone) during the third trimester are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Breast-feeding
Lurasidone was excreted in milk of rats during lactation (see section 5.3). It is not known whether lurasidone or its metabolites are excreted in human milk. Breast feeding in women receiving lurasidone should be considered only if the potential benefit of treatment justifies the potential risk to the child.

Fertility
Studies in animals have shown a number of effects on fertility, mainly related to prolactin increase, which are not considered to be relevant to human reproduction (see section 5.3).

4.7 Effects on ability to drive and use machines

Lurasidone has minor influence on the ability to drive and use machines. Patients should be cautioned about operating hazardous machines, including motor vehicles and cycles, until they are reasonably certain that lurasidone does not affect them adversely (see section 4.8).
Regarding road safety, adolescents who may not be old enough to drive may nevertheless cycle.

4.8 Undesirable effects

Summary of the safety profile
The safety of lurasidone has been evaluated at doses of 18.5 -148 mg in clinical studies in patients with schizophrenia treated for up to 52 weeks and in the post-marketing setting. The most common adverse drug reactions (ADRs) (≥ 10%) were akathisia, nausea and insomnia.

Tabulated summary of adverse reactions
Adverse drug reactions (ADRs) based upon pooled data are shown by system, organ class and by preferred term are listed in Table 1 below. The incidence of ADRs reported in clinical trials is tabulated by frequency category. The following terms and frequencies are applied: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (<1 /10,000) and not known (cannot be estimated from the available data).

Table 1: Adverse drug reactions (ADRs) Based Upon Pooled Data for Adults

System Organ Class	Very Common	Common	Uncommon	Rare	Frequency not known
Infections and infestations			Nasopharyngitis		
Blood and lymphatic system disorders			Anaemia	Eosinophilia Leukopenia	Neutropenia****
Immune system disorders		Hypersensitivity			
Metabolism and nutrition disorders		Weight increased Decreased appetite	Blood glucose increased Hyponatraemia		
Psychiatric disorders	Insomnia	Agitation Anxiety Restlessness	Nightmare Catatonia Panic attack	Suicidal behaviour	Sleep disorder*****
Nervous system disorders	Akathisia	Somnolence* Parkinsonism** Dizziness Dystonia*** Dyskinesia	Lethargy Dysarthria Tardive dyskinesia Syncope Convulsion	Neuroleptic malignant syndrome (NMS) Cerebrovascular accident	
Eye disorders			Blurred vision		
Ear and labyrinth disorders			Vertigo		
Cardiac disorders		Tachycardia	Angina pectoris Atrioventricular block first degree Bradycardia		

System Organ Class	Very Common	Common	Uncommon	Rare	Frequency not known
Vascular disorders		Hypertension	Hypotension Orthostatic hypotension Hot flush Blood pressure increased		
Gastrointestinal disorders	Nausea	Diarrhoea Vomiting Dyspepsia Salivary hypersecretion Dry mouth Upper abdominal pain Stomach discomfort	Flatulence Dysphagia Gastritis		
Hepatobiliary disorders			Alanine aminotransferase increased		
Skin and subcutaneous tissue disorders		Rash Pruritus	Hyperhidrosis	Angioedema	Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders		Back pain Musculoskeletal stiffness	Joint stiffness Myalgia Neck pain	Rhabdomyolysis	
Renal and urinary disorders		Serum creatinine increased	Dysuria	Renal failure	
Pregnancy, puerperium and perinatal conditions					Drug withdrawal syndrome neonatal (see 4.6)
Reproductive system and breast disorders			Blood prolactin increased Erectile dysfunction Amenorrhoea Dysmenorrhoea	Breast pain Galactorrhoea	Breast enlargement****
General disorders and administration site conditions		Fatigue	Gait disturbance	Sudden death	

System Organ Class	Very Common	Common	Uncommon	Rare	Frequency not known
Investigations		Blood creatinine phosphokinase increased			

*Somnolence includes adverse reaction terms: hypersomnia, hypersomnolence, sedation, and somnolence
**Parkinsonism includes adverse reaction terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor
***Dystonia includes adverse reaction terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus.
****ADRs noted in Phase 2 and 3 controlled and uncontrolled studies; however, the incidence of occurrence for these are too low to estimate frequencies.

Table 2: Adverse Drug Reactions (ADRs) for Adolescents

System Organ Class	Very Common	Common	Uncommon	Rare	Frequency not known
Infections and infestations			Nasopharyngitis Rhinitis Upper respiratory tract infection		
Blood and lymphatic system disorders			Neutropenia		
Immune System Disorders			Hypersensitivity		
Endocrine disorders		Hyperprolactinaemia (including blood prolactin increased)	Autoimmune thyroiditis Hyperandrogenism Hypothyroidism		
Metabolism and nutrition disorders		Decreased appetite Increased appetite	Hyperinsulinemia		
Psychiatric Disorders		Abnormal dreams Agitation Anxiety Depression Insomnia Psychotic disorder Schizophrenia Tension	Aggression Apathy Confusional state Depressed mood Dissociation Hallucination (auditory) Hallucination (visual) Homicidal ideation Impulsive behaviour Initial insomnia Libido decreased Libido increased Listlessness Mental status changes Obsessive thoughts		

System Organ Class	Very Common	Common	Uncommon	Rare	Frequency not known
			Panic Attack Psychomotor hyperactivity Restlessness Sleep disorder Suicidal ideation Terminal insomnia Thinking abnormal		
Nervous System Disorders	Akathisia Headache Somnolence*	Disturbance in attention Dizziness Dyskinesia Dystonia*** Parkinsonism**	Dizziness postural Dysgeusia Hyperkinesia Memory impairment Migraine Paraesthesia Psychomotor hyperactivity Restless legs syndrome Tardive dyskinesia Tension headache		
Eye Disorders			Accommodation disorder Vision blurred		
Ear and labyrinth disorders			Hyperacusis		
Cardiac disorders		Tachycardia	Palpitations Supraventricular extrasystoles		
Vascular disorders			Orthostatic hypotension Hypertension		
Respiratory, thoracic and mediastinal disorders			Oropharyngeal pain Dyspnoea		
Gastrointestinal disorders	Nausea	Constipation Dry mouth Salivary hypersecretion Vomiting	Abdominal discomfort Abdominal pain upper Aptyalism Diarrhoea Dyspepsia Lip dry Toothache		
Skin and subcutaneous tissue disorders		Hyperhidrosis	Alopecia Hair growth abnormal Rash Urticaria		

System Organ Class	Very Common	Common	Uncommon	Rare	Frequency not known
Musculoskeletal and connective tissue disorders		Muscle rigidity	Arthralgia Muscle tightness Musculoskeletal stiffness Myalgia Pain in extremity Pain in jaw		
Renal and urinary disorders			Bilirubinuria Dysuria Micturition disorder Polyuria Proteinuria Renal disorder		
Reproductive system and breast disorders		Erectile dysfunction	Amenorrhoea Breast pain Ejaculation disorder Galactorrhoea Gynaecomastia Menstruation irregular Oligomenorrhoea Sexual dysfunction		
Congenital, familial and genetic disorders			Tourette's disorder		
General disorders and administration site conditions		Asthenia Fatigue Irritability	Chills Gait disturbance Malaise Non-cardiac chest pain Pyrexia		

System Organ Class	Very Common	Common	Uncommon	Rare	Frequency not known
Investigations		Blood creatine phosphokinase increased C-reactive protein increased Weight decreased Weight increased	Alanine aminotransferase increased Anti-thyroid antibody positive Aspartate aminotransferase increased Blood alkaline phosphatase decreased Blood alkaline phosphokinase increased Blood cholesterol increased Blood glucose increased Blood insulin increased Blood testosterone decreased Blood thyroid stimulating hormone increased Blood triglycerides increased Electrocardiogram PR shortened Haemoglobin decreased High density lipoprotein decreased Low density lipoprotein decreased		
Injury, poisoning and procedural complications			Intentional overdose		

*Somnolence includes the following adverse reactions observed in adolescents: hypersomnia, sedation, and somnolence.
**Parkinsonism includes the following adverse reactions observed in adolescents: cogwheel rigidity, extrapyramidal disorder, hypokinesia, parkinsonism, and tremor.
*** Dystonia includes the following adverse reactions observed in adolescents: dystonia, oculogyric crisis and torticollis.

Description of selected adverse reactions

Post marketing reports of clinically serious cases of skin and other hypersensitivity reactions have been reported in association with lurasidone treatment, including some reports of Stevens-Johnson syndrome.

Events of interest to the class

Extrapyramidal symptoms (EPS): In the adult short-term placebo-controlled studies, the incidence of reported events related to EPS, excluding akathisia and restlessness, was 13.5% for lurasidone-treated

subjects versus 5.8% for placebo-treated subjects. The incidence of akathisia for lurasidone-treated subjects was 12.9% versus 3.0% for placebo-treated subjects. In the adolescent short-term placebo-controlled study, the incidence of reported events related to EPS, excluding akathisia, was 5.1% for lurasidone-treated subjects versus 1.8% for placebo-treated subjects. The incidence of akathisia for lurasidone-treated subjects was 8.9% versus 1.8% for placebo-treated subjects.

Dystonia: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, difficulty swallowing, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity, higher potency and at higher doses of first generation antipsychotic medicinal products. An elevated risk of acute dystonia is observed in males and younger age groups.

Venous thromboembolism: Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs -Frequency unknown.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Management of overdose
There is no specific antidote to lurasidone, therefore, appropriate supportive measures should be instituted, and close medical supervision and monitoring should continue until the patient recovers.

Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of QT-prolonging effects when administered in patients with an acute overdose of lurasidone. Similarly, the alpha-blocking properties of bretylium might be additive to those of lurasidone, resulting in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate measures. Adrenaline and dopamine should not be used, or other sympathomimetics with beta agonist activity, since beta stimulation may worsen hypotension in the setting of lurasidone-induced alpha blockade. In case of severe extrapyramidal symptoms, anticholinergic medicinal products should be administered.

Gastric lavage (after intubation if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, antipsychotics. ATC code: N05AE05

Mechanism of action
Lurasidone is a selective blocking agent of dopamine and monoamine effects. Lurasidone binds strongly to dopaminergic D2- and to serotonergic 5-HT2A and 5-HT7- receptors with high binding

affinity of 0.994, 0.47 and 0.495 nM, respectively. It also blocks α2c-adrenergic receptors and α2a-adrenergic receptors with a binding affinity of 10.8 and 40.7 nM respectively. Lurasidone also exhibits partial agonism at the 5HT-1A receptor with a binding affinity of 6.38 nM. Lurasidone does not bind to histaminergic or muscarinic receptors.

The mechanism of action of the minor active metabolite of lurasidone ID-14283 is similar to that of lurasidone.

Lurasidone doses ranging from 9 to 74 mg administered to healthy subjects produced a dose-dependent reduction in the binding of 11C-raclopride, a D2/D3 receptor ligand, in the caudate, putamen and ventral striatum detected by positron emission tomography.

Pharmacodynamic effects
In the main clinical efficacy studies, lurasidone was administered at doses of 37-148 mg lurasidone.

Clinical efficacy
The efficacy of lurasidone in the treatment of schizophrenia was demonstrated in five multi-centre, placebo-controlled, double-blind, 6-week trials in subjects who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for schizophrenia. Lurasidone doses, which varied across the five trials, ranged from 37 to 148 mg lurasidone once daily. In the short-term trials, the primary efficacy endpoint was defined as the mean change from baseline to Week 6 in Positive and Negative Syndrome Scale (PANSS) total scores, a validated multi-item inventory composed of five factors to evaluate positive symptoms, negative symptoms, disorganised thoughts, uncontrolled hostility/excitement, and anxiety/depression. Lurasidone demonstrated superior efficacy compared with placebo across Phase 3 studies (see Table 2). Lurasidone showed significant separation from placebo from as early as Day 4. Additionally, lurasidone was superior to placebo on the predefined secondary endpoint Clinical Global Impression – Severity (CGI-S) scale. Efficacy was also confirmed in a secondary analysis of treatment response (defined as ≥ 30% decrease from Baseline in PANSS total score).

Table 3: Schizophrenia Adult Studies: Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score - Change from Baseline to Week 6- MMRM for Studies D1050229, D1050231, and D1050233: Intent-to-Treat Analysis Set

Study Statistic	Placebo	Lurasidone dose (b)				Active Control (a)
		37 mg	74 mg	111 mg	148 mg	
Study D1050229	N=124	N=121	N=118	N=123	--	--
Baseline Mean (SD)	96.8 (11.1)	96.5 (11.6)	96.0 (10.8)	96.0 (9.7)	--	--
LS Mean Change (SE)	-17.0 (1.8)	-19.2 (1.7)	-23.4 (1.8)	-20.5 (1.8)	--	--
Treatment Difference vs. placebo						
Estimate (SE)	--	-2.1 (2.5)	-6.4 (2.5)	-3.5 (2.5)	--	--
p-value	--	0.591	0.034	0.391	--	--
Study D1050231	N=114	N=118	--	N=118	--	N=121
Baseline Mean (SD)	95.8 (10.8)	96.6 (10.7)	--	97.9 (11.3)	--	96.3 (12.2)
LS Mean Change (SE)	-16.0 (2.1)	-25.7 (2.0)	--	-23.6 (2.1)	--	-28.7 (1.9)
Treatment Difference vs. placebo						
Estimate (SE)	--	-9.7 (2.9)	--	-7.5 (3.0)	--	-12.6 (2.8)
p-value	--	0.002	--	0.022	--	<0.001
Study D1050233	N=120	--	N=125	--	N=121	N=116
Baseline Mean (SD)	96.6 (10.2)	--	97.7 (9.7)	--	97.9 (11.8)	97.7 (10.2)
LS Mean Change (SE)	-10.3 (1.8)	--	-22.2 (1.8)	--	-26.5 (1.8)	-27.8 (1.8)
Treatment Difference vs. placebo						
Estimate (SE)	--	--	-11.9 (2.6)	--	-16.2 (2.5)	-17.5 (2.6)
p-value	--	--	<0.001	--	<0.001	<0.001

(a) Olanzapine 15 mg in Study D1050231, quetiapine extended-release (XR) 600 mg in Study D1050233.
N is number of subjects per model estimate.
(b) p-values for lurasidone vs. placebo were adjusted for multiple comparisons. P-values for olanzapine and quetiapine XR vs. placebo were unadjusted.

In the short-term studies there was no consistent dose-response correlation observed.

Long-term maintenance efficacy of lurasidone (37 to 148 mg lurasidone once daily) was demonstrated in a 12 month non-inferiority trial with quetiapine extended release (200 to 800 mg once daily). Lurasidone was non-inferior to quetiapine extended release in time to relapse of schizophrenia. Lurasidone had a small increase from baseline to Month 12 in body weight and body mass index (Mean (SD): 0.73 (3.36) kg and 0.28 (1.17) kg/m2, respectively) compared to quetiapine extended release (1.23 (4.56) kg and 0.45 (1.63) kg/m2, respectively). Overall, lurasidone had a negligible effect on weight and other metabolic parameters including total cholesterol, triglycerides, and glucose levels.

In a long-term safety study clinically stable patients were treated using 37 – 111 mg lurasidone or risperidone 2 – 6 mg. In that study the rate of relapse over a 12-month period was 20% for lurasidone and 16% for risperidone. This difference neared, but did not reach, statistical significance.

In a long-term trial designed to assess the maintenance of effect, lurasidone was more effective than placebo in maintaining symptom control and delaying relapse of schizophrenia. After having been treated for an acute episode and stabilized for a minimum of 12 weeks with lurasidone, patients were then randomised in a double-blind manner to either continue on lurasidone or on placebo until they

experienced a relapse in schizophrenia symptoms. In the primary analysis of time to relapse in which patients that withdrew without relapse were censored at the time of withdrawal, patients on lurasidone showed a significantly longer time to relapse compared with patients on placebo (p=0.039). The Kaplan-Meier estimates of the probability of relapse at Week 28 were 42.2% for lurasidone and 51.2% for placebo. The probability of all-cause discontinuation at Week 28 were 58.2% for lurasidone and 69.9% for placebo (p=0.072).

Paediatric population

Schizophrenia

The efficacy of Latuda, was established in a 6-week, randomized, double-blind, placebo-controlled study of adolescents (13 to 17 years) who met DSM-IV-TR criteria for schizophrenia (N=326). Patients were randomized to one of two fixed-doses of Latuda (37 or 74 mg/day) or placebo.

The primary rating instrument used to assess psychiatric signs and symptoms was the PANSS. The key secondary instrument was the CGI-S.

For both dose groups, Latuda was superior to placebo in reduction of PANSS and CGI-S scores at Week 6. On average, the 74 mg/day dose did not provide additional benefit compared to the 37 mg/day dose.

The primary efficacy results are provided in Table 4.

Table 4 Primary Efficacy Results (PANSS Total Score) - Change From Baseline to Week 6- MMRM for the Adolescent Schizophrenia Study D1050301: Intent-to-Treat Analysis Set

Study Statistic	Placebo	Lurasidone dose (a)	
		37 mg	74 mg
Study D1050301	N=112	N=108	N=106
Baseline Mean (SD)	92.8 (11.08)	94.5 (10.97)	94.0 (11.12)
LS Mean Change (SE)	-10.5 (1.59)	-18.6 (1.59)	-18.3 (1.60)
Treatment Difference vs. placebo			
Estimate (SE)	--	-8.0 (2.21)	-7.7 (2.22)
p-value	--	0.0006	0.0008

N is number of subjects per model estimate.
(a) p-values for lurasidone vs. placebo were adjusted for multiple comparisons.

The improvements in the CGI-S scores at Week 6 were significantly different from placebo for both the lurasidone 74 mg/day (-0.42 ± 0.130, adjusted p = 0.0015) and lurasidone 37 mg/day (-0.47 ± 0.130, adjusted p = 0.0008) treatment groups.

A 104-week extension study (Study D1050302) was designed to evaluate the long-term safety, tolerability, and effectiveness of flexibly dosed lurasidone (18.5, 37, 55.5, or 74 mg/day) in paediatric subjects who completed a 6-week treatment period in three preceding studies of various indications. Only results for 271 subjects with schizophrenia who enrolled from Study D1050301 are hereinafter presented. Of these, 186 subjects (68.6%) completed through 52 weeks and 156 (57.6%) subjects completed 104 weeks of flexible dosing with lurasidone 18.5 to 74 mg/day.

For subjects who continued from D1050301, the mean (95% CI) in PANSS total score from DB Baseline was -26.5 (-28.5, -24.5) at Week 28 LOCF, -28.2 (-30.2, -26.2) at Week 52 LOCF, and -29.5 (-31.8, -27.3) at Week 104 LOCF/post-OL Endpoint, and mean change (95% CI) from OL Baseline was -9.2 (-11.1, -7.2) at Week 28 LOCF, -10.8 (-13.0, -8.7) at Week 52 LOCF, and -12.2 (-14.5, -9.8) at Week 104 LOCF/post-OL Endpoint.

Bipolar Depression

The short-term efficacy of lurasidone was studied in a 6-week multicentre, randomized, double-blind, placebo-controlled, study of children and adolescent patients (10-17 years of age) who met Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) criteria for a major depressive episode associated with bipolar I disorder, with or without rapid cycling, and without psychotic features (N=350). Patients were randomized to flexibly dosed lurasidone 18-74 mg once daily or placebo.

The primary efficacy endpoint was defined as the mean change from baseline to Week 6 in Children's Depression Rating Scale, Revised (CDRS-R) Total Score. The key secondary endpoint was Clinical Global Impression – Bipolar Version, Severity of Illness (CGI-BP-S) Depression Score. Statistically significant differences favouring lurasidone over placebo were shown for these endpoints for the total population studied, beginning at Week 2 and were maintained at each study visit through to the end of the study. However, the primary and key secondary efficacy endpoints were not met in younger patients (below 15 years of age). Placebo-adjusted LS mean change (95% CI) from Baseline to Week 6 LOCF in CDRS-R total score for the lurasidone group was -1.8 (-5.6, 2.0) for subjects in the 10- to 14-year-old age patients and was -8.6 (-12.4, -4.8) for subjects in the 15- to 17-year-old age patients (Table 5).

The safety profile of lurasidone in children included in this short-term study is in general consistent with that observed when treated within the approved indication in adults, however, differences in frequency of the most commonly occurred adverse reactions have been observed in paediatric patients for nausea (very common), diarrhea (common) and decreased appetite (common), compared with adults (common, unknown, and uncommon, respectively).

Table 5 Bipolar Depression Paediatric Study: Children's Depression Rating Scale, Revised (CDRS-R) Total Score and Clinical Global Impression-Bipolar Version, Severity of Illness (CGI-BP-S) Depression Score (Depression) - Change From Baseline to Week 6 - MMRM for Study D1050326: Intent-to-Treat Analysis Set

Parameters	Study Statistic	Placebo	Lurasidone dose 18.5-74 mg (a) (b)
Primary Endpoint: CDRS-R Total Score		N=170	N=173
	Baseline Mean (SD)	58.6 (8.26)	59.2 (8.24)
	LS Mean Change (SE)	-15.3 (1.08)	-21.0 (1.06)
	Treatment Difference vs. placebo		
	Estimate (SE; 95% CI)	--	-5.7 (1.39; -8.4 to -3.0)
	p-value	--	<0.0001
Key Secondary Endpoint: CGI-BP-S Depression Score		N=170	N=173
	Baseline Mean (SD)	4.5	4.6
	LS Mean Change (SE)	-1.05 (0.087)	-1.49 (0.085)
	Treatment Difference vs. placebo		
	Estimate (SE; 95% CI)	--	-0.44 (0.112; -0.66 to -0.22)
	p-value	--	<0.0001

N is number of subjects.
(a) p-values for lurasidone vs. placebo were adjusted for multiple comparisons.
(b) Lurasidone doses of 18.5, 37, 55.5, 74 mg are equivalent to 20, 40, 60 and 80 amounts of lurasidone hydrochloride.

5.2 Pharmacokinetic properties

Absorption
Lurasidone reaches peak serum concentrations in approximately 1-3 hours.

In a food effect study, lurasidone mean Cmax and AUC increased approximately by 2-3-times and 1.5-2-times, respectively, when administered with food compared to the levels observed under fasting conditions.

Distribution
Following administration of 37 mg of lurasidone, the mean approximate apparent volume of distribution was 6000 L. Lurasidone is highly bound (~99%) to serum proteins.

Biotransformation
Lurasidone is metabolised mainly via CYP3A4. The major biotransformation pathways are oxidative N-dealkylation, hydroxylation of norbornane ring, and S-oxidation.

Lurasidone is metabolised into two active metabolites (ID-14283 and ID-14326) and two non-active metabolites (ID-20219 and ID-20220). Lurasidone and its metabolites ID-14283, ID-14326, ID-20219 and ID-20220 correspond to approximately 11.4, 4.1, 0.4, 24 and 11% respectively, of serum radioactivity respectively.

CYP3A4 is the major enzyme responsible for metabolism of the active metabolite ID-14283. Lurasidone and its active metabolite ID-14283 both contribute to the pharmacodynamic effect at the dopaminergic and serotonergic receptors.

Based on *in vitro* studies lurasidone is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP4A11, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 enzymes.

In vitro, lurasidone demonstrated no direct, or weak inhibition (direct or time-dependent) (IC50>5.9 μM) of the enzymes cytochrome P450 (CYP)1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4. Based on this data, lurasidone is not expected to affect the pharmacokinetics of medicinal products that are substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1. For administration of medicinal products that are substrates of CYP3A4 with a narrow therapeutic range, see section 4.5.

Lurasidone is an *in vitro* substrate of the efflux transporters P-gp and BCRP. Lurasidone is not subject to active uptake transport by OATP1B1 or OATP1B3.

Lurasidone is an inhibitor of P-gp, BCRP and OCT1 *in vitro* (see section 4.5). Lurasidone is not expected to have a clinically relevant inhibitory potential on transporters OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1, MATE2K or BSEP based on *in vitro* data.

Elimination
Following administration of lurasidone, the elimination half-life was 20-40 hours. Following oral administration of a radiolabelled dose, approximately 67% dose was recovered in faeces and 19% in urine. Urine comprised mostly of a number of metabolites with minimal renal excretion of parent compound.

Linearity/non-linearity
The pharmacokinetics of lurasidone is dose-proportional within a total daily dose range of 18.5 mg to 148 mg. Steady-state concentrations of lurasidone are reached within 7 days of starting lurasidone.

Pharmacokinetics in special patient groups

Elderly people
Limited data have been collected in healthy subjects ≥ 65 years. Of the data collected, similar exposure was obtained compared with subjects < 65 years. However, an increase in exposure in elderly subjects may be expected for patients if they have impaired renal or hepatic function.

Hepatic impairment
The serum concentrations of lurasidone are increased in healthy subjects with Child-Pugh Class A, B and C hepatic impairment with an increased exposure of 1.5-, 1.7- and 3-fold respectively.

Renal impairment
The serum concentrations of lurasidone are increased in healthy subjects with mild, moderate and severe renal impairment with an increased exposure of 1.5, 1.9 and 2.0-fold respectively. Subjects with ESRD (CrCl<15 ml/min) have not been investigated.

Gender
There were no clinically relevant differences between genders in the pharmacokinetics of lurasidone in a population pharmacokinetic analysis in patients with schizophrenia.

Race
There were no clinically relevant differences in the pharmacokinetics of lurasidone in a population pharmacokinetic analysis in patients with schizophrenia. It was noted that Asian subjects had 1.5-fold increased exposure to lurasidone compared to Caucasian subjects.

Smoking
Based on *in vitro* studies utilising human liver enzymes, lurasidone is not a substrate for CYP1A2; smoking should, therefore, not have an effect on the pharmacokinetics of lurasidone.

Paediatric population
The pharmacokinetics of lurasidone in paediatric patients was evaluated in 47 children aged 6-12 years and 234 adolescents aged 13-17 years. Lurasidone was administered as lurasidone hydrochloride at daily doses of either 20, 40, 80, 120 mg (6-17 years) or 160 mg (10-17 years only) for up to 42 days. There was no clear correlation between obtained serum exposure and age or body weight. The pharmacokinetics of lurasidone in paediatric patients aged 6–17 years was generally comparable to those observed in adults.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. Major findings in repeat-dose toxicity studies of lurasidone were centrally-mediated endocrine changes resulting from serum prolactin elevations in rats, dogs and monkeys. High serum prolactin levels in long-term repeat-dose studies in female rats were associated with effects on bones, adrenal glands, and reproductive tissues. In a long-term dog repeat-dose study, high serum prolactin levels were associated with effects on male and female reproductive tissues.

In rats, lurasidone had no effect on male and female reproduction at oral doses of 150 and 0.1 mg/kg/day lurasidone hydrochloride, respectively, or on early embryonic development at an oral dose of 15 mg/kg/day lurasidone hydrochloride.

A fertility study in female rats resulted in prolonged oestrous cycle and delayed copulation at ≥1.5 mg/kg/day lurasidone hydrochloride, whilst the copulation and fertility indices, and the numbers of corpora lutea, implantations and live foetuses were decreased at 150 mg/kg/day lurasidone hydrochloride. These effects were due to the hyperprolactinemia following lurasidone treatment, affecting the oestrous cycle and copulatory behaviour as well as the maintenance of corpus luteum of the female rats, resulting in a decrease in implantation and the number of live foetuses. These prolactin-related effects are not considered to be relevant to human reproduction.

A single dose of 10 mg/kg lurasidone hydrochloride to pregnant rats resulted in fetal exposure. In a dose range finding study in pregnant rats, 150 mg/kg/day lurasidone hydrochloride caused fetal growth retardation without signs of teratogenicity. Lurasidone was not teratogenic in rats or rabbits at an exposure similar to or below the maximum recommended human dose (148 mg lurasidone).

In the definitive juvenile rat toxicity study, no increased sensitivity of juvenile animals to lurasidone-related effects on body weight, food consumption, and clinical observations were apparent, but similar effects as in adult rat were noted (delays in growth and development and hyperprolactinaemia). Hyperactivity that was evident at ≥3 mg/kg/day during the post-treatment period has also been reported for other D2 receptor antagonists. Slightly lower birth weights and body weights/body weight gains during the postnatal period were noted in the offspring of juvenile rats previously treated with ≥30 mg/kg/day. At the NOAEL of 3 mg/kg/day, the exposures of lurasidone and most metabolites were lower than that achieved at the recommended clinical dose in adolescents aged 13 years or above.

Lurasidone was excreted in milk of rats during lactation.

Lurasidone was not genotoxic in a battery of tests. Mammary gland and/or pituitary gland tumours were observed in the mouse and rat carcinogenicity studies and are most likely due to the increased blood prolactin levels. These findings are common in rodents treated with antipsychotic medicinal products with dopamine D2 blocking activity and are considered to be rodent-specific.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Latuda 18.5 mg film-coated tablets
Core
Mannitol (E 421)
Starch, pregelatinised
Croscarmellose sodium (E468)
Hypromellose 2910 (E 464)
Magnesium stearate (E 470b)

Tablet coating
Hypromellose 2910 (E 464)
Titanium dioxide (E 171)
Macrogol 8000
Carnauba wax (E 903)

Latuda 37 mg film-coated tablets
Core
Mannitol (E 421)
Starch, pregelatinised
Croscarmellose sodium (E468)
Hypromellose 2910 (E 464)
Magnesium stearate (E 470b)

Tablet coating
Hypromellose 2910 (E 464)
Titanium dioxide (E 171)
Macrogol 8000
Carnauba wax (E 903)

Latuda 74 mg film-coated tablets
Core
Mannitol (E 421)
Starch, pregelatinised
Croscarmellose sodium (E468)
Hypromellose 2910 (E 464)
Magnesium stearate (E 470b)

Tablet coating
Hypromellose 2910 (E 464)
Titanium dioxide (E 171)
Macrogol 8000
Iron oxide, Yellow (E 172)
Indigotine (E 132)
Carnauba wax (E 903)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Store in the original package in order to protect from light.

6.5 Nature and contents of container

Cartons contain 14 x 1, 28 x 1, 30 x 1, 56 x 1, 60 x 1, 90 x 1 or 98 x 1 tablets in aluminium/aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Aziende Chimiche Riunite Angelini Francesco – A.C.R.A.F. S.p.A.
Viale Amelia 70, 00181
Rome - Italy

8. MARKETING AUTHORISATION NUMBER(S)

Latuda 18.5 mg film-coated tablet
EU/1/14/913/001-007

Latuda 37 mg film-coated tablet
EU/1/14/913/008-014

Latuda 74 mg film-coated tablet
EU/1/14/913/015-021

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 March 2014
Date of latest renewal: 14 November 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Aziende Chimiche Riunite Angelini Francesco – A.C.R.A.F. S.p.A.
Via Vecchia del Pinocchio, 22 60100
Ancona (AN),
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of PSUR(s) for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Latuda 18.5 mg film-coated tablets
lurasidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains lurasidone hydrochloride equivalent to18.6 mg lurasidone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 x 1 film-coated tablets
28 x 1 film-coated tablets
30 x 1 film-coated tablets
56 x 1 film-coated tablets
60 x 1 film-coated tablets
90 x 1 film-coated tablets
98 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aziende Chimiche Riunite Angelini Francesco – A.C.R.A.F. S.p.A.
Viale Amelia 70, 00181
Rome – Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/913/001 14 x 1 film-coated tablets
EU/1/14/913/002 28 x 1 film-coated tablets
EU/1/14/913/003 30 x 1 film-coated tablets
EU/1/14/913/004 56 x 1 film-coated tablets
EU/1/14/913/005 60 x 1 film-coated tablets
EU/1/14/913/006 90 x 1 film-coated tablets
EU/1/14/913/007 98 x 1 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Latuda 18.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Latuda 18.5 mg tablets
lurasidone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

A.C.R.A.F. S.p.A.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Latuda 37 mg film-coated tablets
lurasidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains lurasidone hydrochloride equivalent to 37.2 mg lurasidone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 x 1 film-coated tablets
28 x 1 film-coated tablets
30 x 1 film-coated tablets
56 x 1 film-coated tablets
60 x 1 film-coated tablets
90 x 1 film-coated tablets
98 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aziende Chimiche Riunite Angelini Francesco – A.C.R.A.F. S.p.A.
Viale Amelia 70, 00181
Rome - Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/913/008 14 x 1 film-coated tablets
EU/1/14/913/009 28 x 1 film-coated tablets
EU/1/14/913/010 30 x 1 film-coated tablets
EU/1/14/913/011 56 x 1 film-coated tablets
EU/1/14/913/012 60 x 1 film-coated tablets
EU/1/14/913/013 90 x 1 film-coated tablets
EU/1/14/913/014 98 x 1 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Latuda 37 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Latuda 37 mg tablets
lurasidone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

A.C.R.A.F. S.p.A.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Latuda 74 mg film-coated tablets
lurasidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains lurasidone hydrochloride equivalent to 74.5 mg lurasidone.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

14 x 1 film-coated tablets
28 x 1 film-coated tablets
30 x 1 film-coated tablets
56 x 1 film-coated tablets
60 x 1 film-coated tablets
90 x 1 film-coated tablets
98 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Aziende Chimiche Riunite Angelini Francesco – A.C.R.A.F. S.p.A.
Viale Amelia 70, 00181
Rome - Italy

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/913/015 14 x 1 film-coated tablets
EU/1/14/913/016 28 x 1 film-coated tablets
EU/1/14/913/017 30 x 1 film-coated tablets
EU/1/14/913/018 56 x 1 film-coated tablets
EU/1/14/913/019 60 x 1 film-coated tablets
EU/1/14/913/020 90 x 1 film-coated tablets
EU/1/14/913/021 98 x 1 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Latuda 74 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Latuda 74 mg tablets
lurasidone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

A.C.R.A.F. S.p.A.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Latuda 18.5 mg film-coated tablets
Latuda 37 mg film-coated tablets
Latuda 74 mg film-coated tablets
lurasidone

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Latuda is and what it is used for

Latuda contains the active substance lurasidone and belongs to a group of medicines called antipsychotics. It is used to treat symptoms of schizophrenia in adults (aged 18 years and over) and adolescents aged 13-17 years. Lurasidone works by blocking receptors in the brain to which the substances dopamine and serotonin attach. Dopamine and serotonin are neurotransmitters (substances that allow nerve cells to communicate with each other) that are involved in the symptoms of schizophrenia. By blocking their receptors, lurasidone helps to normalise the activity of the brain, reducing the symptoms of schizophrenia.

Schizophrenia is a disorder with symptoms such as hearing things, seeing or sensing things that are not there, mistaken beliefs, unusual suspiciousness, becoming withdrawn, incoherent speech and behaviour and emotional flatness. People with this disorder may also feel depressed, anxious, guilty, or tense. This medicine is used to improve your symptoms of schizophrenia.

2. What you need to know before you take Latuda

Do not take Latuda:
- if you are allergic to lurasidone or any of the other ingredients of this medicine (listed in section 6)
- if you are taking medicines which may affect the level of lurasidone in your blood such as:
  - medicines for fungal infections such as itraconazole, ketoconazole (except as a shampoo), posaconazole or voriconazole
  - medicines for an infection such as the antibiotic clarithromycin or telithromycin
  - medicines for HIV infections such as cobicistat, indinavir, nelfinavir, ritonavir, and saquinavir
  - medicines for chronic hepatitis such as boceprevir, and telaprevir
  - a medicine for depression, nefazodone
  - a medicine for tuberculosis, rifampicin
  - medicines for seizures such as carbamazepine, phenobarbital and phenytoin
  - herbal medicine for depression, St John's wort (Hypericum *perforatum*).

Warnings and precautions
It may take several days or even weeks before this medicine will have a full effect. Contact your doctor if you have questions on this medicine.

Talk to your doctor or pharmacist before taking Latuda, or during treatment, especially if you have:
- suicidal thoughts or behaviour
- Parkinson's disease or dementia
- ever been diagnosed with a condition whose symptoms include high temperature and muscle stiffness (also known as neuroleptic malignant syndrome) or if you have ever experienced rigidity, tremors or problems moving (extrapyramidal symptoms) or abnormal movements of the tongue or face (tardive dyskinesia). You should be aware that these conditions may be caused by this medicine
- heart disease or heart disease treatment that makes you prone to low blood pressure or have a family history of irregular heartbeat (including QT prolongation)
- a history of seizures (fits) or epilepsy
- a history of blood clots, or if someone else in your family has a history of blood clots, as medicines for schizophrenia have been associated with formation of blood clots
- enlarged breasts in male (gynecomastia), milky nipple discharge (galactorrhea), absence of menstruation (amenorrhea) or erectile dysfunction
- diabetes or are prone to diabetes
- decreased kidney function
- decreased liver function
- an increase in your weight
- blood pressure dropping upon your standing up which may cause fainting
- opioid dependence (treated with buprenorphine) or severe pain (treated with opioids) or depression or other conditions that are treated with antidepressants. The use of these medicines together with Latuda can lead to serotonin syndrome, a potentially life-threatening condition (see "Other medicines and Latuda").

If you have any of these conditions, please talk to your doctor as he/she may want to adjust your dose, monitor you more closely or stop treatment with Latuda.

Children and adolescents
Do not give this medicine to children below 13 years of age.

Other medicines and Latuda
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is especially important if you are taking:
- any medicines that also work in the brain, as their effects could be additive in a negative way with the effects of Latuda on your brain
- medicines that lower blood pressure, as this medicine can also lower blood pressure
- medicines for Parkinson's disease and restless legs syndrome (e.g. levodopa) as this medicine can reduce their effects
- medicines containing ergot alkaloid derivatives (used for treating migraines), and other medicines including terfenadine and astemizole (used for treating hay fever and other allergic conditions), cisapride (used for treating digestive problems), pimozide (used to treating psychiatric illnesses), quinidine (used for treating heart conditions), bepridil (used for treating chest pain)
- medicines containing buprenorphine (used for treating opioid dependence) or opioids (used for treating sever pain) or anti-depressants such as moclobemide, tranylcypromine, citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, duloxetine, venlafaxine, amitriptyline, doxepine, or trimipramine. These medicines may interact with Latuda and you may experience symptoms such as involuntary, rhythmic contractions of muscles, including the muscles that control movement of the eye, agitation, hallucinations, coma, excessive sweating,

tremor, exaggeration of reflexes, increased muscle tension, body temperature above 38°C. Contact your doctor when experiencing such symptoms.

Tell your doctor if you take any of these medicines since your doctor may have to change the dose of that medicine during treatment with Latuda.

The following medicines may increase the level of lurasidone in your blood:
- diltiazem (to treat high blood pressure)
- erythromycin (to treat infections)
- fluconazole (to treat fungal infections)
- verapamil (to treat high blood pressure or chest pain).

The following medicines may decrease the level of lurasidone in your blood:
- amprenavir, efavirenz, etravirine (to treat HIV infection)
- aprepitant (to treat nausea and vomiting)
- armodafinil, modafinil (to treat sleepiness)
- bosentan (to treat high blood pressure or ulcers of the fingers)
- nafcillin (to treat infections)
- prednisone (to treat inflammatory disease)
- rufinamide (to treat seizures).

Tell your doctor if you take any of these medicines since your doctor may change your dose of Latuda.

Latuda with food, drink and alcohol
Alcohol should be avoided when taking this medicine. This is because alcohol will have an additive negative effect.
Do not drink grapefruit juice while you are taking this medicine. Grapefruit can affect the way this medicine works.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

You should not take this medicine during pregnancy unless this has been agreed with your doctor.

If your doctor decides that the potential benefit of treatment during pregnancy justifies the potential risk to your unborn baby, your doctor will monitor your baby closely after birth. This is because the following symptoms may occur in newborn babies of mothers that have used lurasidone in the last trimester (last three months) of their pregnancy:
- shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding.

If your baby develops any of these symptoms you should contact your doctor.

It is not known if lurasidone passes into breast milk. Talk to your doctor if you are breast-feeding, or if you plan to breast-feed.

Driving and using machines
Sleepiness, dizziness and vision problems may occur during treatment with this medicine (see section 4, Possible side effects). Do not drive, cycle or use any tools or machines until you know that this medicine does not affect you in a negative way.

Latuda contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per one tablet, that is to say essentially ‘sodium-free’.

3. How to take Latuda

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Your dose will be decided by your doctor and may depend on:
- how well you respond to a dose
- if you are taking some other medicines (see section 2, Other medicines and Latuda)
- if you have kidney or liver problems.

Adults (aged 18 years and over)
The recommended starting dose is 37 mg once a day.
The dose may be increased or decreased by your doctor within the dose range of 18.5 mg to 148 mg once a day. The maximum dose should not exceed 148 mg once a day.

Adolescents aged 13-17 years
The recommended starting dose is 37 mg of lurasidone once daily.
The dose may be increased or decreased by your doctor within the dose range of 37 to 74 mg once daily. The maximum daily dose should not exceed 74 mg.

How to take Latuda
Swallow your tablet(s) whole with water, in order to mask the bitter taste. You should take your dose regularly every day at the same time of the day, so that it is easier to remember it. You must take this medicine with food or just after eating, as this helps the body to take up the medicine and allows it to work better.

If you take more Latuda than you should
If you take more of this medicine than you should, contact your doctor immediately. You may experience sleepiness, tiredness, abnormal body movements, problems with standing and walking, dizziness from low blood pressure, and abnormal heart beats.

If you forget to take Latuda
Do not take a double dose to make up for a forgotten dose. If you miss one dose, take your next dose on the day after the missed dose. If you miss two or more doses, contact your doctor.

If you stop taking Latuda
If you stop taking this medicine you will lose the effects of the medicine. You should not stop this medicine unless told to do so by your doctor as your symptoms may return.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If you notice any of the following symptoms **seek medical attention immediately**:
- a severe allergic reaction seen as fever, swollen mouth, face, lip or tongue, shortness of breath, itching, skin rash and sometimes a drop in blood pressure (hypersensitivity). These reactions are seen commonly (may affect up to 1 in 10 people)
- a serious blistering rash affecting the skin, mouth, eyes and genitals (Stevens-Johnson syndrome). This reaction is seen with unknown frequency
- fever, sweating, muscle stiffness, and reduced consciousness. These could be symptoms of a condition known as neuroleptic malignant syndrome. These reactions are seen rarely (may affect up to 1 in 1,000 people)

- blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing. If you notice any of these symptoms seek medical advice immediately.

The following side effects may also happen in adults:

Very common (may affect more than 1 in 10 people):
- feeling of restlessness and inability to sit still
- nausea (feeling sick)
- insomnia.

Common (may affect up to 1 in 10 people):
- Parkinsonism: this is a medical term that describes many symptoms which include increase in saliva secretion or watery mouth, drooling, jerks when bending the limbs, slow, reduced or impaired body movements, no expression in the face, muscle tightness, stiff neck, muscle stiffness, small, shuffling, hurried steps and lack of normal arm movements when walking, persistent blinking in response to tapping of the forehead (an abnormal reflex)
- speech problems, unusual muscle movements; a collection of symptoms known as extrapyramidal symptoms (EPS) which typically will involve unusual purposeless involuntary muscle movements
- fast heartbeat
- increased blood pressure
- dizziness
- muscle spasms and stiffness
- vomiting (being sick)
- diarrhoea
- back pain
- rash and itching
- indigestion
- dry mouth or excess saliva
- abdominal pain
- somnolence, tiredness, agitation and anxiety
- weight gain
- increase in creatine phosphokinase (an enzyme in muscles) seen in blood tests
- increase in creatinine (a marker of kidney function) seen in blood tests
- reduced appetite.

Uncommon (may affect up to 1 in 100 people):
- slurred speech
- nightmares
- difficulty swallowing
- irritation to lining of stomach
- sudden feelings of anxiety
- convulsion (fits)
- chest pain
- muscle aches
- temporary loss of consciousness
- spinning sensation
- abnormal nerve impulses in the heart
- slow heart rate
- joint pains
- problems walking
- rigid posture
- increased blood prolactin, increased blood glucose (blood sugar), increase in some liver enzymes, seen in blood tests

- blood pressure dropping upon standing up which may cause fainting
- common cold
- hot flush
- blurred vision
- sweating
- pain when passing urine
- uncontrollable movements of mouth, tongue and limbs (tardive dyskinesia)
- low blood levels of sodium which can cause tiredness and confusion, muscle twitching, fits and coma (hyponatremia)
- lack of energy (lethargy)
- gas (flatulence)
- neck pain
- problems with erections
- painful or absence of menstrual periods
- reduced levels of red blood cells (which carry oxygen around the body).

Rare (may affect up to 1 in 1,000 people):
- Rhabdomyolysis which is the breakdown of muscle fibres that leads to the release of muscle fibre contents (myoglobin) into the bloodstream, seen as muscle pain, being sick, being confused, an abnormal heart rate and rhythm, and possibly dark urine
- increase in eosinophils (a type of white blood cell)
- swelling beneath the skin surface (angioedema)
- deliberate injury to oneself
- cerebrovascular accident
- kidney failure
- reduced levels of white blood cells (which fight infection)
- breast pain, milk secretion from breasts
- sudden death.

Not known (frequency cannot be estimated from the available data):
- reduced levels of a subgroup of white blood cells (neutrophils)
- sleep disorder
- newborn babies may show the following: agitation, increase or decreases in muscle tone, tremor, sleepiness, breathing or feeding problems
- abnormal breast enlargement.

In elderly people with dementia, a small increase in the number of deaths has been reported for patients taking medicines for schizophrenia compared with those not receiving these medicines.

<u>The following side effects may happen in adolescents:</u>

Very common (may affect more than 1 in 10 people):
- feeling of restlessness and inability to sit still
- headache
- sleepiness
- nausea (feeling sick).

Common (may affect up to 1 in 10 people):
- reduced or increased appetite
- abnormal dreams
- difficulty in sleeping, tension, agitation, anxiety and irritability
- physical weakness, tiredness
- depression
- psychotic disorder: this is a medical term that describes many mental diseases that cause abnormal thinking and perceptions; people with psychoses lose touch with reality

- symptoms of schizophrenia
- difficulty in attention
- spinning sensation
- abnormal involuntary movements (dyskinesia)
- abnormal muscle tone, including torticollis and involuntary upward deviation of the eyes,
- Parkinsonism: this is a medical term that describes many symptoms which include increase in saliva secretion or watery mouth, drooling, jerks when bending the limbs, slow, reduced or impaired body movements, no expression in the face, muscle tightness, stiff neck, muscle stiffness, small, shuffling, hurried steps and lack of normal arm movements when walking, persistent blinking in response to tapping of the forehead (an abnormal reflex)
- fast heartbeat
- difficulty in emptying the bowels (constipation)
- dry mouth or excess saliva
- vomiting (being sick)
- sweating
- muscle rigidity
- problems with erections
- increase in creatine phosphokinase (an enzyme in muscles) seen in blood tests
- increase in blood prolactin (a hormone), seen in blood tests
- weight gain or loss.

Uncommon (may affect up to 1 in 100 people):
- hypersensitivity
- common cold, infection of throat and nose
- decreased activity of thyroid, inflammation of thyroid
- aggressive behaviour, impulsive behaviour
- apathy
- confusional state
- depressed mood
- separation of normal mental processes (dissociation)
- hallucination (auditory or visual)
- homicidal thoughts
- difficulty in sleeping
- sexual desire increased or decreased
- lack of energy
- mental condition changes
- obsessive thoughts
- feeling of acute and disabling anxiety (panic attack)
- engage in involuntary movements that serve no purpose (psychomotor hyperactivity)
- hyperactivity of the muscles in the body (hyperkinesia), inability to rest (restlessness)
- uncontrollable urge to move legs (restless legs syndrome), uncontrollable movements of mouth, tongue and limbs (tardive dyskinesia)
- sleep disorder
- deliberate suicidal thoughts
- thinking abnormal
- unsteadiness (spinning sensation)
- alteration of taste
- memory impairment
- abnormal skin sensation (paraesthesia)
- feeling like with a tight band around head (tension headache), migraine
- difficulty of the eyes in focusing, vision blurred
- increased sensitivity of hearing
- palpitations, alterations in heart rhythm
- blood pressure dropping upon standing up which may cause fainting

- increased blood pressure
- abdominal pain or disturbance
- absence of or deficiency in secretion of saliva
- diarrhoea
- indigestion
- lip dry
- toothache
- partial or complete absence of hair, hair growth abnormal
- rash, urticaria
- muscle spasms and stiffness, muscle aches
- joint pains, pain in arms and legs, pain in jaw
- presence of bilirubin in urine, presence of protein in urine, a marker of kidney function
- pain or difficulty when passing urine, frequent urination, renal disorder
- sexual dysfunction
- difficulty in ejaculation
- abnormal breast enlargement, breast pain, milk secretion from breasts
- menstruation absent or irregular
- make uncontrolled noises and movements (Tourette's disorder)
- chills
- problems walking
- malaise
- chest pain
- fever
- intentional overdose
- effects on the thyroid function, seen in blood tests increased blood cholesterol, increased blood triglycerides, decreased high density lipoprotein, decreased low density lipoprotein, seen in blood tests
- increased blood glucose (blood sugar), increased blood insulin, increase in some liver enzymes (a marker of liver function), seen in blood tests
- increased or decreased blood testosterone, increased blood thyroid stimulating hormone, seen in blood tests
- electrocardiogram alterations
- decreased haemoglobin, reduced levels of white blood cells (which fight infection) seen in blood tests.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Latuda

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Store in the original package in order to protect from light.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Latuda contains

- The active substance is lurasidone.
  Each 18.5 mg tablet contains lurasidone hydrochloride equivalent to 18.6 mg lurasidone.
  Each 37 mg tablet contains lurasidone hydrochloride equivalent to 37.2 mg lurasidone.
  Each 74 mg tablet contains lurasidone hydrochloride equivalent to 74.5 mg lurasidone.
- The other ingredients are mannitol, pregelatinised starch, croscarmellose sodium, hypromellose 2910, magnesium stearate (E470b), titanium dioxide (E171), macrogol, yellow iron oxide (E172) (present in 74 mg tablets), indigotine (E132) (present in 74 mg tablets) and carnauba wax (E903).

What Latuda looks like and contents of the pack

- Latuda 18.5 mg film-coated tablets are white to off-white, film-coated round tablets debossed with “LA”
- Latuda 37 mg film-coated tablets are white to off-white, film-coated round tablets debossed with “LB”
- Latuda 74 mg film-coated tablets are pale green, film-coated oval tablets debossed with “LD”.

Latuda film-coated tablets are available in pack sizes containing 14 x 1, 28 x 1, 30 x 1, 56 x 1, 60 x 1, 90 x 1 or 98 x 1 film-coated tablet in aluminium/aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Aziende Chimiche Riunite Angelini Francesco – A.C.R.A.F. S.p.A.
Viale Amelia 70, 00181
Rome - Italy

Manufacturer

Aziende Chimiche Riunite Angelini Francesco – A.C.R.A.F. S.p.A.
Via Vecchia del Pinocchio, 22 60100
Ancona (AN), Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/ Belgique/ Belgien CNX Therapeutics Netherlands B.V. medinfo@cnx-therapeutics.com	**Lithuania/ Lietuva** CNX Therapeutics Netherlands B.V. medinfo@cnx-therapeutics.com
Bulgaria/ България Анджелини Фарма България ЕООД office@angelini.bg	**Luxembourg/ Luxemburg** CNX Therapeutics Netherlands B.V. medinfo@cnx-therapeutics.com
Czech Republic/ Česká republika Angelini Pharma Česká republika s.r.o. info@angelini.cz	**Hungary/ Magyarország** Angelini Pharma Magyarország Kft office@angelini.hu
Denmark/ Danmark CNX Therapeutics Netherlands B.V. medinfo@cnx-therapeutics.com	**Malta** CNX Therapeutics Netherlands B.V. medinfo@cnx-therapeutics.com

Germany/ Deutschland CNX Therapeutics Netherlands B.V. mailto:medinfo@cnx-therapeutics.com	**Netherlands/ Nederland** CNX Therapeutics Netherlands B.V. mailto:medinfo@cnx-therapeutics.com
Estonia/ Eesti CNX Therapeutics Netherlands B.V. mailto:medinfo@cnx-therapeutics.com	**Norway/ Norge** CNX Therapeutics Netherlands B.V. mailto:medinfo@cnx-therapeutics.com
Greece/ Ελλάδα Angelini Pharma Hellas Μονοπρόσωπη ABEE info@angelinipharma.gr	**Austria/ Österreich** Angelini Pharma Österreich GmbH office@angelini.at
Spain/ España ANGELINI PHARMA ESPAÑA, S.L. Tel: + 34 93 253 45 00	**Poland/ Polska** Angelini Pharma Polska Sp. z o.o. angelini@angelini.pl
France CNX Therapeutics Netherlands B.V. mailto:medinfo@cnx-therapeutics.com	**Portugal** Angelini Pharma Portugal, Unipessoal Lda apoio.utente@angelini.pt
Croatia/ Hrvatska Aziende Chimiche Riunite Angelini Francesco – A.C.R.A.F. S.p.A. Tel: + 39 06 78 0531	**Romania/ România** Angelini Pharmaceuticals România SRL office@angelini.ro
Ireland CNX Therapeutics Netherlands B.V. mailto:medinfo@cnx-therapeutics.com	**Slovenia/ Slovenija** Bonifar d.o.o. Tel: + 386 1 235 0490
Iceland/ Ísland CNX Therapeutics Netherlands B.V. mailto:medinfo@cnx-therapeutics.com	**Slovak republic/ Slovenská republika** Angelini Pharma Slovenská republika s.r.o. office@angelini.sk
Italy/ Italia Angelini S.p.A. Tel: + 39 06 78 0531	**Suomi/ Finland** CNX Therapeutics Netherlands B.V. mailto:medinfo@cnx-therapeutics.com
Cyprus/Κύπρος Angelini Pharma Hellas Μονοπρόσωπη ABEE info@angelinipharma.gr	**Sweden/ Sverige** CNX Therapeutics Netherlands B.V. mailto:medinfo@cnx-therapeutics.com
Latvia/ Latvija CNX Therapeutics Netherlands B.V. mailto:medinfo@cnx-therapeutics.com	**Northern Ireland** CNX Therapeutics Netherlands B.V. mailto:medinfo@cnx-therapeutics.com

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Olanzapine

EMA

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ZYPREXA 2.5 mg coated tablets
ZYPREXA 5 mg coated tablets
ZYPREXA 7.5 mg coated tablets
ZYPREXA 10 mg coated tablets
ZYPREXA 15 mg coated tablets
ZYPREXA 20 mg coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZYPREXA 2.5 mg coated tablets

Each coated tablet contains 2.5 mg olanzapine.
Excipient with known effect: Each coated tablet contains 102 mg lactose monohydrate.

ZYPREXA 5 mg coated tablets

Each coated tablet contains 5 mg olanzapine.
Excipient with known effect: Each coated tablet contains 156 mg lactose monohydrate.

ZYPREXA 7.5 mg coated tablets

Each coated tablet contains 7.5 mg olanzapine.
Excipient with known effect: Each coated tablet contains 234 mg lactose monohydrate.

ZYPREXA 10 mg coated tablets

Each coated tablet contains 10 mg olanzapine.
Excipient with known effect: Each coated tablet contains 312 mg lactose monohydrate.

ZYPREXA 15 mg coated tablets

Each coated tablet contains 15 mg olanzapine.
Excipient with known effect: Each coated tablet contains 178 mg lactose monohydrate.

ZYPREXA 20 mg coated tablets

Each coated tablet contains 20 mg olanzapine.
Excipient with known effect: Each coated tablet conatins 238 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Coated tablet

ZYPREXA 2.5 mg coated tablets
Round, white, coated tablets imprinted with “LILLY” and a numeric identicode “4112”.

ZYPREXA 5 mg coated tablets
Round, white, coated tablets imprinted with “LILLY” and a numeric identicode “4115”.

ZYPREXA 7.5 mg coated tablets
Round, white, coated tablets imprinted with “LILLY” and a numeric identicode “4116”.

ZYPREXA 10 mg coated tablets
Round, white, coated tablets imprinted with “LILLY” and a numeric identicode “4117”.

ZYPREXA 15 mg coated tablets
Elliptical, blue, coated tablets debossed with “LILLY” and a numeric identicode “4415”.

ZYPREXA 20 mg coated tablets
Pink, elliptical, coated tablets debossed with “LILLY” and a numeric identicode, “4420”.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults
Olanzapine is indicated for the treatment of schizophrenia.

Olanzapine is effective in maintaining the clinical improvement during continuation therapy in patients who have shown an initial treatment response.

Olanzapine is indicated for the treatment of moderate to severe manic episode.

In patients whose manic episode has responded to olanzapine treatment, olanzapine is indicated for the prevention of recurrence in patients with bipolar disorder (see section 5.1).

4.2 Posology and method of administration

Adults
Schizophrenia: The recommended starting dose for olanzapine is 10 mg/day.

Manic episode: The starting dose is 15 mg as a single daily dose in monotherapy or 10 mg daily in combination therapy (see section 5.1).

Preventing recurrence in bipolar disorder: The recommended starting dose is 10 mg/day. For patients who have been receiving olanzapine for treatment of manic episode, continue therapy for preventing recurrence at the same dose. If a new manic, mixed, or depressive episode occurs, olanzapine treatment should be continued (with dose optimisation as needed), with supplementary therapy to treat mood symptoms, as clinically indicated.

During treatment for schizophrenia, manic episode and recurrence prevention in bipolar disorder, daily dosage may subsequently be adjusted on the basis of individual clinical status within the range 5-20 mg/day. An increase to a dose greater than the recommended starting dose is advised only after appropriate clinical reassessment and should generally occur at intervals of not less than 24 hours. Olanzapine can be given without regards for meals as absorption is not affected by food. Gradual tapering of the dose should be considered when discontinuing olanzapine.

Special populations

Elderly
A lower starting dose (5 mg/day) is not routinely indicated but should be considered for those 65 and over when clinical factors warrant (see section 4.4).

Renal and/or hepatic impairment
A lower starting dose (5 mg) should be considered for such patients. In cases of moderate hepatic insufficiency (cirrhosis, Child-Pugh Class A or B), the starting dose should be 5 mg and only increased with caution.

Smokers
The starting dose and dose range need not be routinely altered for non-smokers relative to smokers. The metabolism of olanzapine may be induced by smoking. Clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary (see section 4.5).

When more than one factor is present which might result in slower metabolism (female gender, geriatric age, non-smoking status), consideration should be given to decreasing the starting dose. Dose escalation, when indicated, should be conservative in such patients.

(See sections 4.5 and 5.2)

Paediatric population
Olanzapine is not recommended for use in children and adolescents below 18 years of age due to a lack of data on safety and efficacy. A greater magnitude of weight gain, lipid and prolactin alterations has been reported in short term studies of adolescent patients than in studies of adult patients (see sections 4.4, 4.8, 5.1 and 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Patients with known risk of narrow-angle glaucoma.

4.4 Special warnings and precautions for use

During antipsychotic treatment, improvement in the patient's clinical condition may take several days to some weeks. Patients should be closely monitored during this period.

Dementia-related psychosis and/or behavioural disturbances
Olanzapine is not recommended for use in patients with dementia-related psychosis and/or behavioural disturbances because of an increase in mortality and the risk of cerebrovascular accident. In placebo-controlled clinical trials (6-12 weeks duration) of elderly patients (mean age 78 years) with dementia-related psychosis and/or disturbed behaviours, there was a 2-fold increase in the incidence of death in olanzapine-treated patients compared to patients treated with placebo (3.5 % vs. 1.5 %, respectively). The higher incidence of death was not associated with olanzapine dose (mean daily dose 4.4 mg) or duration of treatment. Risk factors that may predispose this patient population to increased mortality include age > 65 years, dysphagia, sedation, malnutrition and dehydration, pulmonary conditions (e.g., pneumonia, with or without aspiration), or concomitant use of benzodiazepines. However, the incidence of death was higher in olanzapine-treated than in placebo-treated patients independent of these risk factors.

In the same clinical trials, cerebrovascular adverse events (CVAE e.g., stroke, transient ischemic attack), including fatalities, were reported. There was a 3-fold increase in CVAE in patients treated with olanzapine compared to patients treated with placebo (1.3 % vs. 0.4 %, respectively). All olanzapine- and placebo-treated patients who experienced a cerebrovascular event had pre-existing risk factors. Age > 75 years and vascular/mixed type dementia were identified as risk factors for CVAE in association with olanzapine treatment. The efficacy of olanzapine was not established in these trials.

Parkinson's disease
The use of olanzapine in the treatment of dopamine agonist associated psychosis in patients with Parkinson's disease is not recommended. In clinical trials, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo (see section 4.8), and olanzapine was not more effective than placebo in the treatment of psychotic symptoms. In these trials, patients were initially required to be stable on the lowest effective dose of anti-Parkinsonian medicinal products (dopamine agonist) and to remain on the same anti-Parkinsonian

medicinal products and dosages throughout the study. Olanzapine was started at 2.5 mg/day and titrated to a maximum of 15 mg/day based on investigator judgement.

Neuroleptic Malignant Syndrome (NMS)
NMS is a potentially life-threatening condition associated with antipsychotic medicinal products. Rare cases reported as NMS have also been received in association with olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicines, including olanzapine must be discontinued.

Hyperglycaemia and diabetes
Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported uncommonly, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines, e.g. measuring of blood glucose at baseline, 12 weeks after starting olanzapine treatment and annually thereafter. Patients treated with any antipsychotic medicines, including ZYPREXA, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly, e.g. at baseline, 4, 8 and 12 weeks after starting olanzapine treatment and quarterly thereafter.

Lipid alterations
Undesirable alterations in lipids have been observed in olanzapine-treated patients in placebo-controlled clinical trials (see section 4.8). Lipid alterations should be managed as clinically appropriate, particularly in dyslipidemic patients and in patients with risk factors for the development of lipids disorders. Patients treated with any antipsychotic medicines, including ZYPREXA, should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines, e.g. at baseline, 12 weeks after starting olanzapine treatment and every 5 years thereafter.

Anticholinergic activity
While olanzapine demonstrated anticholinergic activity *in vitro*, experience during the clinical trials revealed a low incidence of related events. However, as clinical experience with olanzapine in patients with concomitant illness is limited, caution is advised when prescribing for patients with prostatic hypertrophy, or paralytic ileus and related conditions.

Hepatic function
Transient, asymptomatic elevations of hepatic aminotransferases, ALT, AST have been seen commonly, especially in early treatment. Caution should be exercised and follow-up organised in patients with elevated ALT and/or AST, in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic medicines. In cases where hepatitis (including hepatocellular, cholestatic or mixed liver injury) has been diagnosed, olanzapine treatment should be discontinued.

Neutropenia
Caution should be exercised in patients with low leukocyte and/or neutrophil counts for any reason, in patients receiving medicines known to cause neutropenia, in patients with a history of drug-induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy and in patients with hypereosinophilic conditions or with myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly (see section 4.8).

Discontinuation of treatment
Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported rarely (≥ 0.01 % and < 0.1 %) when olanzapine is stopped abruptly.

QT interval
In clinical trials, clinically meaningful QTc prolongations (Fridericia QT correction [QTcF] ≥ 500 milliseconds [msec] at any time post baseline in patients with baseline QTcF < 500 msec) were uncommon (0.1 % to 1 %) in patients treated with olanzapine, with no significant differences in associated cardiac events compared to placebo. However, caution should be exercised when olanzapine is prescribed with medicines known to increase QTc interval, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.

Thromboembolism
Temporal association of olanzapine treatment and venous thromboembolism has been reported uncommonly (≥ 0.1 % and < 1 %). A causal relationship between the occurrence of venous thromboembolism and treatment with olanzapine has not been established. However, since patients with schizophrenia often present with acquired risk factors for venous thromboembolism all possible risk factors of VTE e.g. immobilisation of patients, should be identified and preventive measures undertaken.

General CNS activity
Given the primary CNS effects of olanzapine, caution should be used when it is taken in combination with other centrally acting medicines and alcohol. As it exhibits *in vitro* dopamine antagonism, olanzapine may antagonize the effects of direct and indirect dopamine agonists.

Seizures
Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur uncommonly in patients when treated with olanzapine. In most of these cases, a history of seizures or risk factors for seizures were reported.

Tardive Dyskinesia
In comparator studies of one year or less duration, olanzapine was associated with a statistically significant lower incidence of treatment emergent dyskinesia. However the risk of tardive dyskinesia increases with long term exposure, and therefore if signs or symptoms of tardive dyskinesia appear in a patient on olanzapine, a dose reduction or discontinuation should be considered. These symptoms can temporally deteriorate or even arise after discontinuation of treatment.

Postural hypotension
Postural hypotension was infrequently observed in the elderly in olanzapine clinical trials. It is recommended that blood pressure is measured periodically in patients over 65 years.

Sudden cardiac death
In postmarketing reports with olanzapine, the event of sudden cardiac death has been reported in patients with olanzapine. In a retrospective observational cohort study, the risk of presumed sudden cardiac death in patients treated with olanzapine was approximately twice the risk in patients not using antipsychotics. In the study, the risk of olanzapine was comparable to the risk of atypical antipsychotics included in a pooled analysis.

Paediatric population
Olanzapine is not indicated for use in the treatment of children and adolescents. Studies in patients aged 13-17 years showed various adverse reactions, including weight gain, changes in metabolic parameters and increases in prolactin levels (see sections 4.8 and 5.1).

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

Potential interactions affecting olanzapine
Since olanzapine is metabolised by CYP1A2, substances that can specifically induce or inhibit this isoenzyme may affect the pharmacokinetics of olanzapine.

Induction of CYP1A2
The metabolism of olanzapine may be induced by smoking and carbamazepine, which may lead to reduced olanzapine concentrations. Only slight to moderate increase in olanzapine clearance has been observed. The clinical consequences are likely to be limited, but clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary (see section 4.2).

Inhibition of CYP1A2
Fluvoxamine, a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of olanzapine. The mean increase in olanzapine C_{max} following fluvoxamine was 54 % in female non-smokers and 77 % in male smokers. The mean increase in olanzapine AUC was 52 % and 108 % respectively. A lower starting dose of olanzapine should be considered in patients who are using fluvoxamine or any other CYP1A2 inhibitors, such as ciprofloxacin. A decrease in the dose of olanzapine should be considered if treatment with an inhibitor of CYP1A2 is initiated.

Decreased bioavailability
Activated charcoal reduces the bioavailability of oral olanzapine by 50 to 60 % and should be taken at least 2 hours before or after olanzapine.

Fluoxetine (a CYP2D6 inhibitor), single doses of antacid (aluminium, magnesium) or cimetidine have not been found to significantly affect the pharmacokinetics of olanzapine.

Potential for olanzapine to affect other medicinal products
Olanzapine may antagonise the effects of direct and indirect dopamine agonists.

Olanzapine does not inhibit the main CYP450 isoenzymes *in vitro* (e.g. 1A2, 2D6, 2C9, 2C19, 3A4). Thus no particular interaction is expected as verified through *in vivo* studies where no inhibition of metabolism of the following active substances was found: tricyclic antidepressant (representing mostly CYP2D6 pathway), warfarin (CYP2C9), theophylline (CYP1A2) or diazepam (CYP3A4 and 2C19).

Olanzapine showed no interaction when co-administered with lithium or biperiden.

Therapeutic monitoring of valproate plasma levels did not indicate that valproate dosage adjustment is required after the introduction of concomitant olanzapine.

General CNS activity
Caution should be exercised in patients who consume alcohol or receive medicinal products that can cause central nervous system depression.

The concomitant use of olanzapine with anti-Parkinsonian medicinal products in patients with Parkinson's disease and dementia is not recommended (see section 4.4).

QTc interval
Caution should be used if olanzapine is being administered concomitantly with medicinal products known to increase QTc interval (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate and well-controlled studies in pregnant women. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with olanzapine. Nevertheless, because human experience is limited, olanzapine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

New born infants exposed to antipsychotics (including olanzapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Breast-feeding
In a study in breast-feeding, healthy women, olanzapine was excreted in breast milk. Mean infant exposure (mg/kg) at steady state was estimated to be 1.8 % of the maternal olanzapine dose (mg/kg). Patients should be advised not to breast feed an infant if they are taking olanzapine.

Fertility
Effects on fertility are unknown (see section 5.3 for preclinical information).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Because olanzapine may cause somnolence and dizziness, patients should be cautioned about operating machinery, including motor vehicles.

4.8 Undesirable effects

Summary of the safety profile

Adults
The most frequently (seen in ≥ 1 % of patients) reported adverse reactions associated with the use of olanzapine in clinical trials were somnolence, weight gain, eosinophilia, elevated prolactin, cholesterol, glucose and triglyceride levels (see section 4.4), glucosuria, increased appetite, dizziness, akathisia, parkinsonism, leukopenia, neutropenia (see section 4.4), dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic aminotransferases (see section 4.4), rash, asthenia, fatigue, pyrexia, arthralgia, increased alkaline phosphatase, high gamma glutamyltransferase, high uric acid, high creatine phosphokinase and oedema.

Tabulated list of adverse reactions
The following table lists the adverse reactions and laboratory investigations observed from spontaneous reporting and in clinical trials. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the data available).

Very common	**Common**	**Uncommon**	**Rare**	**Not known**
Blood and the lymphatic system disorders				
	Eosinophilia Leukopenia[10] Neutropenia[10]		Thrombocytopenia[11]	
Immune system disorders				
		Hypersensitivity[11]		

Metabolism and nutrition disorders				
Weight gain[1]	Elevated cholesterol levels[2,3] Elevated glucose levels[4] Elevated triglyceride levels[2,5] Glucosuria Increased appetite	Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases (see section 4.4) [11]	Hypothermia[12]	
Nervous system disorders				
Somnolence	Dizziness Akathisia[6] Parkinsonism[6] Dyskinesia[6]	Seizures where in most cases a history of seizures or risk factors for seizures were reported [11] Dystonia (including oculogyration) [11] Tardive dyskinesia[11] Amnesia [9] Dysarthria Stuttering[11] Restless Legs Syndrome[11]	Neuroleptic malignant syndrome (see section 4.4)[12] Discontinuation symptoms[7, 12]	
Cardiac disorders				
		Bradycardia QT_c prolongation (see section 4.4)	Ventricular tachycardia/fibrillation, sudden death (see section 4.4)[11]	
Vascular disorders				
Orthostatic hypotension[10]		Thromboembolism (including pulmonary embolism and deep vein thrombosis) (see section 4.4)		
Respiratory, thoracic and mediastinal disorders				
		Epistaxis[9]		
Gastrointestinal disorders				
	Mild, transient anticholinergic effects including constipation and dry mouth	Abdominal distension[9] Salivary hypersecretion[11]	Pancreatitis[11]	
Hepatobiliary disorders				
	Transient, asymptomatic elevations of hepatic aminotransferases (ALT, AST), especially in early treatment (see section 4.4)		Hepatitis (including hepatocellular, cholestatic or mixed liver injury) [11]	

Skin and subcutaneous tissue disorders				
	Rash	Photosensitivity reaction Alopecia		
				Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders				
	Arthralgia[9]		Rhabdomyolysis[11]	
Renal and urinary disorders				
		Urinary incontinence, urinary retention Urinary hesitation[11]		
Pregnancy, puerperium and perinatal conditions				
				Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders				
	Erectile dysfunction in males Decreased libido in males and females	Amenorrhea Breast enlargement Galactorrhea in females Gynaecomastia/breast enlargement in males	Priapism[12]	
General disorders and administration site conditions				
	Asthenia Fatigue Oedema Pyrexia[10]			
Investigations				
Elevated plasma prolactin levels[8]	Increased alkaline phosphatase[10] High creatine phosphokinase[11] High Gamma Glutamyltransferase[10] High uric acid [10]	Increased total bilirubin		

[1] Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Following short term treatment (median duration 47 days), weight gain ≥ 7 % of baseline body weight was very common (22.2 %), ≥ 15 % was common (4.2 %) and ≥ 25 % was uncommon (0.8 %). Patients gaining ≥ 7 %, ≥ 15 % and ≥ 25 % of their baseline body weight with long-term exposure (at least 48 weeks) were very common (64.4 %, 31.7 % and 12.3 % respectively).

[2] Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline.

[3] Observed for fasting normal levels at baseline (< 5.17 mmol/l) which increased to high (≥ 6.2 mmol/l). Changes in total fasting cholesterol levels from borderline at baseline (≥ 5.17 - < 6.2 mmol/l) to high (≥ 6.2 mmol/l) were very common.

[4] Observed for fasting normal levels at baseline (< 5.56 mmol/l) which increased to high (≥ 7 mmol/l). Changes in fasting glucose from borderline at baseline (≥ 5.56 - < 7 mmol/l) to high (≥ 7 mmol/l) were very common.

[5] Observed for fasting normal levels at baseline (< 1.69 mmol/l) which increased to high (≥ 2.26 mmol/l). Changes in fasting triglycerides from borderline at baseline (≥ 1.69 mmol/l - < 2.26 mmol/l) to high (≥ 2.26 mmol/l) were very common.

[6] In clinical trials, the incidence of Parkinsonism and dystonia in olanzapine-treated patients was numerically higher, but not statistically significantly different from placebo. Olanzapine-treated patients had a lower incidence of Parkinsonism, akathisia and dystonia compared with titrated doses of haloperidol. In the absence of detailed information on the pre-existing history of individual acute and tardive extrapyramidal movement disorders, it cannot be concluded at present that olanzapine produces less tardive dyskinesia and/or other tardive extrapyramidal syndromes.

[7] Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea and vomiting have been reported when olanzapine is stopped abruptly.

[8] In clinical trials of up to 12 weeks, plasma prolactin concentrations exceeded the upper limit of normal range in approximately 30 % of olanzapine treated patients with normal baseline prolactin value. In the majority of these patients the elevations were generally mild, and remained below two times the upper limit of normal range.

[9] Adverse event identified from clinical trials in the Olanzapine Integrated Database.

[10] As assessed by measured values from clinical trials in the Olanzapine Integrated Database.

[11] Adverse event identified from spontaneous post-marketing reporting with frequency determined utilising the Olanzapine Integrated Database.

[12] Adverse event identified from spontaneous post-marketing reporting with frequency estimated at the upper limit of the 95 % confidence interval utilising the Olanzapine Integrated Database.

Long-term exposure (at least 48 weeks)
The proportion of patients who had adverse, clinically significant changes in weight gain, glucose, total/LDL/HDL cholesterol or triglycerides increased over time. In adult patients who completed 9-12 months of therapy, the rate of increase in mean blood glucose slowed after approximately 6 months.

Additional information on special populations
In clinical trials in elderly patients with dementia, olanzapine treatment was associated with a higher incidence of death and cerebrovascular adverse reactions compared to placebo (see section 4.4). Very common adverse reactions associated with the use of olanzapine in this patient group were abnormal gait and falls. Pneumonia, increased body temperature, lethargy, erythema, visual hallucinations and urinary incontinence were observed commonly.

In clinical trials in patients with drug-induced (dopamine agonist) psychosis associated with Parkinson's disease, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo.

In one clinical trial in patients with bipolar mania, valproate combination therapy with olanzapine resulted in an incidence of neutropenia of 4.1 %; a potential contributing factor could be high plasma valproate levels. Olanzapine administered with lithium or valproate resulted in increased levels (≥ 10 %) of tremor, dry mouth, increased appetite, and weight gain. Speech disorder was also reported commonly. During treatment with olanzapine in combination with lithium or divalproex, an increase of ≥ 7 % from baseline body weight occurred in 17.4 % of patients during acute treatment (up to

6 weeks). Long-term olanzapine treatment (up to 12 months) for recurrence prevention in patients with bipolar disorder was associated with an increase of ≥ 7 % from baseline body weight in 39.9 % of patients.

Paediatric population
Olanzapine is not indicated for the treatment of children and adolescent patients below 18 years. Although no clinical studies designed to compare adolescents to adults have been conducted, data from the adolescent trials were compared to those of the adult trials.

The following table summarises the adverse reactions reported with a greater frequency in adolescent patients (aged 13-17 years) than in adult patients or adverse reactions only identified during short-term clinical trials in adolescent patients. Clinically significant weight gain (≥ 7 %) appears to occur more frequently in the adolescent population compared to adults with comparable exposures. The magnitude of weight gain and the proportion of adolescent patients who had clinically significant weight gain were greater with long-term exposure (at least 24 weeks) than with short-term exposure.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows: Very common (≥ 1/10), common (≥ 1/100 to < 1/10).

Metabolism and nutrition disorders *Very common:* Weight gain[13], elevated triglyceride levels[14], increased appetite. *Common:* Elevated cholesterol levels[15]
Nervous system disorders *Very common:* Sedation (including: hypersomnia, lethargy, somnolence).
Gastrointestinal disorders *Common:* Dry mouth
Hepatobiliary disorders *Very common:* Elevations of hepatic aminotransferases (ALT/AST; see section 4.4).
Investigations *Very common:* Decreased total bilirubin, increased GGT, elevated plasma prolactin levels[16].

[13] Following short term treatment (median duration 22 days), weight gain ≥ 7 % of baseline body weight (kg) was very common (40.6 %), ≥ 15 % of baseline body weight was common (7.1 %) and ≥ 25 % was common (2.5 %). With long-term exposure (at least 24 weeks), 89.4 % gained ≥ 7 %, 55.3 % gained ≥ 15 % and 29.1 % gained ≥ 25 % of their baseline body weight.

[14] Observed for fasting normal levels at baseline (< 1.016 mmol/l) which increased to high (≥ 1.467 mmol/l) and changes in fasting triglycerides from borderline at baseline (≥ 1.016 mmol/l - < 1.467 mmol/l) to high (≥ 1.467 mmol/l).

[15] Changes in total fasting cholesterol levels from normal at baseline (< 4.39 mmol/l) to high (≥ 5.17 mmol/l) were observed commonly. Changes in total fasting cholesterol levels from borderline at baseline (≥ 4.39 - < 5.17 mmol/l) to high (≥ 5.17 mmol/l) were very common.

[16] Elevated plasma prolactin levels were reported in 47.4 % of adolescent patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Signs and symptoms
Very common symptoms in overdose (> 10 % incidence) include tachycardia, agitation/aggressiveness, dysarthria, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma.

Other medically significant sequelae of overdose include delirium, convulsion, coma, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (< 2 % of overdose cases) and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg but survival has also been reported following acute overdose of approximately 2 g of oral olanzapine.

Management
There is no specific antidote for olanzapine. Induction of emesis is not recommended. Standard procedures for management of overdose may be indicated (i.e. gastric lavage, administration of activated charcoal). The concomitant administration of activated charcoal was shown to reduce the oral bioavailability of olanzapine by 50 to 60 %.

Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation, including treatment of hypotension and circulatory collapse and support of respiratory function. Do not use epinephrine, dopamine, or other sympathomimetic agents with beta-agonist activity since beta stimulation may worsen hypotension. Cardiovascular monitoring is necessary to detect possible arrhythmias. Close medical supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics, diazepines, oxazepines, thiazepines and oxepines, ATC code N05A H03.

Pharmacodynamic effects
Olanzapine is an antipsychotic, antimanic and mood stabilising agent that demonstrates a broad pharmacologic profile across a number of receptor systems.

In preclinical studies, olanzapine exhibited a range of receptor affinities (K_i < 100 nM) for serotonin 5 $HT_{2A/2C}$, 5 HT_3, 5 HT_6; dopamine D_1, D_2, D_3, D_4, D_5; cholinergic muscarinic receptors M_1-M_5; α_1 adrenergic; and histamine H_1 receptors. Animal behavioural studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater *in vitro* affinity for serotonin $5HT_2$ than dopamine D_2 receptors and greater 5 HT_2 than D_2 activity *in vivo* models. Electrophysiological studies demonstrated that olanzapine selectively reduced the firing of mesolimbic (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other antipsychotic agents, olanzapine increases responding in an “anxiolytic” test.

In a single oral dose (10 mg) Positron Emission Tomography (PET) study in healthy volunteers, olanzapine produced a higher 5 HT_{2A} than dopamine D_2 receptor occupancy. In addition, a Single Photon Emission Computed Tomography (SPECT) imaging study in schizophrenic patients revealed that olanzapine-responsive patients had lower striatal D_2 occupancy than some other antipsychotic- and risperidone-responsive patients, while being comparable to clozapine-responsive patients.

Clinical efficacy
In two of two placebo and two of three comparator controlled trials with over 2,900 schizophrenic patients presenting with both positive and negative symptoms, olanzapine was associated with statistically significantly greater improvements in negative as well as positive symptoms.

In a multinational, double-blind, comparative study of schizophrenia, schizoaffective, and related disorders which included 1,481 patients with varying degrees of associated depressive symptoms (baseline mean of 16.6 on the Montgomery-Asberg Depression Rating Scale), a prospective secondary analysis of baseline to endpoint mood score change demonstrated a statistically significant improvement ($p = 0.001$) favouring olanzapine (-6.0) versus haloperidol (-3.1).

In patients with a manic or mixed episode of bipolar disorder, olanzapine demonstrated superior efficacy to placebo and valproate semisodium (divalproex) in reduction of manic symptoms over 3 weeks. Olanzapine also demonstrated comparable efficacy results to haloperidol in terms of the proportion of patients in symptomatic remission from mania and depression at 6 and 12 weeks. In a co-therapy study of patients treated with lithium or valproate for a minimum of 2 weeks, the addition of olanzapine 10 mg (co-therapy with lithium or valproate) resulted in a greater reduction in symptoms of mania than lithium or valproate monotherapy after 6 weeks.

In a 12 month recurrence prevention study in manic episode patients who achieved remission on olanzapine and were then randomised to olanzapine or placebo, olanzapine demonstrated statistically significant superiority over placebo on the primary endpoint of bipolar recurrence. Olanzapine also showed a statistically significant advantage over placebo in terms of preventing either recurrence into mania or recurrence into depression.

In a second 12 month recurrence prevention study in manic episode patients who achieved remission with a combination of olanzapine and lithium and were then randomised to olanzapine or lithium alone, olanzapine was statistically non-inferior to lithium on the primary endpoint of bipolar recurrence (olanzapine 30.0 %, lithium 38.3 %; $p = 0.055$).

In an 18 month co-therapy study in manic or mixed episode patients stabilised with olanzapine plus a mood stabiliser (lithium or valproate), long-term olanzapine co-therapy with lithium or valproate was not statistically significantly superior to lithium or valproate alone in delaying bipolar recurrence, defined according to syndromic (diagnostic) criteria.

Paediatric population
Controlled efficacy data in adolescents (ages 13 to 17 years) are limited to short term studies in schizophrenia (6 weeks) and mania associated with bipolar I disorder (3 weeks), involving less than 200 adolescents. Olanzapine was used as a flexible dose starting with 2.5 and ranging up to 20 mg/day. During treatment with olanzapine, adolescents gained significantly more weight compared with adults. The magnitude of changes in fasting total cholesterol, LDL cholesterol, triglycerides, and prolactin (see sections 4.4 and 4.8) were greater in adolescents than in adults. There are no controlled data on maintenance of effect or long term safety (see sections 4.4 and 4.8). Information on long term safety is primarily limited to open-label, uncontrolled data.

5.2 Pharmacokinetic properties

Absorption
Olanzapine is well absorbed after oral administration, reaching peak plasma concentrations within 5 to 8 hours. The absorption is not affected by food. Absolute oral bioavailability relative to intravenous administration has not been determined.

Distribution
The plasma protein binding of olanzapine was about 93 % over the concentration range of about 7 to about 1000 ng/ml. Olanzapine is bound predominantly to albumin and α_1-acid-glycoprotein.

Biotransformation
Olanzapine is metabolized in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which does not pass the blood brain barrier. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites, both exhibited significantly less *in vivo* pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent olanzapine.

Elimination
After oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender.

In healthy elderly (65 and over) versus non-elderly subjects, the mean elimination half-life was prolonged (51.8 versus 33.8 hr) and the clearance was reduced (17.5 versus 18.2 l/hr). The pharmacokinetic variability observed in the elderly is within the range for the non-elderly. In 44 patients with schizophrenia > 65 years of age, dosing from 5 to 20 mg/day was not associated with any distinguishing profile of adverse events.

In female versus male subjects the mean elimination half life was somewhat prolonged (36.7 versus 32.3 hr) and the clearance was reduced (18.9 versus 27.3 l/hr). However, olanzapine (5-20 mg) demonstrated a comparable safety profile in female (n = 467) as in male patients (n = 869).

Renal impairment
In renally impaired patients (creatinine clearance < 10 ml/min) versus healthy subjects, there was no significant difference in mean elimination half-life (37.7 versus 32.4 hr) or clearance (21.2 versus 25.0 l/hr). A mass balance study showed that approximately 57 % of radiolabelled olanzapine appeared in urine, principally as metabolites.

Hepatic impairment
A small study of the effect of impaired liver function in 6 subjects with clinically significant (Childs Pugh Classification A (n = 5) and B (n = 1)) cirrhosis revealed little effect on the pharmacokinetics of orally administered olanzapine (2.5 – 7.5 mg single dose): Subjects with mild to moderate hepatic dysfunction had slightly increased systemic clearance and faster elimination half-time compared to subjects with no hepatic dysfunction (n = 3). There were more smokers among subjects with cirrhosis (4/6; 67 %) than among subjects with no hepatic dysfunction (0/3; 0 %).
Smoking
In non-smoking versus smoking subjects (males and females) the mean elimination half-life was prolonged (38.6 versus 30.4 hr) and the clearance was reduced (18.6 versus 27.7 l/hr).

The plasma clearance of olanzapine is lower in elderly versus young subjects, in females versus males, and in non-smokers versus smokers. However, the magnitude of the impact of age, gender, or smoking on olanzapine clearance and half-life is small in comparison to the overall variability between individuals.

In a study of Caucasians, Japanese, and Chinese subjects, there were no differences in the pharmacokinetic parameters among the three populations.

Paediatric population
Adolescents (ages 13 to 17 years): The pharmacokinetics of olanzapine are similar between adolescents and adults. In clinical studies, the average olanzapine exposure was approximately 27 % higher in adolescents. Demographic differences between the adolescents and adults include a lower average body weight and fewer adolescents were smokers. Such factors possibly contribute to the higher average exposure observed in adolescents.

5.3 Preclinical safety data

Acute (single-dose) toxicity
Signs of oral toxicity in rodents were characteristic of potent neuroleptic compounds: hypoactivity, coma, tremors, clonic convulsions, salivation, and depressed weight gain. The median lethal doses were approximately 210 mg/kg (mice) and 175 mg/kg (rats). Dogs tolerated single oral doses up to 100 mg/kg without mortality. Clinical signs included sedation, ataxia, tremors, increased heart rate, labored respiration, miosis, and anorexia. In monkeys, single oral doses up to 100 mg/kg resulted in prostration and, at higher doses, semi-consciousness.

Repeated-dose toxicity
In studies up to 3 months duration in mice and up to 1 year in rats and dogs, the predominant effects were CNS depression, anticholinergic effects, and peripheral haematological disorders. Tolerance developed to the CNS depression. Growth parameters were decreased at high doses. Reversible effects consistent with elevated prolactin in rats included decreased weights of ovaries and uterus and morphologic changes in vaginal epithelium and in mammary gland.

Haematologic toxicity
Effects on haematology parameters were found in each species, including dose-related reductions in circulating leukocytes in mice and non-specific reductions of circulating leukocytes in rats; however, no evidence of bone marrow cytotoxicity was found. Reversible neutropenia, thrombocytopenia, or anaemia developed in a few dogs treated with 8 or 10 mg/kg/day (total olanzapine exposure [AUC] is 12- to 15-fold greater than that of a man given a 12-mg dose). In cytopenic dogs, there were no adverse effects on progenitor and proliferating cells in the bone marrow.

Reproductive toxicity
Olanzapine had no teratogenic effects. Sedation affected mating performance of male rats. Estrous cycles were affected at doses of 1.1 mg/kg (3 times the maximum human dose) and reproduction parameters were influenced in rats given 3 mg/kg (9 times the maximum human dose). In the offspring of rats given olanzapine, delays in foetal development and transient decreases in offspring activity levels were seen.

Mutagenicity
Olanzapine was not mutagenic or clastogenic in a full range of standard tests, which included bacterial mutation tests and *in vitro* and *in vivo* mammalian tests.

Carcinogenicity
Based on the results of studies in mice and rats, it was concluded that olanzapine is not carcinogenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Hyprolose
Crospovidone
Microcrystalline cellulose
Magnesium stearate

Tablet coat

ZYPREXA 2.5 mg , 5 mg, 7.5 mg and 10 mg coated tablets
Hypromellose
Colour mixture white (hypromellose, titanium dioxide E171, macrogol, polysorbate 80)

Carnauba wax
Edible blue ink (shellac, ethanol anhydrous, isopropyl alcohol, butyl alcohol, propylene glycol, ammonium hydroxide, indigo carmine E132)

ZYPREXA 15 mg coated tablets
Hypromellose
Colour mixture light blue (titanium dioxide E171, lactose monohydrate, hypromellose, triacetin, indigo carmine colour (E132))
Carnauba wax

ZYPREXA 20 mg coated tablets
Hypromellose
Colour mixture pink (titanium dioxide E171, macrogol, lactose monohydrate, hypromellose, synthetic red iron oxide)
Carnauba wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

ZYPREXA 2.5 mg coated tablets
2 years.

ZYPREXA 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg coated tablets
3 years.

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Cold-formed aluminium blister strips in cartons of 28, 35, 56, 70 or 98 tablets per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

CHEPLAPHARM Registration GmbH, Weiler Straße 5e, 79540 Lörrach, Germany.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/022/002 - ZYPREXA - 2.5 mg - coated tablets - 28 tablets, per box.
EU/1/96/022/019 - ZYPREXA - 2.5 mg - coated tablets - 56 tablets, per box.
EU/1/96/022/023 - ZYPREXA - 2.5 mg - coated tablets - 35 tablets, per box.
EU/1/96/022/029 - ZYPREXA - 2.5 mg - coated tablets - 70 tablets, per box.
EU/1/96/022/035 - ZYPREXA - 2.5 mg - coated tablets - 98 tablets, per box.
EU/1/96/022/004 - ZYPREXA - 5 mg - coated tablets - 28 tablets, per box.
EU/1/96/022/020 - ZYPREXA - 5 mg - coated tablets - 56 tablets, per box.

EU/1/96/022/024 - ZYPREXA - 5 mg - coated tablets - 35 tablets, per box.
EU/1/96/022/030 - ZYPREXA - 5 mg - coated tablets - 70 tablets, per box.
EU/1/96/022/036 - ZYPREXA - 5 mg - coated tablets - 98 tablets, per box.
EU/1/96/022/011 - ZYPREXA - 7.5 mg - coated tablets - 28 tablets, per box.
EU/1/96/022/006 - ZYPREXA - 7.5 mg - coated tablets - 56 tablets, per box.
EU/1/96/022/025 - ZYPREXA – 7.5 mg - coated tablets - 35 tablets, per box.
EU/1/96/022/031 - ZYPREXA – 7.5 mg - coated tablets - 70 tablets, per box.
EU/1/96/022/037 - ZYPREXA - 7.5 mg - coated tablets - 98 tablets, per box.
EU/1/96/022/009 - ZYPREXA - 10 mg - coated tablets - 28 tablets, per box.
EU/1/96/022/010 - ZYPREXA - 10 mg - coated tablets - 56 tablets, per box.
EU/1/96/022/026 - ZYPREXA - 10 mg - coated tablets - 35 tablets, per box.
EU/1/96/022/032 - ZYPREXA - 10 mg - coated tablets - 70 tablets, per box.
EU/1/96/022/038 - ZYPREXA - 10 mg - coated tablets - 98 tablets, per box.
EU/1/96/022/012 - ZYPREXA - 15 mg - coated tablets - 28 tablets, per box.
EU/1/96/022/021 - ZYPREXA - 15 mg - coated tablets - 56 tablets, per box.
EU/1/96/022/027 - ZYPREXA - 15 mg - coated tablets - 35 tablets, per box.
EU/1/96/022/033 - ZYPREXA - 15 mg - coated tablets - 70 tablets, per box.
EU/1/96/022/039 - ZYPREXA - 15 mg - coated tablets - 98 tablets, per box.
EU/1/96/022/014 - ZYPREXA - 20 mg - coated tablets - 28 tablets, per box.
EU/1/96/022/022 - ZYPREXA - 20 mg - coated tablets - 56 tablets, per box.
EU/1/96/022/028 - ZYPREXA - 20 mg - coated tablets - 35 tablets, per box.
EU/1/96/022/034 - ZYPREXA - 20 mg - coated tablets - 70 tablets, per box.
EU/1/96/022/040 - ZYPREXA - 20 mg - coated tablets - 98 tablets, per box.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 September 1996
Date of latest renewal: 12 September 2006

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

1. NAME OF THE MEDICINAL PRODUCT

ZYPREXA 10 mg powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 10 mg olanzapine. After reconstitution each ml of the solution contains 5 mg olanzapine.

Excipient with known effect: Each vial contains 50 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection
Yellow lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults
ZYPREXA powder for solution for injection is indicated for the rapid control of agitation and disturbed behaviours in patients with schizophrenia or manic episode, when oral therapy is not appropriate. Treatment with ZYPREXA powder for solution for injection should be discontinued and the use of oral olanzapine should be initiated as soon as clinically appropriate.

4.2 Posology and method of administration

Adults
For intramuscular use. Do not administer intravenously or subcutaneously. ZYPREXA powder for solution for injection is intended for short term use only, for up to a maximum of three consecutive days.

The maximum daily dose of olanzapine (including all formulations of olanzapine) is 20 mg.

The recommended initial dose for olanzapine injection is 10 mg, administered as a single intramuscular injection. A lower dose (5 mg or 7.5 mg) may be given, on the basis of individual clinical status, which should also include consideration of medicinal products already administered either for maintenance or acute treatment (see section 4.4). A second injection, 5-10 mg, may be administered 2 hours after the first injection on the basis of individual clinical status. Not more than three injections should be given in any 24 hour period and the maximum daily dose of olanzapine of 20 mg (including all formulations) should not be exceeded.

ZYPREXA powder for solution for injection should be reconstituted in accordance with the recommendation in section 6.6.

For further information on continued treatment with oral olanzapine (5 to 20 mg daily), see the Summary of Product Characteristics for ZYPREXA coated tablets or ZYPREXA VELOTAB orodispersible tablets.

Special populations

Elderly
The recommended starting dose in elderly patients (> 60 years) is 2.5 - 5 mg. Depending on the patient's clinical status (see section 4.4), a second injection, 2.5 - 5 mg, may be administered 2 hours after the first injection. Not more than 3 injections should be given in any 24 hour period and the maximum daily dose of 20 mg (including all formulations) of olanzapine should not be exceeded.

Renal and/or hepatic impairment
A lower starting dose (5 mg) should be considered for such patients. In cases of moderate hepatic insufficiency (cirrhosis, Child-Pugh Class A or B), the starting dose should be 5 mg and only increased with caution.

Smokers
The dose and dose range need not be routinely altered for non-smokers relative to smokers. The metabolism of olanzapine may be induced by smoking. Clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary (see section 4.5).

When more than one factor is present which might result in slower metabolism (female gender, geriatric age, non-smoking status), consideration should be given to decreasing the dose. Additional injections, when indicated, should be conservative in such patients.

(See sections 4.5 and 5.2)

Paediatric population
There is no experience in children. ZYPREXA powder for solution for injection is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Patients with known risk of narrow-angle glaucoma.

4.4 Special warnings and precautions for use

The efficacy of IM olanzapine has not been established in patients with agitation and disturbed behaviours related to conditions other than schizophrenia or manic episode.

Unstable medical conditions
IM olanzapine should not be administered to patients with unstable medical conditions, such as acute myocardial infarction, unstable angina pectoris, severe hypotension and/or bradycardia, sick sinus syndrome, or following heart surgery. If the patient’s medical history with regard to these unstable medical conditions cannot be determined, the risks and benefits of IM olanzapine should be considered in relation to other alternative treatments.

Concomitant use of benzodiazepines and other medicinal products
Special caution is necessary in patients who have received treatment with other medicinal products having haemodynamic properties similar to those of intramuscular olanzapine including other antipsychotics (oral and/or intramuscular) and benzodiazepines (see section 4.5). Temporal association of treatment with IM olanzapine with hypotension, bradycardia, respiratory depression and death has been very rarely (< 0.01 %) reported particularly in patients who have received benzodiazepines and/or other antipsychotics (see section 4.8).

Simultaneous injection of intramuscular olanzapine and parenteral benzodiazepine is not recommended due to the potential for excessive sedation, cardiorespiratory depression and in very rare cases, death (see sections 4.5 and 6.2). If the patient is considered to need parenteral benzodiazepine treatment, this should not be given until at least one hour after IM olanzapine administration. If the

patient has received parenteral benzodiazepine, IM olanzapine administration should only be considered after careful evaluation of clinical status and the patient should be closely monitored for excessive sedation and cardiorespiratory depression.

Hypotension
It is extremely important that patients receiving intramuscular olanzapine should be closely observed for hypotension including postural hypotension, bradyarrhythmia and/or hypoventilation, particularly for the first 4 hours following injection and close observation should be continued after this period if clinically indicated. Blood pressure, pulse, respiratory rate and level of consciousness should be observed regularly and remedial treatment provided if required. Patients should remain recumbent if dizzy or drowsy after injection until examination indicates that they are not experiencing hypotension including postural hypotension, bradyarrhythmia and/or hypoventilation.

The safety and efficacy of IM olanzapine has not been evaluated in patients with alcohol or drug intoxication (either with prescribed or illicit drugs) (see section 4.5).

Dementia-related psychosis and/or behavioural disturbances
Olanzapine is not recommended for use in patients with dementia-related psychosis and/or behavioural disturbances because of an increase in mortality and the risk of cerebrovascular accident. In placebo-controlled clinical trials (6-12 weeks duration) of elderly patients (mean age 78 years) with dementia-related psychosis and/or disturbed behaviours, there was a 2-fold increase in the incidence of death in olanzapine-treated patients compared to patients treated with placebo (3.5 % vs. 1.5 %, respectively). The higher incidence of death was not associated with olanzapine dose (mean daily dose 4.4 mg) or duration of treatment. Risk factors that may predispose this patient population to increased mortality include age > 65 years, dysphagia, sedation, malnutrition and dehydration, pulmonary conditions (e.g., pneumonia, with or without aspiration), or concomitant use of benzodiazepines. However, the incidence of death was higher in olanzapine-treated than in placebo-treated patients independent of these risk factors.

In the same clinical trials, cerebrovascular adverse events (CVAE e.g., stroke, transient ischemic attack), including fatalities, were reported. There was a 3-fold increase in CVAE in patients treated with olanzapine compared to patients treated with placebo (1.3% vs. 0.4%, respectively). All olanzapine- and placebo-treated patients who experienced a cerebrovascular event had pre-existing risk factors. Age > 75 years and vascular/mixed type dementia were identified as risk factors for CVAE in association with olanzapine treatment. The efficacy of olanzapine was not established in these trials.

Parkinson's disease
The use of olanzapine in the treatment of dopamine agonist associated psychosis in patients with Parkinson's disease is not recommended. In clinical trials, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo (see section 4.8), and olanzapine was not more effective than placebo in the treatment of psychotic symptoms. In these trials, patients were initially required to be stable on the lowest effective dose of anti-Parkinsonian medicinal products (dopamine agonist) and to remain on the same anti-Parkinsonian medicinal products and dosages throughout the study. Olanzapine was started at 2.5 mg/day and titrated to a maximum of 15 mg/day based on investigator judgement.

Neuroleptic Malignant Syndrome (NMS)
NMS is a potentially life-threatening condition associated with antipsychotic medicinal products. Rare cases reported as NMS have also been received in association with olanzapine. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicines, including olanzapine must be discontinued.

Hyperglycaemia and diabetes
Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported uncommonly, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines, e.g. measuring of blood glucose at baseline, 12 weeks after starting olanzapine treatment and annually thereafter. Patients treated with any antipsychotic medicines, including ZYPREXA, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly, e.g. at baseline, 4, 8 and 12 weeks after starting olanzapine treatment and quarterly thereafter.

Lipid alterations
Undesirable alterations in lipids have been observed in olanzapine-treated patients in placebo-controlled clinical trials (see section 4.8). Lipid alterations should be managed as clinically appropriate, particularly in dyslipidemic patients and in patients with risk factors for the development of lipids disorders. Patients treated with any antipsychotic medicines, including ZYPREXA, should be monitored regularly for lipids in accordance with utilised antipsychotic guidelines, e.g. at baseline, 12 weeks after starting olanzapine treatment and every 5 years thereafter.

Anticholinergic activity
While olanzapine demonstrated anticholinergic activity *in vitr*o, experience during oral clinical trials revealed a low incidence of related events. However, as clinical experience with olanzapine in patients with concomitant illness is limited, caution is advised when prescribing for patients with prostatic hypertrophy, or paralytic ileus and related conditions.

Hepatic function
Transient, asymptomatic elevations of hepatic aminotransferases, ALT, AST have been seen commonly, especially in early treatment. Caution should be exercised and follow-up organised in patients with elevated ALT and/or AST, in patients with signs and symptoms of hepatic impairment, in patients with pre-existing conditions associated with limited hepatic functional reserve, and in patients who are being treated with potentially hepatotoxic medicines. In cases where hepatitis (including hepatocellular, cholestatic or mixed liver injury) has been diagnosed, olanzapine treatment should be discontinued.

Neutropenia
Caution should be exercised in patients with low leukocyte and/or neutrophil counts for any reason, in patients receiving medicines known to cause neutropenia, in patients with a history of drug-induced bone marrow depression/toxicity, in patients with bone marrow depression caused by concomitant illness, radiation therapy or chemotherapy and in patients with hypereosinophilic conditions or with myeloproliferative disease. Neutropenia has been reported commonly when olanzapine and valproate are used concomitantly (see section 4.8).

Discontinuation of treatment
Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea, or vomiting have been reported rarely ($\geq$ 0.01 % and < 0.1 %) when olanzapine is stopped abruptly.

QT interval
In clinical trials with oral administration, clinically meaningful QTc prolongations (Fridericia QT correction [QTcF] $\geq$ 500 milliseconds [msec] at any time post baseline in patients with baseline QTcF < 500 msec) were uncommon (0.1 % to 1 %) in patients treated with olanzapine, with no significant differences in associated cardiac events compared to placebo. In clinical trials with ZYPREXA powder for solution for injection, olanzapine was not associated with a persistent increase in absolute QT or in QTc intervals. However, caution should be exercised when olanzapine is prescribed with medicines known to increase QTc interval, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia.

Thromboembolism
Temporal association of olanzapine treatment and venous thromboembolism has been reported uncommonly (≥ 0.1 % and < 1 %). A causal relationship between the occurrence of venous thromboembolism and treatment with olanzapine has not been established. However, since patients with schizophrenia often present with acquired risk factors for venous thromboembolism all possible risk factors of VTE e.g. immobilisation of patients, should be identified and preventive measures undertaken.

General CNS activity
Given the primary CNS effects of olanzapine, caution should be used when it is taken in combination with other centrally acting medicines and alcohol. As it exhibits *in vitro* dopamine antagonism, olanzapine may antagonize the effects of direct and indirect dopamine agonists.

Seizures
Olanzapine should be used cautiously in patients who have a history of seizures or are subject to factors which may lower the seizure threshold. Seizures have been reported to occur uncommonly in patients when treated with olanzapine. In most of these cases, a history of seizures or risk factors for seizures were reported.

Tardive Dyskinesia
In comparator oral studies of one year or less duration, olanzapine was associated with a statistically significant lower incidence of treatment emergent dyskinesia. However the risk of tardive dyskinesia increases with long term exposure, and therefore if signs or symptoms of tardive dyskinesia appear in a patient on olanzapine, a dose reduction or discontinuation should be considered. These symptoms can temporally deteriorate or even arise after discontinuation of treatment.

Postural hypotension
Postural hypotension was infrequently observed in the elderly in oral olanzapine clinical trials. It is recommended that blood pressure is measured periodically in patients over 65 years.

Sudden cardiac death:
In postmarketing reports with olanzapine, the event of sudden cardiac death has been reported in patients with olanzapine. In a retrospective observational cohort study, the risk of presumed sudden cardiac death in patients treated with olanzapine was approximately twice the risk in patients not using antipsychotics. In the study, the risk of olanzapine was comparable to the risk of atypical antipsychotics included in a pooled analysis.

Lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

IM olanzapine has not been studied in patients with alcohol or drug intoxication (see section 4.4).

Caution should be exercised in patients who consume alcohol or receive medicinal products that can induce hypotension, bradycardia, respiratory or central nervous system depression (see section 4.4).

Potential for interaction following intramuscular injection
In a single dose intramuscular study of olanzapine 5 mg, administered 1 hour before intramuscular lorazepam 2 mg (metabolised by glucuronidation), the pharmacokinetics of both medicines were

unchanged. However, the combination added to the somnolence observed with either medicines alone. Concomitant injection of olanzapine and parenteral benzodiazepine is not recommended (see sections 4.4 and 6.2).

Potential interactions affecting olanzapine
Since olanzapine is metabolised by CYP1A2, substances that can specifically induce or inhibit this isoenzyme may affect the pharmacokinetics of olanzapine.

Induction of CYP1A2
The metabolism of olanzapine may be induced by smoking and carbamazepine, which may lead to reduced olanzapine concentrations. Only slight to moderate increase in olanzapine clearance has been observed. The clinical consequences are likely to be limited, but clinical monitoring is recommended and an increase of olanzapine dose may be considered if necessary (see section 4.2).

Inhibition of CYP1A2
Fluvoxamine, a specific CYP1A2 inhibitor, has been shown to significantly inhibit the metabolism of olanzapine. The mean increase in olanzapine C_{max} following fluvoxamine was 54 % in female non-smokers and 77 % in male smokers. The mean increase in olanzapine AUC was 52 % and 108 % respectively. A lower starting dose of olanzapine should be considered in patients who are using fluvoxamine or any other CYP1A2 inhibitors, such as ciprofloxacin. A decrease in the dose of olanzapine should be considered if treatment with an inhibitor of CYP1A2 is initiated.

Decreased bioavailability
Activated charcoal reduces the bioavailability of oral olanzapine by 50 to 60 % and should be taken at least 2 hours before or after olanzapine.

Fluoxetine (a CYP2D6 inhibitor), single doses of antacid (aluminium, magnesium) or cimetidine have not been found to significantly affect the pharmacokinetics of olanzapine.

Potential for olanzapine to affect other medicinal products
Olanzapine may antagonise the effects of direct and indirect dopamine agonists (see section 6.2).

Olanzapine does not inhibit the main CYP450 isoenzymes *in vitro* (e.g. 1A2, 2D6, 2C9, 2C19, 3A4). Thus no particular interaction is expected as verified through *in vivo* studies where no inhibition of metabolism of the following active substances was found: tricyclic antidepressant (representing mostly CYP2D6 pathway), warfarin (CYP2C9), theophylline (CYP1A2) or diazepam (CYP3A4 and 2C19).

Olanzapine showed no interaction when co-administered with lithium or biperiden.

Therapeutic monitoring of valproate plasma levels did not indicate that valproate dosage adjustment is required after the introduction of concomitant olanzapine.

The concomitant use of olanzapine with anti-Parkinsonian medicinal products in patients with Parkinson's disease and dementia is not recommended (see section 4.4).

QTc interval
Caution should be used if olanzapine is being administered concomitantly with medicinal products known to increase QTc interval (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate and well-controlled studies in pregnant women. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with olanzapine. Nevertheless, because human experience is limited, olanzapine should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

New born infant exposed to antipsychotics (including olanzapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Breast-feeding
In a study in breast-feeding, healthy women, olanzapine was excreted in breast milk. Mean infant exposure (mg/kg) at steady state was estimated to be 1.8 % of the maternal olanzapine dose (mg/kg). Patients should be advised not to breast feed an infant if they are taking olanzapine.

Fertility
Effects on fertility are unknown (see section 5.3 for preclinical information).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Because olanzapine may cause somnolence and dizziness, patients should be cautioned about operating machinery, including motor vehicles.

4.8 Undesirable effects

Summary of the safety profile
A common (≥ 1/100 to < 1/10) undesirable effect associated with the use of intramuscular olanzapine in clinical trials was somnolence.

In post marketing reports, temporal association of treatment with IM olanzapine with cases of respiratory depression, hypotension or bradycardia and death have been very rarely reported, mostly in patients who concomitantly received benzodiazepines, and/or other antipsychotic medicinal products or who were treated in excess of olanzapine recommended daily doses (see sections 4.4 and 4.5).

The following table is based on the undesirable effects and laboratory investigations from clinical trials with ZYPREXA powder for solution for injection rather than oral olanzapine.

Cardiac disorders *Common (≥ 1/100 to < 1/10):* Bradycardia with or without hypotension or syncope, tachycardia. *Uncommon (≥ 1/1,000 to < 1/100):* Sinus pause.
Vascular Disorders *Common (≥ 1/100 to < 1/10):* Postural hypotension, hypotension.
Respiratory disorders *Uncommon (≥ 1/1,000 to < 1/100):* Hypoventilation.
General disorders and administration site conditions *Common (≥ 1/100 to < 1/10):* Injection site discomfort.

The undesirable effects listed below have been observed following administration of oral and prolonged release intramuscular injection olanzapine, but may also occur following administration of ZYPREXA powder for solution for injection.

Adults
The most frequently (seen in ≥ 1% of patients) reported adverse reactions associated with the use of olanzapine in clinical trials were somnolence, weight gain, eosinophilia, elevated prolactin, cholesterol, glucose and triglyceride levels (see section 4.4), glucosuria, increased appetite, dizziness, akathisia, parkinsonism, leukopenia, neutropenia (see section 4.4), dyskinesia, orthostatic hypotension, anticholinergic effects, transient asymptomatic elevations of hepatic aminotransferases (see section 4.4), rash, asthenia, fatigue, pyrexia, arthralgia, increased alkaline phosphatase, high gamma glutamyltransferase, high uric acid, high creatine phosphokinase and oedema.

Tabulated list of adverse reactions

The following table lists the adverse reactions and laboratory investigations observed from spontaneous reporting and in clinical trials. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The frequency terms listed are defined as follows: Very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the data available).

Very common	**Common**	**Uncommon**	**Rare**	**Not known**
Blood and the lymphatic system disorders				
	Eosinophilia Leukopenia[10] Neutropenia[10]		Thrombocytopenia[11]	
Immune system disorders				
		Hypersensitivity[11]		
Metabolism and nutrition disorders				
Weight gain[1]	Elevated cholesterol levels[2,3] Elevated glucose levels[4] Elevated triglyceride levels[2,5] Glucosuria Increased appetite	Development or exacerbation of diabetes occasionally associated with ketoacidosis or coma, including some fatal cases (see section 4.4) [11]	Hypothermia[12]	
Nervous system disorders				
Somnolence	Dizziness Akathisia[6] Parkinsonism[6] Dyskinesia[6]	Seizures where in most cases a history of seizures or risk factors for seizures were reported[11] Dystonia (including oculogyration)[11] Tardive dyskinesia[11] Amnesia[9] Dysarthria Stuttering[11, 13] Restless Legs Syndrome[11]	Neuroleptic malignant syndrome (see section 4.4)[12] Discontinuation symptoms[7,12]	
Cardiac disorders				
		Bradycardia QT_c prolongation (see section 4.4)	Ventricular tachycardia/fibrillation, sudden death (see section 4.4)[11]	
Vascular disorders				
Orthostatic hypotension[10]		Thromboembolism (including pulmonary embolism and deep vein thrombosis) (see section 4.4)		

Respiratory, thoracic and mediastinal disorders				
		Epistaxis[9]		
Gastrointestinal disorders				
	Mild, transient anticholinergic effects including constipation and dry mouth	Abdominal distension[9] Salivary hypersecretion[11]	Pancreatitis[11]	
Hepatobiliary disorders				
	Transient, asymptomatic elevations of hepatic aminotransferases (ALT, AST), especially in early treatment (see section 4.4)		Hepatitis (including hepatocellular, cholestatic or mixed liver injury)[11]	
Skin and subcutaneous tissue disorders				
	Rash	Photosensitivity reaction Alopecia		Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders				
	Arthralgia[9]		Rhabdomyolysis[11]	
Renal and urinary disorders				
		Urinary incontinence, urinary retention Urinary hesitation[11]		
Pregnancy, puerperium and perinatal conditions				
				Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders				
	Erectile dysfunction in males Decreased libido in males and females	Amenorrhea Breast enlargement Galactorrhea in females Gynaecomastia/breast enlargement in males	Priapism[12]	
General disorders and administration site conditions				
	Asthenia Fatigue Oedema Pyrexia[10]			

Investigations				
Elevated plasma prolactin levels[8]	Increased alkaline phosphatase[10] High creatine phosphokinase[11] High Gamma Glutamyltransferase [10] High Uric acid [10]	Increased total bilirubin		

[1] Clinically significant weight gain was observed across all baseline Body Mass Index (BMI) categories. Following short term treatment (median duration 47 days), weight gain ≥ 7% of baseline body weight was very common (22.2 %), ≥ 15 % was common (4.2 %) and ≥ 25 % was uncommon (0.8 %). Patients gaining ≥ 7 %, ≥ 15 % and ≥ 25 % of their baseline body weight with long-term exposure (at least 48 weeks) were very common (64.4 %, 31.7 % and 12.3 % respectively).

[2] Mean increases in fasting lipid values (total cholesterol, LDL cholesterol, and triglycerides) were greater in patients without evidence of lipid dysregulation at baseline.

[3] Observed for fasting normal levels at baseline (< 5.17 mmol/l) which increased to high (≥ 6.2 mmol/l). Changes in total fasting cholesterol levels from borderline at baseline (≥ 5.17 - < 6.2 mmol/l) to high (≥ 6.2 mmol/l) were very common.

[4] Observed for fasting normal levels at baseline (< 5.56 mmol/l) which increased to high (≥ 7 mmol/l). Changes in fasting glucose from borderline at baseline (≥ 5.56 - < 7 mmol/l) to high (≥ 7 mmol/l) were very common.

[5] Observed for fasting normal levels at baseline (< 1.69 mmol/l) which increased to high (≥ 2.26 mmol/l). Changes in fasting triglycerides from borderline at baseline (≥ 1.69 mmol/l - < 2.26 mmol/l) to high (≥ 2.26 mmol/l) were very common.

[6] In clinical trials, the incidence of Parkinsonism and dystonia in olanzapine-treated patients was numerically higher, but not statistically significantly different from placebo. Olanzapine-treated patients had a lower incidence of Parkinsonism, akathisia and dystonia compared with titrated doses of haloperidol. In the absence of detailed information on the pre-existing history of individual acute and tardive extrapyramidal movement disorders, it cannot be concluded at present that olanzapine produces less tardive dyskinesia and/or other tardive extrapyramidal syndromes.

[7] Acute symptoms such as sweating, insomnia, tremor, anxiety, nausea and vomiting have been reported when olanzapine is stopped abruptly.

[8] In clinical trials of up to 12 weeks, plasma prolactin concentrations exceeded the upper limit of normal range in approximately 30% of olanzapine treated patients with normal baseline prolactin value. In the majority of these patients the elevations were generally mild, and remained below two times the upper limit of normal range.

[9] Adverse event identified from clinical trials in the Olanzapine Integrated Database.

[10] As assessed by measured values from clinical trials in the Olanzapine Integrated Database.

[11] Adverse event identified from spontaneous post-marketing reporting with frequency determined utilising the Olanzapine Integrated Database.

[12] Adverse event identified from spontaneous post-marketing reporting with frequency estimated at the upper limit of the 95% confidence interval utilising the Olanzapine Integrated Database.

[13]Undesirable effects listed and observed following administration of oral and LAIM olanzapine, which may also occur following administration of RAIM olanzapine.

Long-term exposure (at least 48 weeks)
The proportion of patients who had adverse, clinically significant changes in weight gain, glucose, total/LDL/HDL cholesterol or triglycerides increased over time. In adult patients who completed 9-12 months of therapy, the rate of increase in mean blood glucose slowed after approximately 6 months.

Additional information on special populations
In clinical trials in elderly patients with dementia, olanzapine treatment was associated with a higher incidence of death and cerebrovascular adverse reactions compared to placebo (see section 4.4). Very common adverse reactions associated with the use of olanzapine in this patient group were abnormal gait and falls. Pneumonia, increased body temperature, lethargy, erythema, visual hallucinations and urinary incontinence were observed commonly.

In clinical trials in patients with drug-induced (dopamine agonist) psychosis associated with Parkinson's disease, worsening of Parkinsonian symptomatology and hallucinations were reported very commonly and more frequently than with placebo.

In one clinical trial in patients with bipolar mania, valproate combination therapy with olanzapine resulted in an incidence of neutropenia of 4.1%; a potential contributing factor could be high plasma valproate levels. Olanzapine administered with lithium or valproate resulted in increased levels (≥ 10%) of tremor, dry mouth, increased appetite, and weight gain. Speech disorder was also reported commonly. During treatment with olanzapine in combination with lithium or divalproex, an increase of ≥ 7% from baseline body weight occurred in 17.4% of patients during acute treatment (up to 6 weeks). Long-term olanzapine treatment (up to 12 months) for recurrence prevention in patients with bipolar disorder was associated with an increase of ≥ 7% from baseline body weight in 39.9% of patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Signs and symptoms
Very common symptoms in overdose (> 10% incidence) include tachycardia, agitation/aggressiveness, dysarthria, various extrapyramidal symptoms, and reduced level of consciousness ranging from sedation to coma.

Other medically significant sequelae of overdose include delirium, convulsion, coma, possible neuroleptic malignant syndrome, respiratory depression, aspiration, hypertension or hypotension, cardiac arrhythmias (< 2% of overdose cases) and cardiopulmonary arrest. Fatal outcomes have been reported for acute overdoses as low as 450 mg but survival has also been reported following acute overdose of approximately 2 g of oral olanzapine.

Management
There is no specific antidote for olanzapine.

Symptomatic treatment and monitoring of vital organ function should be instituted according to clinical presentation, including treatment of hypotension and circulatory collapse and support of respiratory function. Do not use epinephrine, dopamine, or other sympathomimetic agents with beta-agonist activity since beta stimulation may worsen hypotension. Cardiovascular monitoring is necessary to detect possible arrhythmias. Close medical supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: psycholeptics, diazepines, oxazepines, thiazepines and oxepines, ATC code N05A H03.

Pharmacodynamic effects
Olanzapine is an antipsychotic, antimanic and mood stabilising agent that demonstrates a broad pharmacologic profile across a number of receptor systems.

In preclinical studies, olanzapine exhibited a range of receptor affinities ($K_i < 100$ nM) for serotonin 5 $HT_{2A/2C}$, 5 HT_3, 5 HT_6; dopamine D_1, D_2, D_3, D_4, D_5; cholinergic muscarinic receptors M_1-M_5; α_1 adrenergic; and histamine H_1 receptors. Animal behavioural studies with olanzapine indicated 5HT, dopamine, and cholinergic antagonism, consistent with the receptor-binding profile. Olanzapine demonstrated a greater *in vitro* affinity for serotonin $5HT_2$ than dopamine D_2 receptors and greater 5 HT_2 than D_2 activity *in vivo* models. Electrophysiological studies demonstrated that olanzapine selectively reduced the firing of mesolimbic (A10) dopaminergic neurons, while having little effect on the striatal (A9) pathways involved in motor function. Olanzapine reduced a conditioned avoidance response, a test indicative of antipsychotic activity, at doses below those producing catalepsy, an effect indicative of motor side-effects. Unlike some other antipsychotic agents, olanzapine increases responding in an "anxiolytic" test.

In a single oral dose (10 mg) Positron Emission Tomography (PET) study in healthy volunteers, olanzapine produced a higher 5 HT_{2A} than dopamine D_2 receptor occupancy. In addition, a Single Photon Emission Computed Tomography (SPECT) imaging study in schizophrenic patients revealed that olanzapine-responsive patients had lower striatal D_2 occupancy than some other antipsychotic- and risperidone-responsive patients, while being comparable to clozapine-responsive patients.

Clinical efficacy
In two of two placebo and two of three comparator controlled trials with over 2,900 schizophrenic patients presenting with both positive and negative symptoms, olanzapine was associated with statistically significantly greater improvements in negative as well as positive symptoms.

In a multinational, double-blind, comparative study of schizophrenia, schizoaffective, and related disorders which included 1,481 patients with varying degrees of associated depressive symptoms (baseline mean of 16.6 on the Montgomery-Asberg Depression Rating Scale), a prospective secondary analysis of baseline to endpoint mood score change demonstrated a statistically significant improvement ($p= 0.001$) favouring olanzapine (-6.0) versus haloperidol (-3.1).

In patients with a manic or mixed episode of bipolar disorder, olanzapine demonstrated superior efficacy to placebo and valproate semisodium (divalproex) in reduction of manic symptoms over 3 weeks. Olanzapine also demonstrated comparable efficacy results to haloperidol in terms of the proportion of patients in symptomatic remission from mania and depression at 6 and 12 weeks. In a co-therapy study of patients treated with lithium or valproate for a minimum of 2 weeks, the addition of olanzapine 10 mg (co-therapy with lithium or valproate) resulted in a greater reduction in symptoms of mania than lithium or valproate monotherapy after 6 weeks.

In a 12-month recurrence prevention study in manic episode patients who achieved remission on olanzapine and were then randomised to olanzapine or placebo, olanzapine demonstrated statistically significant superiority over placebo on the primary endpoint of bipolar recurrence. Olanzapine also showed a statistically significant advantage over placebo in terms of preventing either recurrence into mania or recurrence into depression.

In a second 12-month recurrence prevention study in manic episode patients who achieved remission with a combination of olanzapine and lithium and were then randomised to olanzapine or lithium alone, olanzapine was statistically non-inferior to lithium on the primary endpoint of bipolar recurrence (olanzapine 30.0%, lithium 38.3%; p = 0.055).

In an 18-month co-therapy study in manic or mixed episode patients stabilised with olanzapine plus a mood stabiliser (lithium or valproate), long-term olanzapine co-therapy with lithium or valproate was not statistically significantly superior to lithium or valproate alone in delaying bipolar recurrence, defined according to syndromic (diagnostic) criteria.

5.2 Pharmacokinetic properties

In a pharmacokinetic study in healthy volunteers, a dose of 5 mg of ZYPREXA powder for solution for injection produced a maximum plasma concentration (Cmax) approximately 5 times higher than that seen with the same dose of olanzapine administered orally. The Cmax occurs earlier after intramuscular compared to oral use (15 to 45 minutes versus 5 to 8 hours). As with oral use, Cmax and area under the curve after intramuscular use are directly proportional to the dose administered. For the same dose of olanzapine administered intramuscularly and orally, the associated area under the curve, half-life, clearance and volume of distribution are similar. The metabolic profiles following intramuscular and oral use are similar.

In non-smoking versus smoking subjects (males and females) administered olanzapine intramuscularly the mean elimination half-life was prolonged (38.6 versus 30.4 hr) and the clearance was reduced (18.6 versus 27.7 l/hr).

Additional pharmacokinetic data following administration of oral olanzapine are described below.

Distribution
The plasma protein binding of olanzapine was about 93 % over the concentration range of about 7 to about 1,000 ng/ml. Olanzapine is bound predominantly to albumin and α_1-acid-glycoprotein.

Biotransformation
Olanzapine is metabolised in the liver by conjugative and oxidative pathways. The major circulating metabolite is the 10-N-glucuronide, which does not pass the blood brain barrier. Cytochromes P450-CYP1A2 and P450-CYP2D6 contribute to the formation of the N-desmethyl and 2-hydroxymethyl metabolites, both exhibited significantly less *in vivo* pharmacological activity than olanzapine in animal studies. The predominant pharmacologic activity is from the parent olanzapine.

Elimination
After oral administration, the mean terminal elimination half-life of olanzapine in healthy subjects varied on the basis of age and gender.

In healthy elderly (65 and over) versus non-elderly subjects administered oral olanzapine, the mean elimination half-life was prolonged (51.8 versus 33.8 hr) and the clearance was reduced (17.5 versus 18.2 l/hr). The pharmacokinetic variability observed in the elderly is within the range for the non-elderly. In 44 patients with schizophrenia > 65 years of age, dosing from 5 to 20 mg/day was not associated with any distinguishing profile of adverse events.

In female versus male subjects administered oral olanzapine the mean elimination half life was somewhat prolonged (36.7 versus 32.3 hrs) and the clearance was reduced (18.9 versus 27.3 l/hr). However, olanzapine (5-20 mg) demonstrated a comparable safety profile in female (n=467) as in male patients (n=869).

Renal impairment
In renally impaired patients (creatinine clearance < 10 ml/min) versus healthy subjects administered oral olanzapine, there was no significant difference in mean elimination half-life (37.7 versus 32.4 hr)

or clearance (21.2 versus 25.0 l/hr). A mass balance study showed that approximately 57 % of radiolabelled olanzapine appeared in urine, principally as metabolites.

Hepatic impairment
A small study of the effect of impaired liver function in 6 subjects with clinically significant (Childs Pugh Classification A (n = 5) and B (n = 1)) cirrhosis revealed little effect on the pharmacokinetics of orally administered olanzapine (2.5 – 7.5 mg single dose): Subjects with mild to moderate hepatic dysfunction had slightly increased systemic clearance and faster elimination half-time compared to subjects with no hepatic dysfunction (n = 3). There were more smokers among subjects with cirrhosis (4/6; 67 %) than among subjects with no hepatic dysfunction (0/3; 0 %).

Smoking
The plasma clearance of olanzapine is lower in elderly versus young subjects, in females versus males, and in non-smokers versus smokers. However, the magnitude of the impact of age, gender, or smoking on olanzapine clearance and half-life is small in comparison to the overall variability between individuals.

In a study of Caucasians, Japanese, and Chinese subjects, there were no differences in the pharmacokinetic parameters among the three populations.

5.3 Preclinical safety data

Acute (single-dose) toxicity
Signs of oral toxicity in rodents were characteristic of potent antipsychotic compounds: hypoactivity, coma, tremors, clonic convulsions, salivation, and depressed weight gain. The median lethal doses were approximately 210 mg/kg (mice) and 175 mg/kg (rats). Dogs tolerated single oral doses up to 100 mg/kg without mortality. Clinical signs included sedation, ataxia, tremors, increased heart rate, laboured respiration, miosis, and anorexia. In monkeys, single oral doses up to 100 mg/kg resulted in prostration and, at higher doses, semi-consciousness.

Repeated-dose toxicity
In studies up to 3 months duration in mice and up to 1 year in rats and dogs, the predominant effects were CNS depression, anticholinergic effects, and peripheral haematological disorders. Tolerance developed to the CNS depression. Growth parameters were decreased at high doses. Reversible effects consistent with elevated prolactin in rats included decreased weights of ovaries and uterus and morphologic changes in vaginal epithelium and in mammary gland.

Haematologic toxicity
Effects on haematology parameters were found in each species, including dose-related reductions in circulating leukocytes in mice and non-specific reductions of circulating leukocytes in rats; however, no evidence of bone marrow cytotoxicity was found. Reversible neutropenia, thrombocytopenia, or anaemia developed in a few dogs treated with 8 or 10 mg/kg/day (total olanzapine exposure [AUC] is 12- to 15-fold greater than that of a man given a 12-mg dose). In cytopenic dogs, there were no undesirable effects on progenitor and proliferating cells in the bone marrow.

Reproductive toxicity
Olanzapine had no teratogenic effects. Sedation affected mating performance of male rats. Oestrous cycles were affected at doses of 1.1 mg/kg (3 times the maximum human dose) and reproduction parameters were influenced in rats given 3 mg/kg (9 times the maximum human dose). In the offspring of rats given olanzapine, delays in foetal development and transient decreases in offspring activity levels were seen.

Mutagenicity
Olanzapine was not mutagenic or clastogenic in a full range of standard tests, which included bacterial mutation tests and *in vitro* and oral *in vivo* mammalian tests.

Carcinogenicity
Based on the results of oral studies in mice and rats, it was concluded that olanzapine is not carcinogenic.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Tartaric acid, E334
Hydrochloric acid.
Sodium hydroxide.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

Olanzapine for injection should not be combined in a syringe with diazepam injection because precipitation occurs when these products are mixed.

Lorazepam injection should not be used to reconstitute olanzapine for injection as this combination results in a delayed reconstitution time.

Olanzapine for injection should not be combined in a syringe with haloperidol injection because the resulting low pH has been shown to degrade olanzapine over time.

6.3 Shelf life

Powder: 3 years.
Solution (after reconstitution): 1 hour. Do not freeze.

6.4 Special precautions for storage

Do not store above 25º C. Store in the original package in order to protect from light. For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I, 5 ml glass vial.
One carton contains 1 or 10 vial(s).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Reconstitute ZYPREXA only with water for injections using standard aseptic techniques for reconstitution of parenteral products. No other solutions should be used for reconstitution (see section 6.2).

1. Withdraw 2.1 ml of water for injection into a sterile syringe. Inject into a vial of ZYPREXA.

2. Rotate the vial until the contents have completely dissolved, giving a yellow coloured solution. The vial contains 11.0 mg olanzapine as a solution of 5 mg/ml (1 mg olanzapine is retained in the vial and syringe, thus allowing delivery of 10 mg olanzapine).

3. The following table provides injection volumes for delivering various doses of olanzapine:

Dose (mg)	Volume of injection (ml)
10	2.0
7.5	1.5
5	1.0
2.5	0.5

4. Administer the solution intramuscularly. Do not administer intravenously or subcutaneously.

5. Discard the syringe and any unused solution in accordance with appropriate clinical procedures.

6. Use the solution immediately within 1 hour of reconstitution.

Parenteral medicines should be inspected visually for particulate matter prior to administration.

7. MARKETING AUTHORISATION HOLDER

CHEPLAPHARM Registration GmbH, Weiler Straße 5e, 79540 Lörrach, Germany.

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/022/016 – ZYPREXA - Powder for solution for injection. 1 vial
EU/1/96/022/017 – ZYPREXA - Powder for solution for injection. 10 vials

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 September 1996
Date of latest renewal: 12 September 2006

10. DATE OF REVISION OF THE TEXT

{MM/YYYY}

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Coated Tablets
Lilly S.A., Avda. de la Industria 30, 28108 Alcobendas, Madrid, Spain.

Powder for solution for injection
Lilly S.A., Avda. de la Industria 30, 28108 Alcobendas, Madrid, Spain.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorization holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency.
- Whenever the risk management system is modified,especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF COATED TABLETS IN BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

ZYPREXA 2.5 mg coated tablets
olanzapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each coated tablet contains 2.5 mg olanzapine

3. LIST OF EXCIPIENTS

Contains lactose monohydrate see package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

28 coated tablets
35 coated tablets
56 coated tablets
70 coated tablets
98 coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CHEPLAPHARM Registration GmbH, Weiler Straße 5e, 79540 Lörrach, Germany.

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/022/002 28 coated tablets
EU/1/96/022/023 35 coated tablets
EU/1/96/022/019 56 coated tablets
EU/1/96/022/029 70 coated tablets
EU/1/96/022/035 98 coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ZYPREXA 2.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ZYPREXA 2.5 mg COATED TABLETS: BLISTER FOIL LABEL

1. NAME OF THE MEDICINAL PRODUCT

ZYPREXA 2.5 mg coated tablets
olanzapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

CHEPLAPHARM

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF COATED TABLETS IN BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

ZYPREXA 5 mg coated tablets
olanzapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each coated tablet contains 5 mg olanzapine

3. LIST OF EXCIPIENTS

Contains lactose monohydrate see package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

28 coated tablets
35 coated tablets
56 coated tablets
70 coated tablets
98 coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CHEPLAPHARM Registration GmbH, Weiler Straße 5e, 79540 Lörrach, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/022/004 28 coated tablets
EU/1/96/022/024 35 coated tablets
EU/1/96/022/020 56 coated tablets
EU/1/96/022/030 70 coated tablets
EU/1/96/022/036 98 coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ZYPREXA 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ZYPREXA 5 mg COATED TABLETS: BLISTER FOIL LABEL

1. NAME OF THE MEDICINAL PRODUCT

ZYPREXA 5 mg coated tablets
olanzapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

CHEPLAPHARM

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF COATED TABLETS IN BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

ZYPREXA 7.5 mg coated tablets
olanzapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each coated tablet contains 7.5 mg olanzapine

3. LIST OF EXCIPIENTS

Contains lactose monohydrate see package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

28 coated tablets
35 coated tablets
56 coated tablets
70 coated tablets
98 coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CHEPLAPHARM Registration GmbH, Weiler Straße 5e, 79540 Lörrach, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/022/011 28 coated tablets
EU/1/96/022/025 35 coated tablets
EU/1/96/022/006 56 coated tablets
EU/1/96/022/031 70 coated tablets
EU/1/96/022/037 98 coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ZYPREXA 7.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ZYPREXA 7.5 mg COATED TABLETS: BLISTER FOIL LABEL

1. NAME OF THE MEDICINAL PRODUCT

ZYPREXA 7.5 mg coated tablets
olanzapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

CHEPLAPHARM

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF COATED TABLETS IN BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

ZYPREXA 10 mg coated tablets
olanzapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each coated tablet contains 10 mg olanzapine

3. LIST OF EXCIPIENTS

Contains lactose monohydrate see package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

28 coated tablets
35 coated tablets
56 coated tablets
70 coated tablets
98 coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CHEPLAPHARM Registration GmbH, Weiler Straße 5e, 79540 Lörrach, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/022/009 28 coated tablets
EU/1/96/022/026 35 coated tablets
EU/1/96/022/010 56 coated tablets
EU/1/96/022/032 70 coated tablets
EU/1/96/022/038 98 coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ZYPREXA 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ZYPREXA 10 mg COATED TABLETS: BLISTER FOIL LABEL

1. NAME OF THE MEDICINAL PRODUCT

ZYPREXA 10 mg coated tablets
olanzapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

CHEPLAPHARM

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF COATED TABLETS IN BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

ZYPREXA 15 mg coated tablets
olanzapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each coated tablet contains 15 mg olanzapine

3. LIST OF EXCIPIENTS

Contains lactose monohydrate see package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

28 coated tablets
35 coated tablets
56 coated tablets
70 coated tablets
98 coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CHEPLAPHARM Registration GmbH, Weiler Straße 5e, 79540 Lörrach, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/022/012 28 coated tablets
EU/1/96/022/027 35 coated tablets
EU/1/96/022/021 56 coated tablets
EU/1/96/022/033 70 coated tablets
EU/1/96/022/039 98 coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ZYPREXA 15 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ZYPREXA 15 mg COATED TABLETS: BLISTER FOIL LABEL

1. NAME OF THE MEDICINAL PRODUCT

ZYPREXA 15 mg coated tablets
olanzapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

CHEPLAPHARM

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF COATED TABLETS IN BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

ZYPREXA 20 mg coated tablets
olanzapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each coated tablet contains 20 mg olanzapine

3. LIST OF EXCIPIENTS

Contains lactose monohydrate see package leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

28 coated tablets
35 coated tablets
56 coated tablets
70 coated tablets
98 coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from light and moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CHEPLAPHARM Registration GmbH, Weiler Straße 5e, 79540 Lörrach, Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/96/022/014 28 coated tablets
EU/1/96/022/028 35 coated tablets
EU/1/96/022/022 56 coated tablets
EU/1/96/022/034 70 coated tablets
EU/1/96/022/040 98 coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ZYPREXA 20 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

ZYPREXA 20 mg COATED TABLETS: BLISTER FOIL LABEL

1. NAME OF THE MEDICINAL PRODUCT

ZYPREXA 20 mg coated tablets
olanzapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

CHEPLAPHARM

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF VIAL OF POWDER

1. NAME OF THE MEDICINAL PRODUCT

ZYPREXA 10 mg powder for solution for injection
olanzapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 10 mg olanzapine. After reconstitution each ml of the solution contains 5 mg olanzapine

3. LIST OF EXCIPIENTS

Lactose monohydrate, tartaric acid, hydrochloric acid, sodium hydroxide

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for solution for injection. 1 vial
Powder for solution for injection. 10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular use. Single use vial. Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
Use solution within 1 hour

9. SPECIAL STORAGE CONDITIONS

Do not store above 25º C. Store in original package in order to protect from light

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard syringe and unused solution appropriately

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

CHEPLAPHARM Registration GmbH, Weiler Straße 5e, 79540 Lörrach, Germany

12. MARKETING AUTHORISATION NUMBER (S)

EU/1/96/022/016 Powder for solution for injection. 1 vial
EU/1/96/022/017 Powder for solution for injection. 10 vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LABEL ON VIAL OF 10 mg POWDER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ZYPREXA 10 mg olanzapine powder for solution for injection
IM use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use

3. EXPIRY DATE

EXP
Use solution within 1 hour

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 mg olanzapine per vial

B. PACKAGE LEAFLET

Package leaflet: Information for the user

ZYPREXA 2.5 mg coated tablets
ZYPREXA 5 mg coated tablets
ZYPREXA 7.5 mg coated tablets
ZYPREXA 10 mg coated tablets
ZYPREXA 15 mg coated tablets
ZYPREXA 20 mg coated tablets
olanzapine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ZYPREXA is and what it is used for

ZYPREXA contains the active substance olanzapine. ZYPREXA belongs to a group of medicines called antipsychotics and is used to treat the following conditions:
- Schizophrenia, a disease with symptoms such as hearing, seeing or sensing things which are not there, mistaken beliefs, unusual suspiciousness, and becoming withdrawn. People with this disease may also feel depressed, anxious or tense.
- Moderate to severe manic episodes, a condition with symptoms of excitement or euphoria.

ZYPREXA has been shown to prevent recurrence of these symptoms in patients with bipolar disorder whose manic episode has responded to olanzapine treatment.

2. What you need to know before you take ZYPREXA

Do not take ZYPREXA
- If you are allergic (hypersensitive) to olanzapine or any of the other ingredients of this medicine (listed in section 6). An allergic reaction may be recognised as a rash, itching, a swollen face, swollen lips or shortness of breath. If this has happened to you, tell your doctor.
- If you have been previously diagnosed with eye problems such as certain kinds of glaucoma (increased pressure in the eye)**.**

Warnings and precautions
Talk to your doctor or pharmacist before you take ZYPREXA.
- The use of ZYPREXA in elderly patients with dementia is not recommended as it may have serious side effects.

- Medicines of this type may cause unusual movements mainly of the face or tongue. If this happens after you have been given ZYPREXA tell your doctor.
- Very rarely, medicines of this type cause a combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness. If this happens, contact your doctor at once.
- Weight gain has been seen in patients taking ZYPREXA. You and your doctor should check your weight regularly. Consider referral to a dietician or help with a diet plan if necessary.
- High blood sugar and high levels of fat (triglycerides and cholesterol) have been seen in patients taking ZYPREXA. Your doctor should do blood tests to check blood sugar and certain fat levels before you start taking ZYPREXA and regularly during treatment.
- Tell the doctor if you or someone else in your family has a history of blood clots, as medicines like these have been associated with the formation of blood clots.

If you suffer from any of the following illnesses tell your doctor as soon as possible:

- Stroke or "mini" stroke (temporary symptoms of stroke)
- Parkinson's disease
- Prostate problems
- A blocked intestine (Paralytic ileus)
- Liver or kidney disease
- Blood disorders
- Heart disease
- Diabetes
- Seizures
- If you know that you may have salt depletion as a result of prolonged severe diarrhoea and vomiting (being sick) or usage of diuretics (water tablets)

If you suffer from dementia, you or your carer/relative should tell your doctor if you have ever had a stroke or "mini" stroke.

As a routine precaution, if you are over 65 years your blood pressure may be monitored by your doctor.

Children and adolescents
ZYPREXA is not for patients who are under 18 years.

Other medicines and ZYPREXA
Only take other medicines while you are on ZYPREXA if your doctor tells you that you can. You might feel drowsy if ZYPREXA is taken in combination with antidepressants or medicines taken for anxiety or to help you sleep (tranquillisers).

Tell your doctor if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor if you are taking:
- medicines for Parkinson's disease.
- carbamazepine (an anti-epileptic and mood stabiliser), fluvoxamine (an antidepressant) or ciprofloxacin (an antibiotic) - it may be necessary to change your ZYPREXA dose.

ZYPREXA with alcohol
Do not drink any alcohol if you have been given ZYPREXA as together with alcohol it may make you feel drowsy.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. You should not be given this medicine when breast-feeding, as small amounts of ZYPREXA can pass into breast milk.

The following symptoms may occur in newborn babies, of mothers that have used ZYPREXA in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.

Driving and using machines
There is a risk of feeling drowsy when you are given ZYPREXA. If this happens do not drive or operate any tools or machines. Tell your doctor.

ZYPREXA contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

3. How to take ZYPREXA

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will tell you how many ZYPREXA tablets to take and how long you should continue to take them. The daily dose of ZYPREXA is between 5 mg and 20 mg. Consult your doctor if your symptoms return but do not stop taking ZYPREXA unless your doctor tells you to.

You should take your ZYPREXA tablets once a day following the advice of your doctor. Try to take your tablets at the same time each day. It does not matter whether you take them with or without food. ZYPREXA coated tablets are for oral use. You should swallow the ZYPREXA tablets whole with water.

If you take more ZYPREXA than you should
Patients who have taken more ZYPREXA than they should have experienced the following symptoms: rapid beating of the heart, agitation/aggressiveness, problems with speech, unusual movements (especially of the face or tongue) and reduced level of consciousness. Other symptoms may be: acute confusion, seizures (epilepsy), coma, a combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness, slowing of the breathing rate, aspiration, high blood pressure or low blood pressure, abnormal rhythms of the heart. Contact your doctor or hospital straight away if you experience any of the above symptoms. Show the doctor your pack of tablets.

If you forget to take ZYPREXA
Take your tablets as soon as you remember. Do not take two doses in one day.

If you stop taking ZYPREXA
Do not stop taking your tablets just because you feel better. It is important that you carry on taking ZYPREXA for as long as your doctor tells you.

If you suddenly stop taking ZYPREXA, symptoms such as sweating, unable to sleep, tremor, anxiety or nausea and vomiting might occur. Your doctor may suggest you to reduce the dose gradually before stopping treatment.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately if you have:

- unusual movement (a common side effect that may affect up to 1 in 10 people) mainly of the face or tongue;
- blood clots in the veins (an uncommon side effect that may affect up to 1 in 100 people) especially in the legs (symptoms include swelling, pain, and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing. If you notice any of these symptoms seek medical advice immediately;
- a combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness (the frequency of this side effect cannot be estimated from the available data).

Very common side effects (may affect more than 1 in 10 people) include weight gain; sleepiness; and increases in levels of prolactin in the blood. In the early stages of treatment, some people may feel dizzy or faint (with a slow heart rate), especially when getting up from a lying or sitting position. This will usually pass on its own but if it does not, tell your doctor.

Common side effects (may affect up to 1 in 10 people) include changes in the levels of some blood cells, circulating fats and early in treatment, temporary increases in liver enzymes; increases in the level of sugars in the blood and urine; increases in levels of uric acid and creatine phosphokinase in the blood; feeling more hungry; dizziness; restlessness; tremor; unusual movements(dyskinesias); constipation; dry mouth; rash; loss of strength; extreme tiredness; water retention leading to swelling of the hands, ankles or feet; fever; joint pain; and sexual dysfunctions such as decreased libido in males and females or erectile dysfunction in males.

Uncommon side effects (may affect up to 1 in 100 people) include hypersensitivity (e.g. swelling in the mouth and throat, itching, rash); diabetes or the worsening of diabetes, occasionally associated with ketoacidosis (ketones in the blood and urine) or coma; seizures, usually associated with a history of seizures (epilepsy); muscle stiffness or spasms (including eye movements); restless legs syndrome; problems with speech; stuttering; slow heart rate; sensitivity to sunlight; bleeding from the nose; abdominal distension; drooling; memory loss or forgetfulness; urinary incontinence; lack of ability to urinate; hair loss; absence or decrease in menstrual periods; and changes in breasts in males and females such as an abnormal production of breast milk or abnormal growth.

Rare side effects (may affect up to 1 in 1000 people) include lowering of normal body temperature; abnormal rhythms of the heart; sudden unexplained death; inflammation of the pancreas causing severe stomach pain, fever and sickness; liver disease appearing as yellowing of the skin and white parts of the eyes; muscle disease presenting as unexplained aches and pains; and prolonged and/or painful erection.

Very rare side effects include serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as flu-like symptoms with a rash on the face and then with an extended rash, high temperature, enlarged lymph nodes, increased levels of liver enzymes seen on blood tests and an increase in a type of white blood cells (eosinophilia).

While taking olanzapine, elderly patients with dementia may suffer from stroke, pneumonia, urinary incontinence, falls, extreme tiredness, visual hallucinations, a rise in body temperature, redness of the skin and have trouble walking. Some fatal cases have been reported in this particular group of patients.

In patients with Parkinson's disease ZYPREXA may worsen the symptoms.

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ZYPREXA

Keep this medicine out of sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the carton**.**

ZYPREXA should be stored in its original pack in order to protect from light and moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What ZYPREXA contains

- The active substance is olanzapine. Each ZYPREXA tablet contains either 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg or 20 mg of the active substance. The exact amount is shown on your ZYPREXA tablet pack.
- The other ingredients are
  - (tablet core) lactose monohydrate, hyprolose, crospovidone, microcrystalline cellulose, magnesium stearate and
  - (tablet coating) hypromellose, titanium dioxide (E171), carnauba wax.
- In addition the different ZYPREXA tablet strengths also contain the following ingredients:

TABLET STRENGTH	OTHER INGREDIENTS
ZYPREXA 2.5 mg, 5 mg, 7.5 mg and 10 mg tablets	(tablet coating) shellac, macrogol, propylene glycol, polysorbate 80 and indigo carmine colour (E132), ethanol anhydrous, isopropyl alcohol, butyl alcohol, ammonium hydroxide
ZYPREXA 15 mg tablets	(tablet coating) triacetin and indigo carmine colour (E132)
ZYPREXA 20 mg tablets	(tablet coating) macrogol and synthetic red iron oxide (E172)

What ZYPREXA looks like and contents of the pack
ZYPREXA 2.5 mg coated tablets are white imprinted with “LILLY” and a numeric identicode “4112”.
ZYPREXA 5 mg coated tablets are white imprinted with “LILLY” and a numeric identicode “4115”.
ZYPREXA 7.5 mg coated tablets are white imprinted with “LILLY” and a numeric identicode “4116”.
ZYPREXA 10 mg coated tablets are white imprinted with “LILLY” and a numeric identicode “4117”.
ZYPREXA 15 mg coated tablets are blue.
ZYPREXA 20 mg coated tablets are pink.

ZYPREXA is available in packs containing 28, 35, 56, 70 or 98 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder
CHEPLAPHARM Registration GmbH, Weiler Straße 5e, 79540 Lörrach, Germany.

Manufacturer
Lilly S.A., Avda. de la Industria 30, 28108 Alcobendas, Madrid, Spain.

This leaflet was last revised in {month XXXX}

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

Package leaflet: Information for the user

ZYPREXA 10 mg powder for solution for injection
olanzapine

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What ZYPREXA is and what it is used for

ZYPREXA contains the active substance olanzapine. ZYPREXA Injection belongs to a group of medicines called antipsychotics and is used to treat symptoms of agitation and distressing behaviour that may occur in the following conditions:

- Schizophrenia, a disease with symptoms such as hearing, seeing or sensing things which are not there, mistaken beliefs, unusual suspiciousness, and becoming withdrawn. People with this disease may also feel depressed, anxious or tense.
- Mania, a condition with symptoms of excitement or euphoria.

ZYPREXA Injection is given when rapid control of agitation and distressing behaviour is needed and treatment with ZYPREXA tablets is not appropriate. Your doctor will change your treatment to ZYPREXA tablets, as soon as appropriate.

2. What you need to know before you are given ZYPREXA

You should not be given ZYPREXA
- If you are allergic (hypersensitive) to olanzapine or any of the other ingredients of this medicine (listed in section 6). An allergic reaction may be recognised as a rash, itching, a swollen face, swollen lips or shortness of breath. If this has happened to you, tell your doctor.
- If you have been previously diagnosed with eye problems such as certain kinds of glaucoma (increased pressure in the eye).

Warnings and precautions
Talk to your doctor or nurse before you are given ZYPREXA Injection
- Tell the doctor or nurse if you feel dizzy or faint after the injection. You will probably need to lie down until you feel better. The doctor or nurse may also want to measure your blood pressure and pulse.
- The use of ZYPREXA in elderly patients with dementia (confusion and memory loss) is not recommended as it may have serious side effects.
- Medicines of this type may cause unusual movements mainly of the face or tongue. If this happens after you have been given ZYPREXA, talk to your doctor.

- Very rarely, medicines of this type cause a combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness. If this happens, contact your doctor at once. No more injections will be given to you.
- Weight gain has been seen in patients taking ZYPREXA. You and your doctor should check your weight regularly. Consider referral to a dietician or help with a diet plan if necessary.
- High blood sugar and high levels of fat (triglycerides and cholesterol) have been seen in patients taking ZYPREXA. Your doctor should do blood tests to check blood sugar and certain fat levels before you start taking ZYPREXA and regularly during treatment.
- Tell the doctor if you or someone else in your family has a history of blood clots, as medicines like these have been associated with formation of blood clots.

If you suffer from any of the following illnesses tell your doctor as soon as possible:
- Stroke or "mini" stroke (temporary symptoms of stroke)
- Parkinson's disease
- Prostate problems
- A blocked intestine (Paralytic ileus)
- Liver or kidney disease
- Blood disorders
- If you have had a recent heart attack, or have heart disease, including sick sinus syndrome, unstable angina or suffer from low blood pressure.
- Diabetes
- Seizures
- If you know that you may have salt depletion as a result of prolonged severe diarrhoea and vomiting (being sick) or usage of diuretics (water tablets)

If you suffer from dementia, you or your carer/relative should tell your doctor if you have ever had a stroke or "mini" stroke.

As a routine precaution, if you are over 65 years your doctor may monitor your blood pressure.

Children and adolescents
ZYPREXA is not for patients who are under 18 years.

Other medicines and ZYPREXA
A combination of ZYPREXA with the following medicines might make you feel drowsy: medicines taken for anxiety or to help you sleep (tranquillisers, including benzodiazepines), and antidepressants. Only take other medicines while you are on ZYPREXA if your doctor tells you that you can.

If you receive ZYPREXA injection, a benzodiazepine injection is not recommended at the same time as this may result in excessive sleepiness, may have serious effects on your heart rate or your breathing, and, in very rare cases, may result in death. If your doctor has to give a benzodiazepine injection to treat your condition, there should be at least a one hour time period after the ZYPREXA injection and you are to be monitored closely after the benzodiazepine injection is given.

Tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Especially tell your doctor if you are taking medicines for Parkinson's disease.

ZYPREXA with alcohol
Do not drink any alcohol if you have been given ZYPREXA as together with alcohol it may make you feel drowsy.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before being given this medicine. You should not be given this medicine when breast-feeding, as small amounts of ZYPREXA can pass into breast milk.

The following symptoms may occur in newborn babies, of mothers that have used ZYPREXA in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.

Driving and using machines
There is a risk of feeling drowsy when you are given ZYPREXA. If this happens do not drive or operate any tools or machines. Tell your doctor.

ZYPREXA contains Lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

ZYPREXA contains Sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

3. How ZYPREXA is given

Information on reconstitution and administration is provided in a detachable section at the end of this leaflet.

Your doctor will decide how much ZYPREXA you need and how long you need it for. The dose is usually 10 mg for the first injection, but it may be less than this. Up to 20 mg in 24 hours may be given. The dose for patients aged over 65 years is 2.5 mg or 5 mg.

ZYPREXA comes as a powder. Your doctor or nurse will make it up into a solution. ZYPREXA Injection is for intramuscular use. The correct amount of solution will be injected into your muscle.

If you are given more ZYPREXA than you think you should be
Patients who have been given more ZYPREXA than they should, have experienced the following symptoms: rapid beating of the heart, agitation/aggressiveness, problems with speech, unusual movements (especially of the face or tongue) and reduced level of consciousness. Other symptoms may include: acute confusion, seizures (epilepsy), coma, a combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness, slowing of the breathing rate, aspiration, high or low blood pressure, abnormal rhythms of the heart. Tell your doctor or nurse of your concern.

Only a few doses of ZYPREXA Injection are needed. Your doctor will decide when you need a dose of ZYPREXA Injection.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, ZYPREXA injection can cause side effects, although not everybody gets them.

Tell your doctor immediately if you have:
- unusual movement (a common side effect that may affect up to 1 in 10 people) mainly of the face or tongue;
- blood clots in the veins (an uncommon side effect that may affect up to 1 in 100 people) especially in the legs (symptoms include swelling, pain, and redness in the leg), which may travel

through blood vessels to the lungs causing chest pain and difficulty in breathing. If you notice any of these symptoms seek medical advice immediately;
- a combination of fever, faster breathing, sweating, muscle stiffness and drowsiness or sleepiness (the frequency of this side effect cannot be estimated from the available data).

Common side effects (may affect up to 1 in 10 people) with ZYPREXA Injection include slower or faster heart rate; sleepiness; low blood pressure; discomfort at the site of injection.

Some people may feel dizzy or faint (with a slow heart rate) after injection, especially when getting up from a lying or sitting position. This will usually pass on its own but if it does not, tell your doctor or a nurse as soon as possible.

Uncommon side effects (may affect up to 1 in 100 people) include breathing more slowly; and abnormal rhythms of the heart, which can be serious.

In addition, the following side effects have been seen after patients have taken ZYPREXA orally.

Other very common side effects (may affect more than 1 in 10 people) include weight gain; and increases in levels of prolactin in the blood. In the early stages of treatment, some people may feel dizzy or faint (with a slow heart rate), especially when getting up from a lying or sitting position. This will usually pass on its own but if it does not, tell your doctor.

Other common side effects(may affect up to 1 in 10 people) include changes in the levels of some blood cells, circulating fats and early in treatment, temporary increases in liver enzymes; increases in the level of sugars in the blood and urine; increases in levels of uric acid and creatine phosphokinase in the blood; feeling more hungry; dizziness; restlessness; tremor; unusual movements (dyskinesias); constipation; dry mouth; rash; loss of strength; extreme tiredness; water retention leading to swelling of the hands, ankles or feet; fever; joint pain; and sexual dysfunctions such as decreased libido in males and females or erectile dysfunction in males.

Other uncommon side effects (may affect up to 1 in 100 people) include hypersensitivity (e.g. swelling in the mouth and throat, itching, rash): diabetes or the worsening of diabetes, occasionally associated with ketoacidosis (ketones in the blood and urine) or coma; seizures, usually associated with a history of seizures (epilepsy); muscle stiffness or spasms (including eye movements); restless legs syndrome; problems with speech; stuttering; slow heart rate; sensitivity to sunlight; bleeding from nose; abdominal distension; drooling; memory loss or forgetfulness; urinary incontinence; lack of ability to urinate; hair loss; absence or decrease in menstrual periods; and changes in breasts in males and females such as an abnormal production of breast milk or abnormal growth.

Rare side effects (may affect up to 1 in 1000 people) include lowering of normal body temperature; abnormal rhythms of the heart; sudden unexplained death; inflammation of the pancreas causing severe stomach pain, fever and sickness; liver disease appearing as yellowing of the skin and white parts of the eyes; muscle disease presenting as unexplained aches and pains; and prolonged and/or painful erection.

Very rare side effects include serious allergic reactions such as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). DRESS appears initially as flu-like symptoms with a rash on the face and then with an extended rash, high temperature, enlarged lymph nodes, increased levels of liver enzymes seen on blood tests and an increase in a type of white blood cells (eosinophilia).

While taking olanzapine, elderly patients with dementia may suffer from stroke, pneumonia, urinary incontinence, falls, extreme tiredness, visual hallucinations, a rise in body temperature, redness of the skin and have trouble walking. Some fatal cases have been reported in this particular group of patients.

In patients with Parkinson's disease ZYPREXA may worsen the symptoms.

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ZYPREXA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the carton.

Do not store above 25°C. Store in original package in order to protect from light.

After ZYPREXA Injection is made into a solution, use within one hour. Do not freeze after reconstitution.

Discard any unused contents.

6. FURTHER INFORMATION

What ZYPREXA Injection contains
- The active substance is olanzapine. Each vial contains 10 mg of the active substance.
- The other ingredients are lactose monohydrate, tartaric acid, hydrochloric acid and sodium hydroxide.

What ZYPREXA Injection looks like and contents of the pack
ZYPREXA comes as a yellow powder in a vial. A vial of ZYPREXA can provide you with 10 mg of olanzapine. Your doctor or nurse will make it up into a solution that will be given as an injection.

ZYPREXA Injection is available in a pack containing 1 or 10 vial(s). Not all pack sizes may be marketed.

Marketing Authorisation Holder
CHEPLAPHARM Registration GmbH, Weiler Straße 5e, 79540 Lörrach, Germany.

Manufacturer

Lilly S.A., Avda. de la Industria 30, 28108 Alcobendas, Madrid, Spain.

This leaflet was last revised in {month XXXX}

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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(Perforation to allow health care provider information to be detached)

INSTRUCTIONS FOR HEALTH CARE PROFESSIONALS

Reconstitution and administration of ZYPREXA

Reconstitute ZYPREXA Powder for Solution for Injection only with water for injections.

ZYPREXA Powder for Solution for Injection must not be combined in the syringe with any commercially available medicinal products because of incompatibilities. See examples below.

Olanzapine for injection should not be combined in a syringe with haloperidol injection because the resulting low pH has been shown to degrade olanzapine over time.

Olanzapine for injection may not be combined in a syringe nor should it be used concomitantly with benzodiazepines.

Powder for Solution for Injection

Reconstitute ZYPREXA Powder for Solution for Injection using standard aseptic techniques for reconstitution of parenteral products.

1. Withdraw 2.1 ml of water for injections into a sterile syringe. Inject into a vial of ZYPREXA Powder for Solution for Injection.

2. Rotate the vial until the contents have completely dissolved, giving a yellow coloured solution. The vial contains 11.0 mg olanzapine as a solution of 5 mg/ml. If 2.0 ml solution is withdrawn, 1 mg olanzapine is retained in the vial and syringe, thus allowing delivery of 10mg olanzapine.

3. The following table provides injection volumes for delivering various doses of olanzapine:

Dose (mg)	Volume of injection (ml)
10	2.0
7.5	1.5
5	1.0
2.5	0.5

4. Administer the solution intramuscularly. Do not administer intravenously or subcutaneously.

5. Discard the syringe and any unused solution in accordance with appropriate clinical procedures.

6. Use the solution immediately within 1 hour of reconstitution. Do not store above 25º C. Do not freeze.

Parenteral medicines should be inspected visually for particulate matter prior to administration.

Paliperidone

EMA

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

INVEGA 3 mg prolonged-release tablets
INVEGA 6 mg prolonged-release tablets
INVEGA 9 mg prolonged-release tablets
INVEGA 12 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains 3 mg of paliperidone.
Each prolonged-release tablet contains 6 mg of paliperidone.
Each prolonged-release tablet contains 9 mg of paliperidone.
Each prolonged-release tablet contains 12 mg of paliperidone.

Excipient with known effect
Each 3 mg tablet contains 13.2 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet

Trilayer capsule-shaped white tablets of 11 mm in length and 5 mm in diameter printed with “PAL 3”
Trilayer capsule-shaped beige tablets of 11 mm in length and 5 mm in diameter printed with “PAL 6”
Trilayer capsule-shaped pink tablets of 11 mm in length and 5 mm in diameter printed with “PAL 9”
Trilayer capsule-shaped yellow tablets of 11 mm in length and 5 mm in diameter printed with “PAL 12”

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

INVEGA is indicated for the treatment of schizophrenia in adults and in adolescents 15 years and older.
INVEGA is indicated for the treatment of schizoaffective disorder in adults.

4.2 Posology and method of administration

Posology

Schizophrenia (adults)
The recommended dose of INVEGA for the treatment of schizophrenia in adults is 6 mg once daily, administered in the morning. Initial dose titration is not required. Some patients may benefit from lower or higher doses within the recommended range of 3 mg to 12 mg once daily. Dosage adjustment, if indicated, should occur only after clinical reassessment. When dose increases are indicated, increments of 3 mg/day are recommended and generally should occur at intervals of more than 5 days.

Schizoaffective disorder (adults)
The recommended dose of INVEGA for the treatment of schizoaffective disorder in adults is 6 mg once daily, administered in the morning. Initial dose titration is not required. Some patients may benefit from higher doses within the recommended range of 6 mg to 12 mg once daily. Dosage adjustment, if indicated, should occur only after clinical reassessment. When dose increases are

indicated, increments of 3 mg/day are recommended and generally should occur at intervals of more than 4 days.

Switching to other antipsychotic medicinal products
There are no systematically collected data to specifically address switching patients from INVEGA to other antipsychotic medicinal products. Due to different pharmacodynamic and pharmacokinetic profiles among antipsychotic medicinal products, supervision by a clinician is needed when switching to another antipsychotic product is considered medically appropriate.

Elderly
Dosing recommendations for elderly patients with normal renal function (≥ 80 mL/min) are the same as for adults with normal renal function. However, because elderly patients may have diminished renal function, dose adjustments may be required according to their renal function status (see Renal impairment below). INVEGA should be used with caution in elderly patients with dementia with risk factors for stroke (see section 4.4). Safety and efficacy of INVEGA in patients > 65 years of age with schizoaffective disorder have not been studied.

Hepatic impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment. As INVEGA has not been studied in patients with severe hepatic impairment, caution is recommended in such patients.

Renal impairment
For patients with mild renal impairment (creatinine clearance ≥ 50 to < 80 mL/min), the recommended initial dose is 3 mg once daily. The dose may be increased to 6 mg once daily based on clinical response and tolerability.

For patients with moderate to severe renal impairment (creatinine clearance ≥ 10 to < 50 mL/min), the recommended initial dose of INVEGA is 3 mg every other day, which may be increased to 3 mg once daily after clinical reassessment. As INVEGA has not been studied in patients with creatinine clearance below 10 mL/min, use is not recommended in such patients.

Paediatric population
Schizophrenia: The recommended starting dose of INVEGA for the treatment of schizophrenia in adolescents 15 years and older is 3 mg once daily, administered in the morning.

Adolescents weighing < 51 kg: the maximum recommended daily dose of INVEGA is 6 mg.

Adolescents weighing ≥ 51 kg: the maximum recommended daily dose of INVEGA is 12 mg.

Dosage adjustment, if indicated, should occur only after clinical reassessment based on the individual need of the patient. When dose increases are indicated, increments of 3 mg/day are recommended and generally should occur at intervals of 5 days or more. The safety and efficacy of INVEGA in the treatment of schizophrenia in adolescents between 12 and 14 years old has not been established. Currently available data are described in sections 4.8 and 5.1 but no recommendation on a posology can be made. There is no relevant use of INVEGA in children aged less than 12 years.

Schizoaffective disorder: The safety and efficacy of INVEGA in the treatment of schizoaffective disorder in patients aged 12 to 17 years has not been studied or established. There is no relevant use of INVEGA in children aged less than 12 years.

Other special populations
No dose adjustment for INVEGA is recommended based on gender, race, or smoking status.

Method of administration
INVEGA is for oral administration. It must be swallowed whole with liquid, and must not be chewed, divided, or crushed. The active substance is contained within a non-absorbable shell designed to

release the active substance at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

The administration of INVEGA should be standardised in relation to food intake (see section 5.2). The patient should be instructed to always take INVEGA in the fasting state or always take it together with breakfast and not to alternate between administration in the fasting state or in the fed state.

4.3 Contraindications

Hypersensitivity to the active substance, risperidone, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patients with schizoaffective disorder treated with paliperidone should be carefully monitored for a potential switch from manic to depressive symptoms.

QT interval
Caution should be exercised when INVEGA is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicines thought to prolong the QT interval.

Neuroleptic malignant syndrome
Neuroleptic Malignant Syndrome (NMS), characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness, and elevated serum creatine phosphokinase levels has been reported to occur with paliperidone. Additional clinical signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. If a patient develops signs or symptoms indicative of NMS, all antipsychotics, including INVEGA, should be discontinued.

Tardive dyskinesia/extrapyramidal symptoms
Medicines with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterised by rhythmical, involuntary movements, predominantly of the tongue and/or face. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotics, including INVEGA, should be considered.

Caution is warranted in patients receiving both, psychostimulants (e.g., methylphenidate) and paliperidone concomitantly, as extrapyramidal symptoms could emerge when adjusting one or both medications. Gradual withdrawal of stimulant treatment is recommended (see section 4.5).

Leucopenia, neutropenia, and agranulocytosis
Events of leucopenia, neutropenia, and agranulocytosis have been reported with antipsychotic agents, including INVEGA. Agranulocytosis has been reported very rarely (< 1/10 000 patients) during post-marketing surveillance. Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leucopenia/neutropenia should be monitored during the first few months of therapy and discontinuation of INVEGA should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1 x 10^9/L) should discontinue INVEGA and have their WBC followed until recovery.

Hyperglycaemia and diabetes mellitus
Hyperglycaemia, diabetes mellitus, and exacerbation of pre-existing diabetes have been reported during treatment with paliperidone. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Association with ketoacidosis has been reported very rarely and rarely with diabetic coma. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any atypical antipsychotic, including INVEGA, should

be monitored for symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia, and weakness) and patients with diabetes mellitus should be monitored regularly for worsening of glucose control.

Weight gain
Significant weight gain has been reported with INVEGA use. Weight should be monitored regularly.

Hyperprolactinaemia
Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics has so far been demonstrated in clinical and epidemiological studies, caution is recommended in patients with relevant medical history. Paliperidone should be used with caution in patients with possible prolactin-dependent tumours.

Orthostatic hypotension
Paliperidone may induce orthostatic hypotension in some patients based on its alpha-blocking activity. Based on pooled data from the three, placebo-controlled, 6-week, fixed-dose trials with INVEGA (3, 6, 9, and 12 mg), orthostatic hypotension was reported by 2.5% of subjects treated with INVEGA compared with 0.8% of subjects treated with placebo. INVEGA should be used with caution in patients with known cardiovascular disease (e.g., heart failure, myocardial infarction or ischaemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration and hypovolaemia).

Seizures
INVEGA should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Potential for gastrointestinal obstruction
Because the INVEGA tablet is non-deformable and does not appreciably change shape in the gastrointestinal tract, INVEGA should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic) or in patients with dysphagia or significant difficulty in swallowing tablets. There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of medicines in non-deformable controlled-release formulations. Due to the controlled-release design of the dosage form, INVEGA should only be used in patients who are able to swallow the tablet whole.

Conditions with decreased gastro-intestinal transit time
Conditions leading to shorter gastrointestinal transit time, e.g., diseases associated with chronic severe diarrhoea, may result in a reduced absorption of paliperidone.

Renal impairment
The plasma concentrations of paliperidone are increased in patients with renal impairment and, therefore, dosage adjustment may be required in some patients (see sections 4.2 and 5.2). No data are available in patients with a creatinine clearance below 10 mL/min. Paliperidone should not be used in patients with creatinine clearance below 10 mL/min.

Hepatic impairment
No data are available in patients with severe hepatic impairment (Child-Pugh class C). Caution is recommended if paliperidone is used in such patients.

Elderly patients with dementia
INVEGA has not been studied in elderly patients with dementia. The experience from risperidone is considered valid also for paliperidone.

Overall mortality
In a meta-analysis of 17 controlled clinical trials, elderly patients with dementia treated with other atypical antipsychotics, including risperidone, aripiprazole, olanzapine, and quetiapine had an

increased risk of mortality compared to placebo. Among those treated with risperidone, the mortality was 4% compared with 3.1% for placebo.

Cerebrovascular adverse reactions
An approximately 3-fold increased risk of cerebrovascular adverse reactions have been seen in randomised placebo-controlled clinical trials in the dementia population with some atypical antipsychotics, including risperidone, aripiprazole, and olanzapine. The mechanism for this increased risk is not known. INVEGA should be used with caution in elderly patients with dementia who have risk factors for stroke.

Parkinson's disease and dementia with Lewy bodies
Physicians should weigh the risks versus the benefits when prescribing INVEGA to patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB) since both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotics. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Priapism
Antipsychotic medicinal products (including risperidone) with α-adrenergic blocking effects have been reported to induce priapism. During post-marketing surveillance priapism has also been reported with paliperidone, which is the active metabolite of risperidone. Patients should be informed to seek urgent medical care in case that priapism has not been resolved within 3-4 hours.

Body temperature regulation
Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicinal products. Appropriate care is advised when prescribing INVEGA to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Venous thromboembolism
Cases of venous thromboembolism (VTE) have been reported with antipsychotic medicinal products. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with INVEGA and preventive measures undertaken.

Antiemetic effect
An antiemetic effect was observed in preclinical studies with paliperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdosage with certain medicines or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumour.

Paediatric population
The sedative effect of INVEGA should be closely monitored in this population. A change in the time of administration of INVEGA may improve the impact of sedation on the patient.

Because of the potential effects of prolonged hyperprolactinaemia on growth and sexual maturation in adolescents, regular clinical evaluation of endocrinological status should be considered, including measurements of height, weight, sexual maturation, monitoring of menstrual functioning, and other potential prolactin-related effects.

During treatment with INVEGA regular examination for extrapyramidal symptoms and other movement disorders should also be conducted.

For specific posology recommendations in the paediatric population see section 4.2.

Intraoperative Floppy Iris Syndrome
Intraoperative floppy iris syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha 1a-adrenergic antagonist effect, such as INVEGA (see section 4.8).

IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with alpha 1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha 1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

Excipients
Lactose content *(pertains only to the 3 mg tablets)*
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, i.e., essentially sodium-free.

4.5 Interaction with other medicinal products and other forms of interaction

Caution is advised when prescribing INVEGA with medicines known to prolong the QT interval, e.g., class IA antiarrhythmics (e.g., quinidine, disopyramide) and class III antiarrhythmics (e.g., amiodarone, sotalol), some antihistaminics, some other antipsychotics and some antimalarials (e.g., mefloquine).

Potential for INVEGA to affect other medicines
Paliperidone is not expected to cause clinically important pharmacokinetic interactions with medicines that are metabolised by cytochrome P-450 isozymes. *In vitro* studies indicate that paliperidone is not an inducer of CYP1A2 activity.

Given the primary CNS effects of paliperidone (see section 4.8), INVEGA should be used with caution in combination with other centrally acting medicines, e.g., anxiolytics, most antipsychotics, hypnotics, opiates, etc. or alcohol.

Paliperidone may antagonise the effect of levodopa and other dopamine agonists. If this combination is deemed necessary, particularly in end-stage Parkinson's disease, the lowest effective dose of each treatment should be prescribed.

Because of its potential for inducing orthostatic hypotension (see section 4.4), an additive effect may be observed when INVEGA is administered with other therapeutic agents that have this potential, e.g., other antipsychotics, tricyclics.

Caution is advised if paliperidone is combined with other medicines known to lower the seizure threshold (i.e., phenothiazines or butyrophenones, clozapine, tricyclics or SSRIs, tramadol, mefloquine, etc.).

No interaction study between INVEGA and lithium has been performed, however, a pharmacokinetic interaction is unlikely to occur.

Co-administration of INVEGA 12 mg once daily with divalproex sodium prolonged-release tablets (500 mg to 2,000 mg once daily) did not affect the steady-state pharmacokinetics of valproate. Co-administration of INVEGA with divalproex sodium prolonged-release tablets increased the exposure to paliperidone (see below).

Potential for other medicines to affect INVEGA
In vitro studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, but there are no indications *in vitro* nor *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. Concomitant administration of INVEGA with paroxetine, a potent CYP2D6 inhibitor, showed no clinically significant effect on the pharmacokinetics of paliperidone. *In vitro* studies have shown that paliperidone is a P-glycoprotein (P-gp) substrate.

Co-administration of INVEGA once daily with carbamazepine 200 mg twice daily caused a decrease of approximately 37% in the mean steady-state C_{max} and AUC of paliperidone. This decrease is caused, to a substantial degree, by a 35% increase in renal clearance of paliperidone likely as a result of induction of renal P-gp by carbamazepine. A minor decrease in the amount of active substance excreted unchanged in the urine suggests that there was little effect on the CYP metabolism or bioavailability of paliperidone during carbamazepine co-administration. Larger decreases in plasma concentrations of paliperidone could occur with higher doses of carbamazepine. On initiation of carbamazepine, the dose of INVEGA should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of INVEGA should be re-evaluated and decreased if necessary. It takes 2-3 weeks for full induction to be achieved and upon discontinuation of the inducer the effect wears off over a similar time period. Other medicinal products or herbals which are inducers, e.g., rifampicin and St. John´s wort (*Hypericum perforatum*) may have similar effects on paliperidone.

Medicinal products affecting gastrointestinal transit time may affect the absorption of paliperidone, e.g., metoclopramide.

Co-administration of a single dose of INVEGA 12 mg with divalproex sodium prolonged-release tablets (two 500 mg tablets once daily) resulted in an increase of approximately 50% in the C_{max} and AUC of paliperidone. Dosage reduction for INVEGA should be considered when INVEGA is co-administered with valproate after clinical assessment.

Concomitant use of INVEGA with risperidone
Concomitant use of INVEGA with oral risperidone is not recommended as paliperidone is the active metabolite of risperidone and the combination of the two may lead to additive paliperidone exposure.

Concomitant use of INVEGA with psychostimulants
The combined use of psychostimulants (e.g., methylphenidate) with paliperidone can lead to extrapyramidal symptoms upon change of either or both treatments (see section 4.4).

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of paliperidone during pregnancy.

Paliperidone was not teratogenic in animal studies, but other types of reproductive toxicity were observed (see section 5.3). Neonates exposed to antipsychotics (including paliperidone) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully. INVEGA should not be used during pregnancy unless clearly necessary. If discontinuation during pregnancy is necessary, it should not be done abruptly.

Breast-feeding
Paliperidone is excreted in the breast milk to such an extent that effects on the breast-fed infant are likely if therapeutic doses are administered to breast-feeding women. INVEGA should not be used while breast feeding.

Fertility
There were no relevant effects observed in the non-clinical studies.

4.7 Effects on ability to drive and use machines

Paliperidone can have minor or moderate influence on the ability to drive and use machines due to potential nervous system and visual effects (see section 4.8). Therefore, patients should be advised not to drive or operate machines until their individual susceptibility to INVEGA is known.

4.8 Undesirable effects

Adults
Summary of the safety profile
The adverse drug reactions (ADRs) most frequently reported in clinical trials with adults were headache, insomnia, sedation/somnolence, parkinsonism, akathisia, tachycardia, tremor, dystonia, upper respiratory tract infection, anxiety, dizziness, weight increased, nausea, agitation, constipation, vomiting, fatigue, depression, dyspepsia, diarrhoea, dry mouth, toothache, musculoskeletal pain, hypertension, asthenia, back pain, electrocardiogram QT prolonged, and cough.

The ADRs that appeared to be dose-related included headache, sedation/somnolence, parkinsonism, akathisia, tachycardia, dystonia, dizziness, tremor, upper respiratory tract infection, dyspepsia, and musculoskeletal pain.

In the schizoaffective disorder studies, a greater proportion of subjects in the total INVEGA dose group who were receiving concomitant therapy with an antidepressant or mood stabiliser experienced adverse events as compared to those subjects treated with INVEGA monotherapy.

Tabulated list of adverse reactions
The following are all the ADRs that were reported in clinical trials and post-marketing experience with paliperidone by frequency category estimated from INVEGA clinical trials in adults. The following terms and frequencies are applied: *very common* (≥ 1/10), *common* (≥ 1/100 to < 1/10), *uncommon* (≥ 1/1 000 to < 1/100), *rare* (≥ 1/10 000 to < 1/1 000), *very rare* (< 1/10 000), and *not known* (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	**Adverse Drug Reaction**				
	Frequency				
	Very common	**Common**	**Uncommon**	**Rare**	**Not known**
Infections and infestations		bronchitis, upper respiratory tract infection, sinusitis, urinary tract infection, influenza	pneumonia, respiratory tract infection, cystitis, ear infection, tonsillitis	eye infection, onychomycosis, cellulitis, acarodermatitis	
Blood and lymphatic system disorders			white blood cell count decreased, thrombocytopenia, anaemia, haematocrit decreased	agranulocytosis[c], neutropenia, eosinophil count increased	
Immune system disorders				anaphylactic reaction, hypersensitivity	

Endocrine disorders			hyperprolactinaemia[a]	inappropriate antidiuretic hormone secretion[c], glucose urine present	
Metabolism and nutrition disorders		weight increased, increased appetite, weight decreased, decreased appetite	diabetes mellitus[d], hyperglycaemia, waist circumference increased, anorexia, blood triglycerides increased	water intoxication, diabetic ketoacidosis[c], hypoglycaemia, polydipsia, blood cholesterol increased	hyperinsulinaemia
Psychiatric disorders	insomnia[e]	mania, agitation, depression, anxiety	sleep disorder, confusional state, libido decreased, anorgasmia, nervousness, nightmare	catatonia, somnambulism, blunted affect[c]	
Nervous system disorders	parkinsonism[b], akathisia[b], sedation/ somnolence, headache	dystonia[b], dizziness, dyskinesia[b], tremor[b]	tardive dyskinesia, convulsion[e], syncope, psychomotor hyperactivity, dizziness postural, disturbance in attention, dysarthria, dysgeusia, hypoaesthesia, paresthaesia	neuroleptic malignant syndrome, cerebral ischaemia, unresponsive to stimuli[c], loss of consciousness, depressed level of consciousness[c], diabetic coma[c] balance disorder, coordination abnormal, head titubation[c]	
Eye disorders		vision blurred	photophobia, conjunctivitis, dry eye	glaucoma, eye movement disorder[c], eye rolling[c], lacrimation increased, ocular hyperaemia	
Ear and labyrinth disorders			vertigo, tinnitus, ear pain		
Cardiac disorders		atrioventricular block, conduction disorder, electrocardiogram QT prolonged, bradycardia, tachycardia	sinus arrhythmia, electrocardiogram abnormal, palpitations	atrial fibrillation, postural orthostatic tachycardia syndrome[c]	
Vascular disorders		orthostatic hypotension, hypertension	hypotension	pulmonary embolism, venous thrombosis, ischaemia, flushing	
Respiratory, thoracic and mediastinal disorders		pharyngolaryngeal pain, cough, nasal congestion	dyspnoea, wheezing, epistaxis	sleep apnoea syndrome, hyperventilation, pneumonia aspiration, respiratory tract congestion, dysphonia	pulmonary congestion
Gastrointestinal disorders		abdominal pain, abdominal discomfort, vomiting, nausea, constipation, diarrhoea, dyspepsia, dry mouth, toothache	swollen tongue, gastroenteritis, dysphagia, flatulence	pancreatitis[c], intestinal obstruction, ileus, faecal incontinence, faecaloma[c], cheilitis	

Hepatobiliary disorders		transaminases increased	gamma-glutamyltransferase increased, hepatic enzyme increased	jaundice	
Skin and subcutaneous tissue disorders		pruritus, rash	urticaria, alopecia, eczema, acne	angioedema, drug eruption[c], hyperkeratosis, dry skin, erythema, skin discolouration, seborrhoeic dermatitis, dandruff	
Musculoskeletal and connective tissue disorders		musculoskeletal pain, back pain, arthralgia	blood creatine phosphokinase increased, muscle spasms, joint stiffness, joint swelling, muscular weakness, neck pain	rhabdomyolysis[c], posture abnormal[c]	
Renal and urinary disorders			urinary incontinence, pollakiuria, urinary retention, dysuria		
Pregnancy, puerperium and perinatal conditions				drug withdrawal syndrome neonatal (see section 4.6)[c]	
Reproductive system and breast disorders		amenorrhoea	erectile dysfunction, ejaculation disorder, menstrual disorder[e], galactorrhoea, sexual dysfunction, breast pain, breast discomfort	priapism[c], menstruation delayed[c], gynaecomastia, breast engorgement, breast enlargement[c], breast discharge, vaginal discharge	
General disorders		pyrexia, asthenia, fatigue	face oedema, oedema[e], chills, body temperature increased, gait abnormal, thirst, chest pain, chest discomfort, malaise	hypothermia[c], body temperature decreased[c], drug withdrawal syndrome[c], induration[c]	
Injury, poisoning and procedural complications			fall		

[a] Refer to 'Hyperprolactinaemia' below.

[b] Refer to 'Extrapyramidal symptoms' below.

[c] Not observed in INVEGA clinical studies but observed in post-marketing environment with paliperidone.

[d] In placebo-controlled pivotal trials, diabetes mellitus was reported in 0.05% in INVEGA-treated subjects compared to a rate of 0% in placebo group. Overall incidence from all clinical trials was 0.14% in all INVEGA-treated subjects.

[e] **Insomnia includes:** initial insomnia, middle insomnia; **Convulsion includes:** grand mal convulsion; **Oedema includes:** generalised oedema, oedema peripheral, pitting oedema; **Menstrual disorder includes:** menstruation irregular, oligomenorrhoea.

Undesirable effects noted with risperidone formulations

Paliperidone is the active metabolite of risperidone, therefore, the adverse reaction profiles of these compounds (including both the oral and injectable formulations) are relevant to one another. In addition to the above adverse reactions, the following adverse reactions have been noted with the use of risperidone products and can be expected to occur with INVEGA.

Psychiatric disorders: sleep-related eating disorder

Nervous system disorders: cerebrovascular disorder

Eye disorders: floppy iris syndrome (intraoperative)

Respiratory, thoracic and mediastinal disorders: rales

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome/toxic epidermal necrolysis

Description of selected adverse reactions

Extrapyramidal symptoms (EPS)

In schizophrenia clinical trials, there was no difference observed between placebo and the 3 and 6 mg doses of INVEGA. Dose dependence for EPS was seen with the two higher doses of INVEGA (9 and 12 mg). In the schizoaffective disorder studies, the incidence of EPS was observed at a higher rate than placebo in all dose groups without a clear relationship to dose.

EPS included a pooled analysis of the following terms: Parkinsonism (includes salivary hypersecretion, musculoskeletal stiffness, parkinsonism, drooling, cogwheel rigidity, bradykinesia, hypokinesia, masked facies, muscle tightness, akinesia, nuchal rigidity, muscle rigidity, parkinsonian gait, and glabellar reflex abnormal, parkinsonian rest tremor), akathisia (includes akathisia, restlessness, hyperkinesia, and restless leg syndrome), dyskinesia (dyskinesia, muscle twitching, choreoathetosis, athetosis, and myoclonus), dystonia (includes dystonia, hypertonia, torticollis, muscle contractions involuntary, muscle contracture, blepharospasm, oculogyration, tongue paralysis, facial spasm, laryngospasm, myotonia, opisthotonus, oropharyngeal spasm, pleurothotonus, tongue spasm, and trismus), and tremor. It should be noted that a broader spectrum of symptoms are included that do not necessarily have an extrapyramidal origin.

Weight gain

In schizophrenia clinical trials, the proportions of subjects meeting a weight gain criterion of ≥ 7% of body weight were compared, revealing a similar incidence of weight gain for INVEGA 3 mg and 6 mg compared with placebo, and a higher incidence of weight gain for INVEGA 9 mg and 12 mg compared with placebo.

In schizoaffective disorder clinical trials, a higher percentage of INVEGA-treated subjects (5%) had an increase in body weight of ≥ 7% compared with placebo-treated subjects (1%). In the study that examined two dose groups (see section 5.1), the increase in body weight of ≥ 7% was 3% in the lower-dose (3-6 mg) group, 7% in the higher-dose (9-12 mg) group, and 1% in the placebo group.

Hyperprolactinaemia

In schizophrenia clinical trials, increases in serum prolactin were observed with INVEGA in 67% of subjects. Adverse reactions that may suggest increase in prolactin levels (e.g., amenorrhoea, galactorrhoea, menstrual disturbances, gynaecomastia) were reported overall in 2% of subjects. Maximum mean increases of serum prolactin concentrations were generally observed on day 15 of treatment, but remained above baseline levels at study endpoint.

Class effects

QT prolongation, ventricular arrythmias (ventricular fibrillation, ventricular tachycardia), sudden unexplained death, cardiac arrest and Torsade de pointes may occur with antipsychotics. Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotic drugs - Frequency unknown.

Paliperidone is the active metabolite of risperidone. The safety profile of risperidone may be pertinent.

Elderly

In a study conducted in elderly subjects with schizophrenia, the safety profile was similar to that seen in non-elderly subjects. INVEGA has not been studied in elderly patients with dementia. In clinical trials with some other atypical antipsychotics, increased risks of death and cerebrovascular accidents have been reported (see section 4.4).

Paediatric population

Summary of the safety profile

In one short-term and two longer-term studies with paliperidone prolonged-release tablets conducted in adolescents 12 years and older with schizophrenia, the overall safety profile was similar to that seen in adults. In the pooled adolescent schizophrenia population (12 years and older, N = 545) exposed to INVEGA, the frequency and type of undesirable effects were similar to those in adults except for the

following ADRs that were reported more frequently in adolescents receiving INVEGA than adults receiving INVEGA (and more frequently than placebo): sedation/somnolence, parkinsonism, weight increase, upper respiratory tract infection, akathisia, and tremor were reported very commonly (≥ 1/10) in adolescents; abdominal pain, galactorrhoea, gynaecomastia, acne, dysarthria, gastroenteritis, epistaxis, ear infection, blood triglyceride increased, and vertigo were reported commonly (≥ 1/100, < 1/10) in adolescents.

Extrapyramidal Symptoms (EPS)
In the short-term, placebo-controlled, fixed-dose adolescent study, the incidence of EPS was higher than placebo for all doses of INVEGA with an increased frequency of EPS at higher doses. Across all adolescent studies, EPS was more common in adolescents than in adults for each INVEGA dose.

Weight gain
In the short-term, placebo-controlled, fixed-dose adolescent study, a higher percentage of INVEGA-treated subjects (6-19% depending on dose) had an increase in body weight of ≥ 7% compared to placebo-treated subjects (2%). There was no clear dose relationship. In the long-term 2-year study, the subjects who were exposed to INVEGA during both the double-blind and open-label studies reported a modest weight gain (4.9 kg).

In adolescents, weight gain should be assessed against that expected with normal growth.

Prolactin
In the up to 2-year, open-label treatment study of INVEGA in adolescents with schizophrenia, incidence of elevated serum prolactin levels occurred in 48% of females and 60% of males. Adverse reactions that may suggest increase in prolactin levels (e.g., amenorrhoea, galactorrhoea, menstrual disturbances, gynaecomastia) were reported overall in 9.3% of subjects.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medical product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In general, expected signs and symptoms are those resulting from an exaggeration of paliperidone's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, QT prolongation, and extrapyramidal symptoms. Torsade de pointes and ventricular fibrillation have been reported in association with overdose. In the case of acute overdosage, the possibility of multiple medicinal product involvement should be considered.

Consideration should be given to the prolonged-release nature of the product when assessing treatment needs and recovery. There is no specific antidote to paliperidone. General supportive measures should be employed. Establish and maintain a clear airway and ensure adequate oxygenation and ventilation. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring for possible arrhythmias. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluid and/or sympathomimetic agents. Administration of activated charcoal together with a laxative should be considered. In case of severe extrapyramidal symptoms, anticholinergic agents should be administered. Close supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacologic group: Psycholeptics, other antipsychotics, ATC code: N05AX13

INVEGA contains a racemic mixture of (+)- and (-)-paliperidone.

Mechanism of action

Paliperidone is a selective blocking agent of monoamine effects, whose pharmacological properties are different from that of traditional neuroleptics. Paliperidone binds strongly to serotonergic 5-HT2- and dopaminergic D2-receptors. Paliperidone also blocks alfa1-adrenergic receptors and blocks, to a lesser extent, H1-histaminergic and alfa2-adrenergic receptors. The pharmacological activity of the (+)- and (-)-paliperidone enantiomers are qualitatively and quantitatively similar.

Paliperidone is not bound to cholinergic receptors. Even though paliperidone is a strong D2-antagonist, which is believed to relieve the positive symptoms of schizophrenia, it causes less catalepsy and decreases motor functions to a lesser extent than traditional neuroleptics. Dominating central serotonin antagonism may reduce the tendency of paliperidone to cause extrapyramidal side effects.

Clinical efficacy

Schizophrenia

The efficacy of INVEGA in the treatment of schizophrenia was established in three multi-centre, placebo-controlled, double-blind, 6-week trials in subjects who met DSM-IV criteria for schizophrenia. INVEGA doses, which varied across the three studies, ranged from 3 to 15 mg once daily. The primary efficacy endpoint was defined as a decrease in total Positive and Negative Syndrome Scale (PANSS) scores as shown in the following table. The PANSS is a validated multi-item inventory composed of five factors to evaluate positive symptoms, negative symptoms, disorganised thoughts, uncontrolled hostility/excitement, and anxiety/depression. All tested doses of INVEGA separated from placebo on day 4 ($p < 0.05$). Predefined secondary endpoints included the Personal and Social Performance (PSP) scale and the Clinical Global Impression – Severity (CGI-S) scale. In all three studies, INVEGA was superior to placebo on PSP and CGI-S. Efficacy was also evaluated by calculation of treatment response (defined as decrease in PANSS Total Score ≥ 30%) as a secondary endpoint.

Schizophrenia Studies: Positive and Negative Syndrome Scale for Schizophrenia (PANSS) Total Score - Change From Baseline to End Point - LOCF for Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Intent-to-Treat Analysis Set

	Placebo	INVEGA 3 mg	INVEGA 6 mg	INVEGA 9 mg	INVEGA 12 mg
R076477-SCH-303	(N = 126)		(N = 123)	(N = 122)	(N = 129)
Mean baseline (SD)	94.1 (10.74)		94.3 (10.48)	93.2 (11.90)	94.6 (10.98)
Mean change (SD)	-4.1 (23.16)		-17.9 (22.23)	-17.2 (20.23)	-23.3 (20.12)
P-value (vs, Placebo)			<0.001	<0.001	<0.001
Diff. of LS Means (SE)			-13.7 (2.63)	-13.5 (2.63)	-18.9 (2.60)
R076477-SCH-304	(N = 105)		(N = 111)		(N = 111)
Mean baseline (SD)	93.6 (11.71)		92.3 (11.96)		94.1 (11.42)
Mean change (SD)	-8.0 (21.48)		-15.7 (18.89)		-17.5 (19.83)
P-value (vs, Placebo)			0.006		<0.001
Diff. of LS Means (SE)			-7.0 (2.36)		-8.5 (2.35)
R076477-SCH-305	(N = 120)	(N = 123)		(N = 123)	
Mean baseline (SD)	93.9 (12.66)	91.6 (12.19)		93.9 (13.20)	
Mean change (SD)	-2.8 (20.89)	-15.0 (19.61)		-16.3 (21.81)	
P-value (vs, Placebo)		<0.001		<0.001	
Diff. of LS Means (SE)		-11.6 (2.35)		-12.9 (2.34)	

Note: Negative change in score indicates improvement. For all 3 studies, an active control (olanzapine at a dose of 10 mg) was included. LOCF = last observation carried forward. The 1-7 version of the PANSS was used. A 15 mg dose was also included in Study R076477-SCH-305, but results are not presented since this is above the maximum recommended daily dose of 12 mg.

Schizophrenia Studies: Proportion of Subjects with Responder Status at LOCF End Point Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Intent-to-Treat Analysis Set					
	Placebo	INVEGA 3 mg	INVEGA 6 mg	INVEGA 9 mg	INVEGA 12 mg
R076477-SCH-303					
N	126		123	122	129
Responder, n (%)	38 (30.2)		69 (56.1)	62 (50.8)	79 (61.2)
Non-responder, n (%)	88 (69.8)		54 (43.9)	60 (49.2)	50 (38.8)
P value (vs Placebo)	--		< 0.001	0.001	< 0.001
R076477-SCH-304					
N	105		110		111
Responder, n (%)	36 (34.3)		55 (50.0)		57 (51.4)
Non-responder, n (%)	69 (65.7)		55 (50.0)		54 (48.6)
P value (vs Placebo)	--		0.025		0.012
R076477-SCH-305					
N	120	123		123	
Responder, n (%)	22 (18.3)	49 (39.8)		56 (45.5)	
Non-responder, n (%)	98 (81.7)	74 (60.2)		67 (54.5)	
P value (vs Placebo)	--	0.001		< 0.001	

In a long-term trial designed to assess the maintenance of effect, INVEGA was significantly more effective than placebo in maintaining symptom control and delaying relapse of schizophrenia. After having been treated for an acute episode for 6 weeks and stabilised for an additional 8 weeks with INVEGA (doses ranging from 3 to 15 mg once daily) patients were then randomised in a double-blind manner to either continue on INVEGA or on placebo until they experienced a relapse in schizophrenia symptoms. The trial was stopped early for efficacy reasons by showing a significantly longer time to relapse in patients treated with INVEGA compared to placebo (p=0.0053).

Schizoaffective disorder
The efficacy of INVEGA in the acute treatment of psychotic or manic symptoms of schizoaffective disorder was established in two placebo-controlled, 6-week trials in non-elderly adult subjects. Enrolled subjects 1) met DSM-IV criteria for schizoaffective disorder, as confirmed by the Structured Clinical Interview for DSM-IV Disorders, 2) had a Positive and Negative Syndrome Scale (PANSS) total score of at least 60, and 3) had prominent mood symptoms as confirmed by a score of at least 16 on the Young Mania Rating Scale (YMRS) and/or Hamilton Rating Scale 21 for Depression (HAM-D 21). The population included subjects with schizoaffective bipolar and depressive types. In one of these trials, efficacy was assessed in 211 subjects who received flexible doses of INVEGA (3-12 mg once daily). In the other study, efficacy was assessed in 203 subjects who were assigned to one of two dose levels of INVEGA: 6 mg with the option to reduce to 3 mg (n = 105) or 12 mg with the option to reduce to 9 mg (n = 98) once daily. Both studies included subjects who received INVEGA either as monotherapy or in combination with mood stabilisers and/or antidepressants. Dosing was in the morning without regard to meals. Efficacy was evaluated using the PANSS.

The INVEGA group in the flexible-dose study (dosed between 3 and 12 mg/day, mean modal dose of 8.6 mg/day) and the higher dose group of INVEGA in the 2 dose-level study (12 mg/day with option to reduce to 9 mg/day) were each superior to placebo in the PANSS at 6 weeks. In the lower dose group of the 2 dose-level study (6 mg/day with option to reduce to 3 mg/day), INVEGA was not significantly different from placebo as measured by the PANSS. Only few subjects received the 3 mg dose in both studies and efficacy of this dose could not be established. Statistically superior improvements in manic symptoms as measured by YMRS (secondary efficacy scale) were observed in patients from the flexible-dose study and the INVEGA higher dose in the second study.

Taking the results of both studies together (pooled study-data), INVEGA improved the psychotic and manic symptoms of schizoaffective disorder at endpoint relative to placebo when administered either as monotherapy or in combination with mood stabilisers and/or antidepressants. However, overall the magnitude of effect in regard to PANSS and YMRS observed on monotherapy was larger than that observed with concomitant antidepressants and/or mood stabilisers. Moreover, in the pooled population, INVEGA was not efficacious in patients concomitantly receiving mood stabiliser and antidepressants in regard to the psychotic symptoms, but this population was small (30 responders in

the paliperidone group and 20 responders in the placebo group). Additionally, in study SCA-3001 in the ITT population the effect on psychotic symptoms measured by PANSS was clearly less pronounced and not reaching statistical significance for patients receiving concomitantly mood stabilisers and/or antidepressants. An effect of INVEGA on depressive symptoms was not demonstrated in these studies, but has been demonstrated in a long-term study with the long-acting injectable formulation of paliperidone (described further down in this section).

An examination of population subgroups did not reveal any evidence of differential responsiveness on the basis of gender, age, or geographic region. There were insufficient data to explore differential effects based on race. Efficacy was also evaluated by calculation of treatment response (defined as decrease in PANSS Total Score ≥ 30% and CGI-C Score ≤ 2) as a secondary endpoint.

Schizoaffective Disorder Studies: Primary Efficacy Parameter, PANSS Total Score Change from Baseline from Studies R076477-SCA-3001 and R076477-SCA-3002: Intent-to-Treat Analysis Set

	Placebo	INVEGA Lower Dose (3-6 mg)	INVEGA Higher Dose (9-12 mg)	INVEGA Flexible Dose (3-12 mg)
R076477-SCA-3001	(N=107)	(N=105)	(N=98)	
Mean baseline (SD)	91.6 (12.5)	95.9 (13.0)	92.7 (12.6)	
Mean change (SD)	-21.7 (21.4)	-27.4 (22.1)	-30.6 (19.1)	
P-value (vs. Placebo)		0.187	0.003	
Diff. of LS Means (SE)		-3.6 (2.7)	-8.3 (2.8)	
R076477-SCA-3002	(N=93)			(N=211)
Mean baseline (SD)	91.7 (12.1)			92.3 (13.5)
Mean change (SD)	-10.8 (18.7)			-20.0 (20.23)
P-value (vs. Placebo)				< 0.001
Diff. of LS Means (SE)				-13.5 (2.63)

Note: Negative change in score indicates improvement. LOCF = last observation carried forward.

Schizoaffective Disorder Studies: Secondary Efficacy Parameter, Proportion of Subjects with Responder Status at LOCF End Point: Studies R076477-SCA-3001 and R076477-SCA-3002: Intent-to-Treat Analysis Set

	Placebo	INVEGA Lower Dose (3-6 mg)	INVEGA Higher Dose (9-12 mg)	INVEGA Flexible Dose (3-12 mg)
R076477-SCA-3001				
N	107	104	98	
Responder, n (%)	43 (40.2)	59 (56.7)	61 (62.2)	
Non-responder, n (%)	64 (59.8)	45 (43.3)	37 (37.8)	
P value (vs Placebo)	--	0.008	0.001	
R076477-SCA-3002				
N	93			210
Responder, n (%)	26 (28.0)			85 (40.5)
Non-responder, n (%)	67 (72.0)			125 (59.5)
P value (vs Placebo)	--			0.046

Response defined as decrease from baseline in PANSS Total Score ≥ 30% and CGI-C Score ≤ 2

In a long-term trial designed to assess the maintenance of effect, the long-acting injectable formulation of paliperidone was significantly more effective than placebo in maintaining symptom control and delaying relapse of psychotic, manic, and depressive symptoms of schizoaffective disorder. After having been successfully treated for an acute psychotic or mood episode for 13 weeks and stabilised for an additional 12 weeks with the long-acting injectable formulation of paliperidone (doses ranging from 50 to 150 mg) patients were then randomised to a 15-month double-blind relapse prevention period of the study to either continue on the long-acting injectable formulation of paliperidone or on placebo until they experienced a relapse of schizoaffective symptoms. The study showed a significantly longer time to relapse in patients treated with the long-acting injectable formulation of paliperidone compared to placebo ($p < 0.001$).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with INVEGA in all subsets of the paediatric population in the treatment of schizoaffective disorders. (See section 4.2 for information on paediatric use).

The efficacy of INVEGA in the treatment of schizophrenia in adolescents between 12 and 14 years old has not been established.

The efficacy of INVEGA in adolescent subjects with schizophrenia (INVEGA N = 149, placebo N = 51) was studied in a randomised, double-blind, placebo-controlled, 6-week study using a fixed-dose weight-based treatment group design over the dose range of 1.5 mg/day to 12 mg/day. Subjects were 12-17 years of age and met DSM-IV criteria for schizophrenia. Efficacy was evaluated using PANSS. This study demonstrated the efficacy of INVEGA of the medium dose group in adolescent subjects with schizophrenia. Secondary by dose analysis demonstrated the efficacy of 3 mg, 6 mg, and 12 mg dose given once daily.

Adolescent Schizophrenia Study: R076477-PSZ-3001: 6-week, fixed-dose, placebo-controlled Intent-to-Treat Analysis Set. LOCF endpoint change from baseline				
	Placebo N=51	INVEGA Low Dose 1.5 mg N=54	INVEGA Medium Dose 3 or 6 mg* N=48	INVEGA High Dose 6 or 12 mg** N=47
Change in PANSS Score				
Mean baseline (SD)	90.6 (12.13)	91.6 (12.54)	90.6 (14.01)	91.5 (13.86)
Mean change (SD)	-7.9 (20.15)	-9.8 (16.31)	-17.3 (14.33)	-13.8 (15.74)
P-value (vs Placebo)		0.508	0.006	0.086
Diff. of LS Means (SE)		-2.1 (3.17)	-10.1 (3.27)	-6.6 (3.29)
Responder Analysis				
Responder, n (%)	17 (33.3)	21 (38.9)	31 (64.6)	24 (51.1)
Non-responder, n (%)	34 (66.7)	33 (61.1)	17 (35.4)	23 (48.9)
P value (vs Placebo)		0.479	0.001	0.043

Response defined as decrease from baseline in PANSS Total Score ≥ 20%

Note: Negative change in score indicates improvement. LOCF = last observation carried forward.

* Medium dose group: 3 mg for subjects < 51 kg, 6 mg for subjects ≥ 51 kg

** High dose group: 6 mg for subjects < 51 kg, 12 mg for subjects ≥ 51 kg

Efficacy of INVEGA over a flexible dose range of 3 mg/day to 9 mg/day in adolescent subjects (12 years and older) with schizophrenia (INVEGA N = 112, aripiprazole N = 114) was also evaluated in a randomised, double-blind, active-controlled study that included an 8-week, double-blind acute phase and an 18-week, double-blind maintenance phase. The changes in PANSS total scores from baseline to week 8 and week 26 were numerically similar between the INVEGA and aripiprazole treatment groups. In addition, the difference in the percentage of patients demonstrating ≥ 20% improvement in PANSS total score at week 26 between the two treatment groups was numerically similar.

Adolescent Schizophrenia Study: R076477-PSZ-3003: 26-week, flexible-dose, active-controlled Intent-to-Treat Analysis Set. LOCF endpoint change from baseline		
	INVEGA 3-9 mg N=112	Aripiprazole 5-15 mg N=114
Change in PANSS Score **8 week, acute endpoint**		
Mean baseline (SD)	89.6 (12.22)	92.0 (12.09)
Mean change (SD)	-19.3 (13.80)	-19.8 (14.56)
P-value (vs aripiprazole)	0.935	
Diff. of LS Means (SE)	0.1 (1.83)	

Change in PANSS Score **26 week endpoint**		
Mean baseline (SD)	89.6 (12.22)	92.0 (12.09)
Mean change (SD)	-25.6 (16.88)	-26.8 (18.82)
P-value (vs aripiprazole)	0.877	
Diff. of LS Means (SE)	-0.3 (2.20)	
Responder Analysis **26 week endpoint**		
Responder, n (%)	86 (76.8)	93 (81.6)
Non-responder, n (%)	26 (23.2)	21 (18.4)
P value (vs aripiprazole)	0.444	

Response defined as decrease from baseline in PANSS Total Score ≥ 20%
Note: Negative change in score indicates improvement. LOCF = last observation carried forward.

5.2 Pharmacokinetic properties

The pharmacokinetics of paliperidone following INVEGA administration are dose proportional within the available dose range.

Absorption
Following a single dose, INVEGA exhibits a gradual ascending release rate, allowing the plasma concentrations of paliperidone to steadily rise to reach peak plasma concentration (C_{max}) approximately 24 hours after dosing. With once-daily dosing of INVEGA, steady-state concentrations of paliperidone are attained within 4-5 days of dosing in most subjects.

Paliperidone is the active metabolite of risperidone. The release characteristics of INVEGA result in minimal peak-trough fluctuations as compared to those observed with immediate-release risperidone (fluctuation index 38% versus 125%).

The absolute oral bioavailability of paliperidone following INVEGA administration is 28% (90% CI of 23%-33%).

Administration of paliperidone prolonged-release tablets with a standard high-fat/high-caloric meal increases C_{max} and AUC of paliperidone by up to 50-60% compared with administration in the fasting state.

Distribution
Paliperidone is rapidly distributed. The apparent volume of distribution is 487 L. The plasma protein binding of paliperidone is 74%. It binds primarily to α1-acid glycoprotein and albumin.

Biotransformation and elimination
One week following administration of a single oral dose of 1 mg immediate-release ^{14}C-paliperidone, 59% of the dose was excreted unchanged into urine, indicating that paliperidone is not extensively metabolised by the liver. Approximately 80% of the administered radioactivity was recovered in urine and 11% in the faeces. Four metabolic pathways have been identified *in vivo*, none of which accounted for more than 6.5% of the dose: dealkylation, hydroxylation, dehydrogenation, and benzisoxazole scission. Although *in vitro* studies suggested a role for CYP2D6 and CYP3A4 in the metabolism of paliperidone, there is no evidence *in vivo* that these isozymes play a significant role in the metabolism of paliperidone. Population pharmacokinetics analyses indicated no discernible difference on the apparent clearance of paliperidone after administration of INVEGA between extensive metabolisers and poor metabolisers of CYP2D6 substrates. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of medicines metabolised by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. The terminal elimination half-life of paliperidone is about 23 hours.

In vitro studies have shown that paliperidone is a P-gp substrate and a weak inhibitor of P-gp at high concentrations. No *in vivo* data are available and the clinical relevance is unknown.

Hepatic impairment
Paliperidone is not extensively metabolised in the liver. In a study in subjects with moderate hepatic impairment (Child-Pugh class B), the plasma concentrations of free paliperidone were similar to those of healthy subjects. No data are available in patients with severe hepatic impairment (Child-Pugh class C).

Renal impairment
Elimination of paliperidone decreased with decreasing renal function. Total clearance of paliperidone was reduced in subjects with impaired renal function by 32% in mild (Creatinine Clearance [CrCl] = 50 to < 80 mL/min), 64% in moderate (CrCl = 30 to < 50 mL/min), and 71% in severe (CrCl = < 30 mL/min) renal impairment. The mean terminal elimination half-life of paliperidone was 24, 40, and 51 hours in subjects with mild, moderate, and severe renal impairment, respectively, compared with 23 hours in subjects with normal renal function (CrCl ≥ 80 mL/min).

Elderly
Data from a pharmacokinetic study in elderly subjects (≥ 65 years of age, n = 26) indicated that the apparent steady-state clearance of paliperidone following INVEGA administration was 20% lower compared to that of adult subjects (18-45 years of age, n = 28). However, there was no discernable effect of age in the population pharmacokinetic analysis involving schizophrenia subjects after correction of age-related decreases in CrCl.

Adolescents
Paliperidone systemic exposure in adolescent subjects (15 years and older) was comparable to that in adults. In adolescents weighing < 51 kg, a 23% higher exposure was observed than in adolescents weighing ≥ 51 kg. Age alone did not influence the paliperidone exposure.

Race
Population pharmacokinetics analysis revealed no evidence of race-related differences in the pharmacokinetics of paliperidone following INVEGA administration.

Gender
The apparent clearance of paliperidone following INVEGA administration is approximately 19% lower in women than men. This difference is largely explained by differences in lean body mass and creatinine clearance between men and women.

Smoking status
Based on *in vitro* studies utilising human liver enzymes, paliperidone is not a substrate for CYP1A2; smoking should, therefore, not have an effect on the pharmacokinetics of paliperidone. A population pharmacokinetic analysis showed a slightly lower exposure to paliperidone in smokers compared with non-smokers. The difference is unlikely to be of clinical relevance, though.

5.3 Preclinical safety data

Repeat-dose toxicity studies of paliperidone in rat and dog showed mainly pharmacological effects, such as sedation and prolactin-mediated effects on mammary glands and genitals. Paliperidone was not teratogenic in rat and rabbit. In rat reproduction studies using risperidone, which is extensively converted to paliperidone in rats and humans, a reduction was observed in the birth weight and survival of the offspring. Other dopamine antagonists, when administered to pregnant animals, have caused negative effects on learning and motor development in the offspring. Paliperidone was not genotoxic in a battery of tests. In oral carcinogenicity studies of risperidone in rats and mice, increases in pituitary gland adenomas (mouse), endocrine pancreas adenomas (rat), and mammary gland adenomas (both species) were seen. These tumours can be related to prolonged dopamine D2 antagonism and hyperprolactinaemia. The relevance of these tumour findings in rodents in terms of human risk is unknown.

In a 7-week juvenile toxicity study in rats administered oral doses of paliperidone up to 2.5 mg/kg/day, corresponding to an exposure approximately equal to the clinical exposure based on AUC, no effects

on growth, sexual maturation and reproductive performance were observed. Paliperidone did not impair the neurobehavioural development in males at doses up to 2.5 mg/kg/day. At 2.5 mg/kg/day in females, an effect on learning and memory was observed. This effect was not observed after discontinuation of treatment. In a 40-week juvenile toxicity study in dogs with oral doses of risperidone (which is extensively converted to paliperidone) up to 5 mg/kg/day, effects on sexual maturation, long bone growth and femur mineral density were observed from 3 times the clinical exposure based on AUC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

3 mg

Core
Polyethylene oxide 200K
Sodium chloride
Povidone (K29-32)
Stearic acid
Butyl hydroxytoluene (E321)
Ferric oxide (yellow) (E172)
Polyethylene oxide 7000K
Ferric oxide (red) (E172)
Hydroxyethyl cellulose
Polyethylene glycol 3350
Cellulose acetate

Overcoat
Hypromellose
Titanium dioxide (E171)
Lactose monohydrate
Triacetin
Carnauba wax

Printing ink
Iron oxide (black) (E172)
Propylene glycol
Hypromellose

6 mg

Core
Polyethylene oxide 200K
Sodium chloride
Povidone (K29-32)
Stearic acid
Butyl hydroxytoluene (E321)
Polyethylene oxide 7000K
Ferric oxide (red) (E172)
Hydroxyethyl cellulose
Polyethylene glycol 3350
Cellulose acetate

Overcoat
Hypromellose
Titanium dioxide (E171)
Polyethylene glycol 400
Ferric oxide (yellow) (E172)

Ferric oxide (red) (E172)
Carnauba wax

Printing ink
Iron oxide (black) (E172)
Propylene glycol
Hypromellose

9 mg
Core
Polyethylene oxide 200K
Sodium chloride
Povidone (K29-32)
Stearic acid
Butyl hydroxytoluene (E321)
Polyethylene oxide 7000K
Ferric oxide (red) (E172)
Iron oxide (black) (E172)
Hydroxyethyl cellulose
Polyethylene glycol 3350
Cellulose acetate

Overcoat
Hypromellose
Titanium dioxide (E171)
Polyethylene glycol 400
Ferric oxide (red) (E172)
Carnauba wax

Printing ink
Iron oxide (black) (E172)
Propylene glycol
Hypromellose

12 mg
Core
Polyethylene oxide 200K
Sodium chloride
Povidone (K29-32)
Stearic acid
Butyl hydroxytoluene (E321)
Polyethylene oxide 7000K
Ferric oxide (red) (E172)
Ferric oxide (yellow) (E172)
Hydroxyethyl cellulose
Polyethylene glycol 3350
Cellulose acetate

Overcoat
Hypromellose
Titanium dioxide (E171)
Polyethylene glycol 400
Ferric oxide (yellow) (E172)
Carnauba wax

Printing ink
Iron oxide (black) (E172)

Propylene glycol
Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Bottles: Do not store above 30°C. Keep the bottle tightly closed in order to protect from moisture.
Blisters: Do not store above 30°C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

Bottles:
White high-density polyethylene (HDPE) bottle with induction sealing and polypropylene child-resistant closure. Each bottle contains two 1 g dessicant silica gel (silicone dioxide) pouches (pouch is food approved polyethylene).

Pack sizes of 30 and 350 prolonged-release tablets.

Blisters:
Polyvinyl chloride (PVC) laminated with polychloro-trifluoroethylene (PCTFE)/aluminium push-through layer.
Pack sizes of 14, 28, 30, 49, 56, and 98 prolonged-release tablets.

Or

White polyvinyl chloride (PVC) laminated with polychloro-trifluoroethylene (PCTFE)/aluminium push-through layer.
Pack sizes of 14, 28, 30, 49, 56, and 98 prolonged-release tablets.

Or

Oriented polyamide (OPA)-aluminium-polyvinyl chloride (PVC)/aluminium push-through child-resistant blister.
Pack sizes of 14, 28, 49, 56, and 98 prolonged-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

3 mg
EU/1/07/395/001 - 005
EU/1/07/395/021 - 025
EU/1/07/395/041 - 044
EU/1/07/395/057 - 058
EU/1/07/395/065 - 067

6 mg
EU/1/07/395/006 - 010
EU/1/07/395/026 - 030
EU/1/07/395/045 - 048
EU/1/07/395/059 - 060
EU/1/07/395/068 - 070

9 mg
EU/1/07/395/011 - 015
EU/1/07/395/031 - 035
EU/1/07/395/049 - 052
EU/1/07/395/061 - 062
EU/1/07/395/071 - 073

12 mg
EU/1/07/395/016 - 020
EU/1/07/395/036 - 040
EU/1/07/395/053 - 056
EU/1/07/395/063 - 064
EU/1/07/395/074 - 076

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 June 2007
Date of latest renewal: 14 May 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu/.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Janssen-Cilag SpA
Via C. Janssen
IT-04100 Borgo San Michele
Latina
Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR PVC-PCTFE/ALUMINIUM BLISTER (for white and clear blister)

1. NAME OF THE MEDICINAL PRODUCT

INVEGA 3 mg prolonged-release tablets
INVEGA 6 mg prolonged-release tablets
INVEGA 9 mg prolonged-release tablets
INVEGA 12 mg prolonged-release tablets

paliperidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 3 mg paliperidone
Each prolonged-release tablet contains 6 mg paliperidone
Each prolonged-release tablet contains 9 mg paliperidone
Each prolonged-release tablet contains 12 mg paliperidone

3. LIST OF EXCIPIENTS

3 mg tablets
Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 prolonged-release tablets
28 prolonged-release tablets
30 prolonged-release tablets
49 prolonged-release tablets
56 prolonged-release tablets
98 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Swallow whole, do not chew, divide or crush.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

3 mg
14 prolonged-release tablets - EU/1/07/395/065 - CLEAR
28 prolonged-release tablets - EU/1/07/395/001 - CLEAR
30 prolonged-release tablets - EU/1/07/395/002 - CLEAR
49 prolonged-release tablets - EU/1/07/395/003 - CLEAR
56 prolonged-release tablets - EU/1/07/395/004 - CLEAR
98 prolonged-release tablets - EU/1/07/395/005 - CLEAR

14 prolonged-release tablets - EU/1/07/395/066 - WHITE
28 prolonged-release tablets - EU/1/07/395/021 - WHITE
30 prolonged-release tablets - EU/1/07/395/022 - WHITE
49 prolonged-release tablets - EU/1/07/395/023 - WHITE
56 prolonged-release tablets - EU/1/07/395/024 - WHITE
98 prolonged-release tablets - EU/1/07/395/025 - WHITE

6 mg
14 prolonged-release tablets - EU/1/07/395/068 - CLEAR
28 prolonged-release tablets - EU/1/07/395/006 - CLEAR
30 prolonged-release tablets - EU/1/07/395/007 - CLEAR
49 prolonged-release tablets - EU/1/07/395/008 - CLEAR
56 prolonged-release tablets - EU/1/07/395/009 - CLEAR
98 prolonged-release tablets - EU/1/07/395/010 - CLEAR

14 prolonged-release tablets - EU/1/07/395/069 - WHITE
28 prolonged-release tablets - EU/1/07/395/026 - WHITE
30 prolonged-release tablets - EU/1/07/395/027 - WHITE
49 prolonged-release tablets - EU/1/07/395/028 - WHITE
56 prolonged-release tablets - EU/1/07/395/029 - WHITE

98 prolonged-release tablets - EU/1/07/395/030 - WHITE

9 mg
14 prolonged-release tablets - EU/1/07/395/071 - CLEAR
28 prolonged-release tablets - EU/1/07/395/011 - CLEAR
30 prolonged-release tablets - EU/1/07/395/012 - CLEAR
49 prolonged-release tablets - EU/1/07/395/013 - CLEAR
56 prolonged-release tablets - EU/1/07/395/014 - CLEAR
98 prolonged-release tablets - EU/1/07/395/015 - CLEAR

14 prolonged-release tablets - EU/1/07/395/072 - WHITE
28 prolonged-release tablets - EU/1/07/395/031 - WHITE
30 prolonged-release tablets - EU/1/07/395/032 - WHITE
49 prolonged-release tablets - EU/1/07/395/033 - WHITE
56 prolonged-release tablets - EU/1/07/395/034 - WHITE
98 prolonged-release tablets - EU/1/07/395/035 - WHITE

12 mg
14 prolonged-release tablets - EU/1/07/395/074 - CLEAR
28 prolonged-release tablets - EU/1/07/395/016 - CLEAR
30 prolonged-release tablets - EU/1/07/395/017 - CLEAR
49 prolonged-release tablets - EU/1/07/395/018 - CLEAR
56 prolonged-release tablets - EU/1/07/395/019 - CLEAR
98 prolonged-release tablets - EU/1/07/395/020 - CLEAR

14 prolonged-release tablets - EU/1/07/395/075 - WHITE
28 prolonged-release tablets - EU/1/07/395/036 - WHITE
30 prolonged-release tablets - EU/1/07/395/037 - WHITE
49 prolonged-release tablets - EU/1/07/395/038 - WHITE
56 prolonged-release tablets - EU/1/07/395/039 - WHITE
98 prolonged-release tablets - EU/1/07/395/040 - WHITE

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

invega 3 mg
invega 6 mg
invega 9 mg
invega 12 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

7 & 10 TABLET PVC-PTFE/ALU BLISTER (for white and clear blister)

1. NAME OF THE MEDICINAL PRODUCT

INVEGA 3 mg prolonged-release tablets
INVEGA 6 mg prolonged-release tablets
INVEGA 9 mg prolonged-release tablets
INVEGA 12 mg prolonged-release tablets

paliperidone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV

3. EXPIRY DATE

EXP MM/YYYY

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR OPA-ALUMINIUM-PVC/ALUMINIUM BLISTER

1. NAME OF THE MEDICINAL PRODUCT

INVEGA 3 mg prolonged-release tablets
INVEGA 6 mg prolonged-release tablets
INVEGA 9 mg prolonged-release tablets
INVEGA 12 mg prolonged-release tablets

paliperidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 3 mg paliperidone
Each prolonged-release tablet contains 6 mg paliperidone
Each prolonged-release tablet contains 9 mg paliperidone
Each prolonged-release tablet contains 12 mg paliperidone

3. LIST OF EXCIPIENTS

3 mg tablets
Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

14 prolonged-release tablets
28 prolonged-release tablets
49 prolonged-release tablets
56 prolonged-release tablets
98 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Swallow whole, do not chew, divide or crush.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC
Store in the original package in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

3 mg
14 prolonged-release tablets - EU/1/07/395/067
28 prolonged-release tablets - EU/1/07/395/041
49 prolonged-release tablets - EU/1/07/395/042
56 prolonged-release tablets - EU/1/07/395/043
98 prolonged-release tablets - EU/1/07/395/044

6 mg
14 prolonged-release tablets - EU/1/07/395/070
28 prolonged-release tablets - EU/1/07/395/045
49 prolonged-release tablets - EU/1/07/395/046
56 prolonged-release tablets - EU/1/07/395/047
98 prolonged-release tablets - EU/1/07/395/048

9 mg
14 prolonged-release tablets - EU/1/07/395/073
28 prolonged-release tablets - EU/1/07/395/049
49 prolonged-release tablets - EU/1/07/395/050
56 prolonged-release tablets - EU/1/07/395/051
98 prolonged-release tablets - EU/1/07/395/052

12 mg
14 prolonged-release tablets - EU/1/07/395/076
28 prolonged-release tablets - EU/1/07/395/053
49 prolonged-release tablets - EU/1/07/395/054
56 prolonged-release tablets - EU/1/07/395/055
98 prolonged-release tablets - EU/1/07/395/056

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

invega 3 mg
invega 6 mg
invega 9 mg
invega 12 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

7 TABLET OPA-ALU-PVC/ALU BLISTER

1. NAME OF THE MEDICINAL PRODUCT

INVEGA 3 mg prolonged-release tablets
INVEGA 6 mg prolonged-release tablets
INVEGA 9 mg prolonged-release tablets
INVEGA 12 mg prolonged-release tablets

paliperidone

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV

3. EXPIRY DATE

EXP MM/YYYY

4. BATCH NUMBER

Lot

5. OTHER

Mon, Tue, Wed, Thu, Fri, Sat, Sun

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

BOTTLE CARTON

1. NAME OF THE MEDICINAL PRODUCT

INVEGA 3 mg prolonged-release tablets
INVEGA 6 mg prolonged-release tablets
INVEGA 9 mg prolonged-release tablets
INVEGA 12 mg prolonged-release tablets

paliperidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 3 mg paliperidone
Each prolonged-release tablet contains 6 mg paliperidone
Each prolonged-release tablet contains 9 mg paliperidone
Each prolonged-release tablet contains 12 mg paliperidone

3. LIST OF EXCIPIENTS

3 mg tablets
Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 prolonged-release tablets
350 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Swallow whole, do not chew, divide or crush.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC
Keep the bottle tightly closed in order to protect from moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

3 mg
30 prolonged-release tablets - EU/1/07/395/057
350 prolonged-release tablets - EU/1/07/395/058

6 mg
30 prolonged-release tablets - EU/1/07/395/059
350 prolonged-release tablets - EU/1/07/395/060

9 mg
30 prolonged-release tablets - EU/1/07/395/061
350 prolonged-release tablets - EU/1/07/395/062

12 mg
30 prolonged-release tablets - EU/1/07/395/063
350 prolonged-release tablets - EU/1/07/395/064

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

invega 3 mg
invega 6 mg
invega 9 mg
invega 12 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

INVEGA 3 mg prolonged-release tablets
INVEGA 6 mg prolonged-release tablets
INVEGA 9 mg prolonged-release tablets
INVEGA 12 mg prolonged-release tablets

paliperidone

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 3 mg paliperidone
Each prolonged-release tablet contains 6 mg paliperidone
Each prolonged-release tablet contains 9 mg paliperidone
Each prolonged-release tablet contains 12 mg paliperidone

3. LIST OF EXCIPIENTS

3 mg tablets
Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENT

30 prolonged-release tablets
350 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use
Swallow whole, do not chew, divide or crush.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC
Keep the bottle tightly closed in order to protect from moisture

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

3 mg
30 prolonged-release tablets - EU/1/07/395/057
350 prolonged-release tablets - EU/1/07/395/058

6 mg
30 prolonged-release tablets - EU/1/07/395/059
350 prolonged-release tablets - EU/1/07/395/060

9 mg
30 prolonged-release tablets - EU/1/07/395/061
350 prolonged-release tablets - EU/1/07/395/062

12 mg
30 prolonged-release tablets - EU/1/07/395/063
350 prolonged-release tablets - EU/1/07/395/064

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

B. PACKAGE LEAFLET

Package leaflet: Information for the user

INVEGA 3 mg prolonged-release tablets
INVEGA 6 mg prolonged-release tablets
INVEGA 9 mg prolonged-release tablets
INVEGA 12 mg prolonged-release tablets
Paliperidone

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What INVEGA is and what it is used for

INVEGA contains the active substance paliperidone which belongs to the class of antipsychotic medicines.

INVEGA is used to treat schizophrenia in adults and in adolescents aged 15 years and older.

Schizophrenia is a disorder with symptoms such as hearing things, seeing or sensing things that are not there, mistaken beliefs, unusual suspiciousness, becoming withdrawn, incoherent speech, and behaviour and emotional flatness. People with this disorder may also feel depressed, anxious, guilty, or tense.

INVEGA is also used to treat schizoaffective disorder in adults.

Schizoaffective disorder is a mental condition in which a person experiences a combination of schizophrenia symptoms (as listed above) in addition to mood disorder symptoms (feeling very high, feeling sad, feeling agitated, distracted, sleeplessness, talkativeness, losing interest in everyday activities, sleeping too much or too little, eating too much or too little, and recurrent thoughts of suicide).

INVEGA can help alleviate the symptoms of your disease and stop your symptoms from coming back.

2. What you need to know before you take INVEGA

Do not take INVEGA
- if you are allergic to paliperidone, risperidone, or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking INVEGA.

- Patients with schizoaffective disorder treated with this medicine should be carefully monitored for a potential switch from manic to depressive symptoms.
- This medicine has not been studied in elderly patients with dementia. However, elderly patients with dementia, who are treated with other similar types of medicine, may have an increased risk of stroke or death. (see section 4, possible side effects).
- if you have Parkinson's disease or Dementia.
- if you have ever been diagnosed with a condition whose symptoms include high temperature and muscle stiffness (also known as Neuroleptic Malignant Syndrome).
- if you have ever experienced abnormal movements of the tongue or face (Tardive Dyskinesia). You should be aware that both of these conditions may be caused by this type of medicine.
- if you know that you have had low levels of white blood cells in the past (which may or may not have been caused by other medicines).
- if you are diabetic or prone to diabetes.
- if you have heart disease or heart disease treatment that makes you prone to low blood pressure.
- if you have epilepsy.
- if you have a swallowing, stomach or intestinal disorder that reduces your ability to swallow or pass foods by normal bowel movements.
- if you have diseases associated with diarrhoea.
- if you have kidney problems.
- if you have liver problems.
- if you have prolonged and/or painful erection.
- if you have difficulty controlling core body temperature or overheating.
- if you have an abnormally high level of the hormone prolactin in your blood or if you have a possible prolactin-dependent tumour.
- if you or someone else in your family has a history of blood clots, as antipsychotics have been associated with formation of blood clots.

If you have any of these conditions, please talk to your doctor as he/she may want to adjust your dose or monitor you for a while.

As dangerously low numbers of a certain type of white blood cell needed to fight infection in your blood has been seen very rarely with patients taking INVEGA, your doctor may check your white blood cell counts.

INVEGA may cause you to gain weight. Significant weight gain may adversely affect your health. Your doctor should regularly measure your body weight.

As diabetes mellitus or worsening of pre-existing diabetes mellitus have been seen with patients taking INVEGA, your doctor should check for signs of high blood sugar. In patients with pre-existing diabetes mellitus blood glucose should be monitored regularly.

During an operation on the eye for cloudiness of the lens (cataract), the pupil (the black circle in the middle of your eye) may not increase in size as needed. Also, the iris (the coloured part of the eye) may become floppy during surgery and that may lead to eye damage. If you are planning to have an operation on your eye, make sure you tell your eye doctor that you are taking this medicine.

Children and adolescents
INVEGA is not for use in children and adolescents under 15 years for the treatment of schizophrenia.

INVEGA is not for use in children and adolescents who are under 18 years for the treatment of schizoaffective disorder.

This is because it is not known if INVEGA is safe or effective in these age groups.

Other medicines and INVEGA
Tell your doctor or pharmacist if you are taking or have recently taken any other medicines.

Abnormalities of electrical function in the heart may occur when this medicine is taken with certain heart medicines that control heart rhythm, or some other types of medicines such as antihistamines, antimalarials, or other antipsychotics.

Since this medicine works primarily in the brain, interference from other medicines (or alcohol) that work in the brain could occur due to additive effect on brain function.

Since this medicine can lower blood pressure, care should be taken when this medicine is taken with other medicines that lower blood pressure.

This medicine can reduce the effect of medicines against Parkinson's disease and restless legs syndrome (e.g., levodopa).

The effects of this medicine may be affected if you are taking medicines that affect the speed of movement in the gut (e.g., metoclopramide).

Dosage reduction for this medicine should be considered when this medicine is co-administered with valproate.

The use of oral risperidone together with this medicine is not recommended as the combination of the two medicines may lead to increased side effects.

INVEGA should be used with caution with medicines that increase the activity of the central nervous system (psychostimulants such as methylphenidate).

INVEGA with alcohol
Alcohol should be avoided when taking this medicine.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. You should not take this medicine during pregnancy unless this has been discussed with your doctor. The following symptoms may occur in newborn babies of mothers that have used paliperidone in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If your baby develops any of these symptoms you may need to contact your doctor.
You should not breastfeed when taking this medicine.

Driving and using machines
Dizziness and vision problems may occur during treatment with this medicine (see section 4, possible side effects). This should be considered in cases where full alertness is required, e.g., when driving a car or handling machines.

The 3 mg tablet of INVEGA contains lactose
The 3 mg tablet of this medicine contains lactose, a type of sugar. If you have been told by a doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

INVEGA contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take INVEGA

Take this medicine exactly as the doctor, pharmacist or nurse has told you to.

Use in adults
The recommended dose in adults is 6 mg once a day taken in the morning. The dose may be increased or decreased by your doctor within the dose range of 3 mg to 12 mg once a day for schizophrenia or 6 mg to 12 mg once a day for schizoaffective disorder. This depends on how well the medicine works for you.

Use in adolescents
The recommended starting dose for treating schizophrenia in adolescents 15 years and older is 3 mg once a day taken in the morning.

For adolescents weighing 51 kg or more the dose may be increased within the range of 6 mg to 12 mg once a day.

For adolescents weighing less than 51 kg the dose may be increased to 6 mg once a day.

Your doctor will decide how much to give you. The amount you take depends on how well the medicine works for you.

How and when to take INVEGA
This medicine must be taken by mouth, swallowed whole with water or other liquids. It must not be chewed, broken, or crushed.

This medicine should be taken every morning with breakfast or without breakfast, but in the same way every day. Do not alternate between taking this medicine with breakfast one day and without having breakfast the next day.

The active ingredient, paliperidone, dissolves once swallowed and the tablet shell is passed out of the body as waste.

Patients with kidney problems
Your doctor may adjust your dose of this medicine based upon your kidney function.

Elderly
Your doctor may reduce your dose of medicine if your kidney function is reduced.

If you take more INVEGA than you should
Contact your doctor right away. You may experience sleepiness, tiredness, abnormal body movements, problems with standing and walking, dizziness from low blood pressure, and abnormal heart beats.

If you forget to take INVEGA
Do not take a double dose to make up for a forgotten dose. If you miss one dose, take your next dose on the day following the missed dose. If you miss two or more doses, contact your doctor.

If you stop INVEGA
Do not stop taking this medicine since you will lose the effects of the medicine. You should not stop this medicine unless told to do so by your doctor as your symptoms may return.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately if you:

- experience blood clots in the veins, especially in the legs (symptoms include swelling, pain, and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty breathing. If you notice any of these symptoms seek medical advice immediately.
- have dementia and experience a sudden change in your mental state or sudden weakness or numbness of your face, arms or legs, especially on one side, or slurred speech, even for a short period of time. These may be signs of a stroke.
- experience fever, muscle stiffness, sweating or a lowered level of consciousness (a disorder called “Neuroleptic Malignant Syndrome”). Immediate medical treatment may be needed.
- are a man and experience prolonged or painful erection. This is called priapism. Immediate medical treatment may be needed.
- experience involuntary rhythmic movements of the tongue, mouth and face. Withdrawal of paliperidone may be needed.
- experience a severe allergic reaction characterised by fever, swollen mouth, face, lip or tongue, shortness of breath, itching, skin rash and sometimes drop in blood pressure (amounting to an ‘anaphylactic reaction’).

Very common: may affect more than 1 in 10 people

- difficulty falling or staying asleep
- parkinsonism: This condition may include slow or impaired movement, sensation of stiffness or tightness of the muscles (making your movements jerky), and sometimes even a sensation of movement "freezing up" and then restarting. Other signs of parkinsonism include a slow shuffling walk, a tremor while at rest, increased saliva and/or drooling, and a loss of expression on the face.
- restlessness
- feeling sleepy or less alert
- headache.

Common side effects: may affect up to 1 in 10 people

- infection of the chest (bronchitis), common cold symptoms, sinus infection, urinary tract infection, feeling like you have the flu
- weight gain, increased appetite, weight loss, decreased appetite
- elated mood (mania), irritability, depression, anxiety
- dystonia: This is a condition involving slow or sustained involuntary contraction of muscles. While it can involve any part of the body (and may result in abnormal posture), dystonia often involves muscles of the face, including abnormal movements of the eyes, mouth, tongue or jaw.
- dizziness
- dyskinesia: This is a condition involving involuntary muscle movements, and can include repetitive, spastic or writhing movements, or twitching.
- tremor (shaking)
- blurry vision
- an interruption in conduction between the upper and lower parts of the heart, abnormal electrical conduction of the heart, prolongation of the QT interval from your heart, slow heart rate, rapid heart rate
- low blood pressure upon standing (consequently, some people taking INVEGA may feel faint, dizzy, or may pass out when they stand up or sit up suddenly), high blood pressure
- sore throat, cough, stuffy nose
- abdominal pain, abdominal discomfort, vomiting, nausea, constipation, diarrhoea, indigestion, dry mouth, toothache
- increased liver transaminases in your blood
- itching, rash
- bone or muscle ache, back pain, joint pain
- loss of menstrual periods
- fever, weakness, fatigue (tiredness).

Uncommon side effects: may affect up to 1 in 100 people

- pneumonia, infection of the breathing passages, bladder infection, ear infection, tonsillitis
- white blood cell count decreased, decrease in platelets (blood cells that help you stop bleeding), anaemia, decrease in red blood cells
- INVEGA can raise your levels of a hormone called "prolactin" found on a blood test (which may or may not cause symptoms). When symptoms of high prolactin occur, they may include: (in men) breast swelling, difficulty in getting or maintaining erections, or other sexual dysfunction, (in women) breast discomfort, leakage of milk from the breasts, missed menstrual periods, or other problems with your cycle.
- diabetes or worsening diabetes, high blood sugar, increased waist size, loss of appetite resulting in malnutrition and low body weight, high blood triglycerides (a fat)
- sleep disorder, confusion, decreased sexual drive, inability to reach orgasm, nervousness, nightmares
- tardive dyskinesia (twitching or jerking movements that you cannot control in your face, tongue, or other parts of your body). Tell your doctor immediately if you experience involuntary rhythmic movements of the tongue, mouth and face. Withdrawal of INVEGA may be needed.
- convulsion (fits), fainting, a restless urge to move parts of your body, dizziness upon standing, disturbance in attention, problems with speech, loss or abnormal sense of taste, reduced sensation of skin to pain and touch, a sensation of tingling, pricking, or numbness of skin
- oversensitivity of the eyes to light, eye infection or "pink eye", dry eye
- a sensation of spinning (vertigo), ringing in the ears, ear pain
- irregular heartbeat, abnormal electrical tracing of the heart (electrocardiogram or ECG), a fluttering or pounding feeling in your chest (palpitations)
- low blood pressure
- shortness of breath, wheezing, nosebleeds
- swollen tongue, stomach or intestinal infection, difficulty swallowing, excessive passing of gas or wind
- increased GGT (a liver enzyme called gamma-glutamyltransferase) in your blood, increased liver enzymes in your blood
- hives (or “nettle rash”), hair loss, eczema, acne
- an increase of CPK (creatine phosphokinase) in your blood, an enzyme which is sometimes released with muscle breakdown, muscle spasms, joint stiffness, joint swelling, muscle weakness, neck pain
- incontinence (lack of control) of urine, frequent passing of urine, inability to pass urine, pain when passing urine
- erectile dysfunction, ejaculation disorder
- missed menstrual periods or other problems with your cycle (females), leakage of milk from the breasts, sexual dysfunction, breast pain, breast discomfort
- swelling of the face, mouth, eyes, or lips, swelling of the body, arms or legs
- chills, an increase in body temperature
- a change in the way you walk
- feeling thirsty
- chest pain, chest discomfort, feeling unwell
- fall.

Rare side effects: may affect up to 1 in 1,000 people

- eye infection, fungal infection of the nails, infection of the skin, skin inflammation caused by mites
- dangerously low numbers of a certain type of white blood cell needed to fight infection in your blood
- decrease in the type of white blood cells that help to protect you against infection, increase in eosinophils (a type of white blood cell) in your blood
- severe allergic reaction characterised by fever, swollen mouth, face, lip or tongue, shortness of breath, itching, skin rash and sometimes drop in blood pressure, allergic reaction
- sugar in the urine

- inappropriate secretion of a hormone that controls urine volume
- life-threatening complications of uncontrolled diabetes
- dangerously excessive intake of water, low blood sugar, excessive drinking of water, increased cholesterol in your blood
- sleep walking
- not moving or responding while awake (catatonia)
- lack of emotion
- neuroleptic malignant syndrome (confusion, reduced or loss of consciousness, high fever, and severe muscle stiffness)
- loss of consciousness, balance disorder, abnormal coordination
- blood vessel problems in the brain, coma due to uncontrolled diabetes, unresponsive to stimuli, low level of consciousness, shaking of the head
- glaucoma (increased pressure within the eyeball), increased tears, redness of the eyes, problems with movement of your eyes, eye rolling
- atrial fibrillation (an abnormal heart rhythm), rapid heartbeat upon standing
- blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing. If you notice any of these symptoms seek medical advice immediately
- decreased oxygen in parts of your body (because of decreased blood flow), flushing
- trouble breathing during sleep (sleep apnea), fast, shallow breathing
- pneumonia caused by inhaling food, congestion of breathing passages, voice disorder
- a blockage in the bowels, stool incontinence, very hard stool, lack of bowel muscle movement that causes blockage
- yellowing of the skin and the eyes (jaundice)
- inflammation of the pancreas
- serious allergic reaction with swelling that may involve the throat and lead to difficulty breathing
- thickening of the skin, dry skin, skin redness, skin discolouration, flaky itchy scalp or skin, dandruff
- breakdown of muscle fibers and pain in muscles (rhabdomyolysis), abnormal posture
- priapism (a prolonged penile erection that may require surgical treatment)
- development of breasts in men, enlargement of the glands in your breasts, discharge from the breasts, vaginal discharge
- a delay in menstrual periods, breast enlargement
- very low body temperature, a decrease in body temperature
- symptoms of drug withdrawal.

Not known: frequency cannot be estimated from the available data
- lung congestion
- increased insulin (a hormone that controls blood sugar levels) in your blood.

The following side effects have been seen with the use of another medicine called risperidone that is very similar to paliperidone, so these can also be expected with INVEGA: sleep-related eating disorder, other types of blood vessel problems in the brain, crackly lung sounds, and severe or life-threatening rash with blisters and peeling skin that may start in and around the mouth, nose, eyes and genitals and spread to other areas of the body (Stevens-Johnson syndrome/toxic epidermal necrolysis). Eye problems during cataract surgery may also occur. During cataract surgery, a condition called intraoperative floppy iris syndrome (IFIS) can happen if you take or have taken INVEGA. If you need to have cataract surgery, be sure to tell your eye doctor if you take or have taken this medicine.

Additional side effects in adolescents
Adolescents generally experienced side effects that were similar to those seen in adults except the following side effects were seen more commonly:
- feeling sleepy or less alert

- parkinsonism: This condition may include slow or impaired movement, sensation of stiffness or tightness of the muscles (making your movements jerky), and sometimes even a sensation of movement "freezing up" and then restarting. Other signs of parkinsonism include a slow shuffling walk, a tremor while at rest, increased saliva and/or drooling, and a loss of expression on the face.
- weight gain
- common cold symptoms
- restlessness
- tremor (shaking)
- stomach pain
- leaking milk from the breasts in girls
- breast swelling in boys
- acne
- problems with speech
- stomach or intestinal infection
- nose bleeds
- ear infection
- high blood triglycerides (a fat)
- sensation of spinning (vertigo).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store INVEGA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister/bottle and carton after EXP. The expiry date refers to the last day of that month.

Bottles: Do not store above 30°C. Keep the bottle tightly closed in order to protect from moisture.
Blisters: Do not store above 30°C. Store in the original package in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What INVEGA contains
The active substance is paliperidone
Each INVEGA 3 mg prolonged-release tablet contains 3 mg of paliperidone.
Each INVEGA 6 mg prolonged-release tablet contains 6 mg of paliperidone.
Each INVEGA 9 mg prolonged-release tablet contains 9 mg of paliperidone.
Each INVEGA 12 mg prolonged-release tablet contains 12 mg of paliperidone.

The other ingredients are:
Coated tablet core:
Polyethylene oxide 200K
Sodium chloride
Povidone (K29-32)
Stearic acid

Butyl hydroxytoluene (E321)
Ferric Oxide (Yellow) (E172) (3, 12 mg tablet only)
Polyethylene Oxide 7000K
Ferric Oxide (Red) (E172)
Hydroxyethyl Cellulose
Polyethylene glycol 3350
Cellulose acetate
Iron oxide (Black) (E172) (9 mg tablet only)

Colour overcoat:
Hypromellose
Titanium dioxide (E171)
Polyethylene glycol 400 (6, 9 and 12 mg tablet only)
Ferric Oxide (Yellow) (E172) (6, 12 mg tablet only)
Ferric Oxide (Red) (E172) (6, 9 mg tablet only)
Lactose monohydrate (3 mg tablet only)
Triacetin (3 mg tablet only)
Carnauba wax

Printing ink:
Iron oxide (Black) (E172)
Propylene glycol
Hypromellose

What INVEGA looks like and contents of the pack
INVEGA prolonged-release tablets are capsule shaped. The 3 mg tablets are white and printed with "PAL 3", the 6 mg tablets are beige and printed with "PAL 6", the 9 mg tablets are pink and printed with "PAL 9", and the 12 mg tablets are dark yellow and printed with "PAL 12". All tablets are available in the following pack sizes:

- Bottles: The tablets are supplied in a plastic bottle with a child-resistant plastic cap. Each bottle contains either 30 tablets or 350 tablets. Each bottle contains two silica gel pouches which are provided to absorb moisture and keep the tablets dry.
- Blisters: The tablets are supplied in blisters packed in cartons of 14, 28, 30, 49, 56, and 98 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Manufacturer
Janssen-Cilag SpA
Via C. Janssen
04100 Borgo San Michele
Latina
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Janssen-Cilag NV
Tel/Tél: +32 14 64 94 11

Lietuva
UAB “JOHNSON & JOHNSON”
Tel: +370 5 278 68 88

България
”Джонсън & Джонсън България” ЕООД
Тел.:+359 2 489 94 00

Luxembourg/Luxemburg
Janssen-Cilag NV
Tél/ Tel: +32 14 64 94 11

Česká republika
Janssen-Cilag s.r.o.
Tel:+420 227 012 227

Magyarország
Janssen-Cilag Kft.
Tel.: +36 1 884 2858

Danmark
Janssen-Cilag A/S
Tlf: +45 4594 8282

Malta
AM MANGION LTD.
Tel: +356 2397 6000

Deutschland
Janssen-Cilag GmbH
Tel: +49 2137 955 955

Nederland
Janssen-Cilag B.V.
Tel: +31 76 711 1111

Eesti
UAB “JOHNSON & JOHNSON” Eesti filiaal
Tel.: +372 617 7410

Norge
Janssen-Cilag AS
Tlf: +47 24 12 65 00

Ελλάδα
Janssen-Cilag Φαρμακευτική Α.Ε.Β.Ε
Τηλ: +30 210 80 90 000

Österreich
Janssen-Cilag Pharma GmbH
Tel: +43 1 610 300

España
Janssen-Cilag, S.A.
Tel: +34 91 722 81 00

Polska
Janssen-Cilag Polska Sp. z o.o.
Tel.: +48 22 237 60 00

France
Janssen-Cilag
Tel: 0 800 25 50 75 / +33 1 55 00 40 03

Portugal
Janssen-Cilag Farmacêutica, Lda.
Tel: +351 214 368 600

Hrvatska
Johnson & Johnson S.E. d.o.o.
Tel: +385 1 6610 700

România
Johnson & Johnson România SRL
Tel: +40 21 207 1800

Ireland
Janssen Sciences Ireland UC
Tel: +353 1 800 709 122

Slovenija
Johnson & Johnson d.o.o.
Tel: +386 1 401 18 00

Ísland
Janssen-Cilag AB
C/o Vistor hf.
Sími: +354 535 7000

Slovenská republika
Johnson & Johnson s.r.o.
Tel: +421 232 408 400

Italia
Janssen-Cilag SpA
Tel: 800.688.777 / +39 02 2510 1

Suomi/Finland
Janssen-Cilag Oy
Puh/Tel: +358 207 531 300

Κύπρος
Βαρνάβας Χατζηπαναγής Λτδ
Τηλ: +357 22 207 700

Latvija
UAB "JOHNSON & JOHNSON" filiāle Latvijā
Tel: +371 678 93561

Sverige
Janssen-Cilag AB
Tfn: +46 8 626 50 00

United Kingdom (Northern Ireland)
Janssen Sciences Ireland UC
Tel: +44 1 494 567 444

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/.

Seroquel XL 150mg prolonged-release tablets

Summary of Product Characteristics Updated 25-Jul-2024 | Luye Pharma Limited

1. Name of the medicinal product

Seroquel XL 50 mg prolonged-release tablets

Seroquel XL 150 mg prolonged-release tablets

Seroquel XL 200 mg prolonged-release tablets

Seroquel XL 300 mg prolonged-release tablets

Seroquel XL 400 mg prolonged-release tablets

2. Qualitative and quantitative composition

Seroquel XL 50 mg contains 50 mg quetiapine (as quetiapine fumarate)

Seroquel XL 150 mg contains 150 mg quetiapine (as quetiapine fumarate)

Seroquel XL 200 mg contains 200 mg quetiapine (as quetiapine fumarate)

Seroquel XL 300 mg contains 300 mg quetiapine (as quetiapine fumarate)

Seroquel XL 400 mg contains 400 mg quetiapine (as quetiapine fumarate)

Excipients with known effect:

Seroquel XL 50 mg contains 119 mg lactose (anhydrous) per tablet

Seroquel XL 150 mg contains 71 mg lactose (anhydrous) per tablet

Seroquel XL 200 mg contains 50 mg lactose (anhydrous) per tablet

Seroquel XL 300 mg contains 47 mg lactose (anhydrous) per tablet

Seroquel XL 300 mg contains 27 mg sodium per tablet

Seroquel XL 400 mg contains 15 mg lactose (anhydrous) per tablet

Seroquel XL 400 mg contains 27 mg sodium per tablet

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Prolonged-release tablet

Seroquel XL 50 mg tablets are peach-coloured and engraved with XR 50 on one side.

Seroquel XL 150 mg tablets are white and engraved with XR 150 on one side.

Seroquel XL 200 mg tablets are yellow and engraved with XR 200 on one side.

Seroquel XL 300 mg tablets are pale yellow and engraved with XR 300 on one side.

Seroquel XL 400 mg tablets are white and engraved with XR 400 on one side.

4. Clinical particulars

4.1 Therapeutic indications

Seroquel XL is indicated for:

treatment of schizophrenia

treatment of bipolar disorder:

- For the treatment of moderate to severe manic episodes in bipolar disorder

- For the treatment of major depressive episodes in bipolar disorder

- For the prevention of recurrence of manic or depressed episodes in patients with bipolar disorder who previously responded to quetiapine treatment.

add-on treatment of major depressive episodes in patients with Major Depressive Disorder (MDD) who have had sub-optimal response to antidepressant monotherapy (see section 5.1). Prior to initiating treatment, clinicians should consider the safety profile of Seroquel XL (see section 4.4).

4.2 Posology and method of administration

Different dosing schedules exist for each indication. It must therefore be ensured that patients receive clear information on the

appropriate dosage for their condition.

Seroquel XL should be administered once daily, without food. The tablets should be swallowed whole and not split, chewed or crushed.

Adults

For the treatment of schizophrenia and moderate to severe manic episodes in bipolar disorder

Seroquel XL should be administrated at least one hour before a meal. The daily dose at the start of therapy is 300 mg on Day 1 and 600 mg on Day 2. The recommended daily dose is 600 mg, however if clinically justified the dose may be increased to 800 mg daily. The dose should be adjusted within the effective dose range of 400 mg to 800 mg per day, depending on the clinical response and tolerability of the patient. For maintenance therapy in schizophrenia no dosage adjustment is necessary.

For the treatment of major depressive episodes in bipolar disorder

Seroquel XL should be administered at bedtime. The total daily dose for the first four days of therapy is 50 mg (Day 1), 100 mg (Day 2), 200 mg (Day 3) and 300 mg (Day 4). The recommended daily dose is 300 mg. In clinical trials, no additional benefit was seen in the 600 mg group compared to the 300 mg group (see section 5.1). Individual patients may benefit from a 600 mg dose. Doses greater than 300 mg should be initiated by physicians experienced in treating bipolar disorder. In individual patients, in the event of tolerance concerns, clinical trials have indicated that dose reduction to a minimum of 200 mg could be considered.

For preventing recurrence in bipolar disorder

For preventing recurrence of manic, mixed or depressive episodes in bipolar disorder, patients who have responded to Seroquel XL for acute treatment of bipolar disorder should continue on Seroquel XL at the same dose administered at bedtime. Seroquel XL dose can be adjusted depending on clinical response and tolerability of the individual patient within the dose range of 300 mg to 800 mg/day. It is important that the lowest effective dose is used for maintenance therapy.

For add-on treatment of major depressive episodes in MDD

Seroquel XL should be administered prior to bedtime. The daily dose at the start of therapy is 50 mg on Day 1 and 2, and 150 mg on Day 3 and 4. Antidepressant effect was seen at 150 and 300 mg/day in short-term trials as add-on therapy (with amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline and venlafaxine - see section 5.1) and at 50 mg/day in short-term monotherapy trials. There is an increased risk of adverse events at higher doses. Clinicians should therefore ensure that the lowest effective dose, starting with 50 mg/day, is used for treatment. The need to increase the dose from 150 to 300 mg/day should be based on individual patient evaluation.

Switching from Seroquel immediate-release tablets

For more convenient dosing, patients who are currently being treated with divided doses of immediate-release Seroquel tablets may be switched to Seroquel XL at the equivalent total daily dose taken once daily. Individual dosage adjustments may be necessary.

Elderly

As with other antipsychotics and antidepressants, Seroquel XL should be used with caution in the elderly, especially during the initial dosing period. The rate of dose titration of Seroquel XL may need to be slower, and the daily therapeutic dose lower, than that used in younger patients. The mean plasma clearance of quetiapine was reduced by 30% to 50% in elderly patients when compared to younger patients. Elderly patients should be started on 50 mg/day. The dose can be increased in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient.

In elderly patients with major depressive episodes in MDD, dosing should begin with 50 mg/day on Days 1-3, increasing to 100 mg/day on Day 4 and 150 mg/day on Day 8. The lowest effective dose, starting from 50 mg/day should be used. Based on individual patient evaluation, if dose increase to 300 mg/day is required this should not be prior to Day 22 of treatment.

Efficacy and safety has not been evaluated in patients over 65 years with depressive episodes in the framework of bipolar disorder.

Paediatric population

Seroquel XL is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. The available evidence from placebo-controlled clinical trials is presented in sections 4.4, 4.8, 5.1 and 5.2.

Renal impairment

Dosage adjustment is not necessary in patients with renal impairment.

Hepatic impairment

Quetiapine is extensively metabolised by the liver. Therefore, Seroquel XL should be used with caution in patients with known hepatic impairment, especially during the initial dosing period. Patients with hepatic impairment should be started on 50 mg/day. The dose can be increased in increments of 50 mg/day to an effective dose, depending on the clinical response and tolerability of the individual patient.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients of this product.

Concomitant administration of cytochrome P450 3A4 inhibitors, such as HIV-protease inhibitors, azole-antifungal agents,

erythromycin, clarithromycin and nefazodone, is contraindicated. (see section 4.5).

4.4 Special warnings and precautions for use

As Seroquel XL has several indications, the safety profile should be considered with respect to the individual patient's diagnosis and the dose being administered.

Long-term efficacy and safety in patients with MDD has not been evaluated as add-on therapy, however long-term efficacy and safety has been evaluated in adult patients as monotherapy (see section 5.1).

Paediatric population

Quetiapine is not recommended for use in children and adolescents below 18 years of age, due to a lack of data to support use in this age group. Clinical trials with quetiapine have shown that in addition to the known safety profile identified in adults (see section 4.8), certain adverse events occurred at a higher frequency in children and adolescents compared to adults (increased appetite, elevations in serum prolactin, vomiting, rhinitis and syncope), or may have different implications for children and adolescents (extrapyramidal symptoms and irritability) and one was identified that has not been previously seen in adult studies (increases in blood pressure). Changes in thyroid function tests have also been observed in children and adolescents.

Furthermore, the long-term safety implications of treatment with quetiapine on growth and maturation have not been studied beyond 26 weeks. Long-term implications for cognitive and behavioural development are not known.

In placebo-controlled clinical trials with children and adolescent patients, quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for schizophrenia, bipolar mania and bipolar depression (see section 4.8).

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self-harm and suicide (suicide-related events). This risk persists until significant remission occurs. As improvement may not occur during the first few weeks or more of treatment, patients should be closely monitored until such improvement occurs. It is general clinical experience that the risk of suicide may increase in the early stages of recovery.

In addition, physicians should consider the potential risk of suicide-related events after abrupt cessation of quetiapine treatment, due to the known risk factors for the disease being treated.

Other psychiatric conditions for which quetiapine is prescribed can also be associated with an increased risk of suicide related events. In addition, these conditions may be co-morbid with major depressive episodes. The same precautions observed when treating patients with major depressive episodes should therefore be observed when treating patients with other psychiatric disorders.

Patients with a history of suicide related events, or those exhibiting a significant degree of suicidal ideation prior to commencement of treatment are known to be at greater risk of suicidal thoughts or suicide attempts, and should receive careful monitoring during treatment. A meta analysis of placebo controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared to placebo in patients less than 25 years old.

Close supervision of patients and in particular those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and caregivers of patients) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

In shorter-term placebo controlled clinical studies of patients with major depressive episodes in bipolar disorder an increased risk of suicide-related events was observed in young adult patients (younger than 25 years of age) who were treated with quetiapine as compared to those treated with placebo (3.0% vs. 0%, respectively). In clinical studies of patients with MDD the incidence of suicide-related events observed in young adult patients (younger than 25 years of age) was 2.1% (3/144) for quetiapine and 1.3% (1/75) for placebo. A population-based retrospective study of quetiapine for the treatment of patients with major depressive disorder showed an increased risk of self-harm and suicide in patients aged 25 to 64 years without a history of self-harm during use of quetiapine with other antidepressants.

Metabolic risk

Given the observed risk for worsening of their metabolic profile, including changes in weight, blood glucose (see hyperglycaemia) and lipids, which was seen in clinical studies, patient's metabolic parameters should be assessed at the time of treatment initiation and changes in these parameters should be regularly controlled for during the course of treatment. Worsening in these parameters should be managed as clinically appropriate (see section 4.8).

Extrapyramidal symptoms

In placebo controlled clinical trials of adult patients quetiapine was associated with an increased incidence of extrapyramidal symptoms (EPS) compared to placebo in patients treated for major depressive episodes in bipolar disorder and major depressive disorder (see sections 4.8 and 5.1).

The use of quetiapine has been associated with the development of akathisia, characterised by a subjectively unpleasant or distressing restlessness and need to move often accompanied by an inability to sit or stand still. This is most likely to occur within the first few weeks of treatment. In patients who develop these symptoms, increasing the dose may be detrimental.

Tardive dyskinesia

If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of quetiapine should be considered. The symptoms of tardive dyskinesia can worsen or even arise after discontinuation of treatment (see section 4.8).

Somnolence and dizziness

Quetiapine treatment has been associated with somnolence and related symptoms, such as sedation (see section 4.8). In clinical trials for treatment of patients with bipolar depression and major depressive disorder, onset was usually within the first 3 days of treatment and was predominantly of mild to moderate intensity. Patients experiencing somnolence of severe intensity may require more frequent contact for a minimum of 2 weeks from onset of somnolence, or until symptoms improve and treatment discontinuation may need to be considered.

Orthostatic hypotension

Quetiapine treatment has been associated with orthostatic hypotension and related dizziness (see section 4.8) which, like somnolence has onset usually during the initial dose-titration period. This could increase the occurrence of accidental injury (fall), especially in the elderly population. Therefore, patients should be advised to exercise caution until they are familiar with the potential effects of the medication.

Quetiapine should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or other conditions predisposing to hypotension. Dose reduction or more gradual titration should be considered if orthostatic hypotension occurs, especially in patients with underlying cardiovascular disease.

Sleep apnoea syndrome

Sleep apnoea syndrome has been reported in patients using quetiapine. In patients receiving concomitant central nervous system depressants and who have a history of or are at risk for sleep apnoea, such as those who are overweight/obese or are male, quetiapine should be used with caution.

Seizures

In controlled clinical trials there was no difference in the incidence of seizures in patients treated with quetiapine or placebo. No data is available about the incidence of seizures in patients with a history of seizure disorder. As with other antipsychotics, caution is recommended when treating patients with a history of seizures (see section 4.8).

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome has been associated with antipsychotic treatment, including quetiapine (see section 4.8). Clinical manifestations include hyperthermia, altered mental status, muscular rigidity, autonomic instability, and increased creatine phosphokinase. In such an event, quetiapine should be discontinued and appropriate medical treatment given.

Serotonin syndrome

Concomitant administration of Seroquel XL and other serotonergic agents, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Severe neutropenia and agranulocytosis

Severe neutropenia (neutrophil count $<0.5 \times 10^9$/L) has been reported in quetiapine clinical trials. Most cases of severe neutropenia have occurred within a couple of months of starting therapy with quetiapine. There was no apparent dose relationship. During post-marketing experience, some cases were fatal. Possible risk factors for neutropenia include pre-existing low white blood cell count (WBC) and history of drug induced neutropenia. However, some cases occurred in patients without pre-existing risk factors. Quetiapine should be discontinued in patients with a neutrophil count $<1.0 \times 10^9$/L. Patients should be observed for signs and symptoms of infection and neutrophil counts followed (until they exceed 1.5×10^9/L) (see section 5.1).

Neutropenia should be considered in patients presenting with infection or fever, particularly in the absence of obvious predisposing factor(s), and should be managed as clinically appropriate.

Patients should be advised to immediately report the appearance of signs/symptoms consistent with agranulocytosis or infection (e.g. fever, weakness, lethargy, or sore throat) at any time during Seroquel therapy. Such patients should have a WBC count and an absolute neutrophil count (ANC) performed promptly, especially in the absence of predisposing factors.

Anti-cholinergic (muscarinic) effects

Norquetiapine, an active metabolite of quetiapine, has moderate to strong affinity for several muscarinic receptor subtypes. This contributes to ADRs reflecting anti-cholinergic effects when quetiapine is used at recommended doses, when used concomitantly with other medications having anti-cholinergic effects, and in the setting of overdose. Quetiapine should be used with caution in patients receiving medications having anti-cholinergic (muscarinic) effects. Quetiapine should be used with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, intestinal obstruction or related conditions, increased intraocular pressure or narrow angle glaucoma (see sections 4.5, 4.8, 5.1, and 4.9).

Interactions

See section 4.5.

Concomitant use of quetiapine with a strong hepatic enzyme inducer such as carbamazepine or phenytoin substantially decreases quetiapine plasma concentrations, which could affect the efficacy of quetiapine therapy. In patients receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate).

Weight

Weight gain has been reported in patients who have been treated with quetiapine, and should be monitored and managed as clinically appropriate as in accordance with utilised antipsychotic guidelines (see sections 4.8 and 5.1).

Hyperglycaemia

Hyperglycaemia and/or development or exacerbation of diabetes occasionally associated with ketoacidosis or coma has been reported rarely, including some fatal cases (see section 4.8). In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any antipsychotic agent including quetiapine, should be observed for signs and symptoms of hyperglycaemia, (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Weight should be monitored regularly.

Lipids

Increases in triglycerides, LDL and total cholesterol, and decreases in HDL cholesterol have been observed in clinical trials with quetiapine (see section 4.8). Lipid changes should be managed as clinically appropriate.

QT prolongation

In clinical trials and use in accordance with the SPC, quetiapine was not associated with a persistent increase in absolute QT intervals. In post-marketing, QT prolongation was reported with quetiapine at the therapeutic doses (see section 4.8) and in overdose (see section 4.9). As with other antipsychotics, caution should be exercised when quetiapine is prescribed in patients with cardiovascular disease or family history of QT prolongation. Also, caution should be exercised when quetiapine is prescribed either with medicines known to increase QT interval, or with concomitant neuroleptics, especially in the elderly, in patients with congenital long QT syndrome, congestive heart failure, heart hypertrophy, hypokalaemia or hypomagnesaemia (see section 4.5).

Cardiomyopathy and myocarditis

Cardiomyopathy and myocarditis have been reported in clinical trials and during the post-marketing experience, (see section 4.8). In patients with suspected cardiomyopathy or myocarditis discontinuation of quetiapine should be considered.

Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson Syndrome (SJS), Toxic epidermal Necrolysis (TEN), Acute Generalized Exanthematous Pustulosis (AGEP), Erythema Multiforme (EM) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) which can be life threatening or fatal have been reported very rarely with quetiapine treatment.

SCARs commonly present with one or more of the following symptoms: extensive cutaneous rash which may be pruritic or associated with pustules, exfoliative dermatitis, fever, lymphadenopathy and possible eosinophilia or neutrophilia. Most of these reactions occurred within 4 weeks after initiation of quetiapine therapy, some DRESS reactions occurred within 6 weeks after initiation of quetiapine therapy.If signs and symptoms suggestive of these severe skin reactions appear, quetiapine should be withdrawn immediately and alternative treatment should be considered.

Withdrawal

Acute withdrawal symptoms such as insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability have been described after abrupt cessation of quetiapine. Gradual withdrawal over a period of at least one to two weeks is advisable (see section 4.8.).

Elderly patients with dementia-related psychosis

Quetiapine is not approved for the treatment of dementia-related psychosis.

An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomised placebo controlled trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Quetiapine should be used with caution in patients with risk factors for stroke.

In a meta-analysis of atypical antipsychotics, it has been reported that elderly patients with dementia-related psychosis are at an increased risk of death compared to placebo. In two 10-week placebo-controlled quetiapine studies in the same patient population (n=710; mean age: 83 years; range: 56-99 years) the incidence of mortality in quetiapine treated patients was 5.5% versus 3.2% in the placebo group. The patients in these trials died from a variety of causes that were consistent with expectations for this population.

Elderly patients with Parkinson's disease (PD)/parkinsonism

A population-based retrospective study of quetiapine for the treatment of patients with MDD, showed an increased risk of death during use of quetiapine in patients aged >65 years. This association was not present when patients with PD were removed from the analysis. Caution should be exercised if quetiapine is prescribed to elderly patients with PD.

Dysphagia

Dysphagia (see section 4.8) has been reported with quetiapine. Quetiapine should be used with caution in patients at risk for aspiration pneumonia.

Constipation and intestinal obstruction

Constipation represents a risk factor for intestinal obstruction. Constipation and intestinal obstruction have been reported with quetiapine (see section 4.8). This includes fatal reports in patients who are at higher risk of intestinal obstruction, including those that are receiving multiple concomitant medications that decrease intestinal motility and/or may not report symptoms of constipation. Patients with intestinal obstruction/ileus should be managed with close monitoring and urgent care.

Venous thromboembolism (VTE)

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with quetiapine and preventive measures undertaken.

Pancreatitis

Pancreatitis has been reported in clinical trials and during post marketing experience. Among post marketing reports, while not all cases were confounded by risk factors, many patients had factors which are known to be associated with pancreatitis such as increased triglycerides (see section 4.4), gallstones and alcohol consumption.

Additional information

Quetiapine data in combination with divalproex or lithium in acute moderate to severe manic episodes is limited; however, combination therapy was well tolerated (see section 4.8 and 5.1). The data showed an additive effect at week 3.

Lactose

Seroquel XL tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Sodium

Seroquel XL 50 mg, 150 mg and 200 mg prolonged-release tablets contain less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Seroquel XL 300 mg prolonged-release tablets and Seroquel XL 400 mg prolonged-release tablets contain 27 mg sodium per tablet, equivalent to 1.35% of the WHO recommended daily intake of 2 g sodium for an adult.

Misuse and abuse

Cases of misuse and abuse have been reported. Caution may be needed when prescribing quetiapine to patients with a history of alcohol or drug abuse.

4.5 Interaction with other medicinal products and other forms of interaction

Given the primary central nervous system effects of quetiapine, quetiapine should be used with caution in combination with other centrally acting medicinal products and alcohol.

Quetiapine should be used with caution in combination with serotonergic medicinal products, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

Caution should be exercised treating patients receiving other medications having anti-cholinergic (muscarinic) effects (see section 4.4).

Cytochrome P450 (CYP) 3A4 is the enzyme that is primarily responsible for the cytochrome P450 mediated metabolism of quetiapine. In an interaction study in healthy volunteers, concomitant administration of quetiapine (dosage of 25 mg) with ketoconazole, a CYP3A4 inhibitor, caused a 5- to 8-fold increase in the AUC of quetiapine. On the basis of this, concomitant use of quetiapine with CYP3A4 inhibitors is contraindicated. It is also not recommended to consume grapefruit juice while on quetiapine therapy.

In a multiple-dose trial in patients to assess the pharmacokinetics of quetiapine given before and during treatment with carbamazepine (a known hepatic enzyme inducer), co-administration of carbamazepine significantly increased the clearance of

quetiapine. This increase in clearance reduced systemic quetiapine exposure (as measured by AUC) to an average of 13% of the exposure during administration of quetiapine alone; although a greater effect was seen in some patients. As a consequence of this interaction, lower plasma concentrations can occur, which could affect the efficacy of quetiapine therapy. Co-administration of quetiapine and phenytoin (another microsomal enzyme inducer) caused a greatly increased clearance of quetiapine by approx. 450%. In patients receiving a hepatic enzyme inducer, initiation of quetiapine treatment should only occur if the physician considers that the benefits of quetiapine outweigh the risks of removing the hepatic enzyme inducer. It is important that any change in the inducer is gradual, and if required, replaced with a non-inducer (e.g. sodium valproate) (see section 4.4).

The pharmacokinetics of quetiapine were not significantly altered by co-administration of the antidepressants imipramine (a known CYP 2D6 inhibitor) or fluoxetine (a known CYP 3A4 and CYP 2D6 inhibitor).

The pharmacokinetics of quetiapine were not significantly altered by co-administration of the antipsychotics risperidone or haloperidol. Concomitant use of quetiapine and thioridazine caused an increased clearance of quetiapine with approx. 70%.

The pharmacokinetics of quetiapine were not altered following co-administration with cimetidine.

The pharmacokinetics of lithium were not altered when co-administered with quetiapine.

In a 6-week, randomised, study of lithium and Seroquel XL versus placebo and Seroquel XL in adult patients with acute mania, a higher incidence of extrapyramidal related events (in particular tremor), somnolence, and weight gain were observed in the lithium add-on group compared to the placebo add-on group (see section 5.1).

The pharmacokinetics of sodium valproate and quetiapine were not altered to a clinically relevant extent when co-administered. A retrospective study of children and adolescents who received valproate, quetiapine, or both, found a higher incidence of leucopenia and neutropenia in the combination group versus the monotherapy groups.

Formal interaction studies with commonly used cardiovascular medicinal products have not been performed.

Caution should be exercised when quetiapine is used concomitantly with medicinal products known to cause electrolyte imbalance or to increase QT interval.

There have been reports of false positive results in enzyme immunoassays for methadone and tricyclic antidepressants in patients who have taken quetiapine. Confirmation of questionable immunoassay screening results by an appropriate chromatographic technique is recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy

First trimester

The moderate amount of published data from exposed pregnancies (i.e. between 300-1000 pregnancy outcomes), including individual reports and some observational studies do not suggest an increased risk of malformations due to treatment. However, based on all available data, a definite conclusion cannot be drawn. Animal studies have shown reproductive toxicity (see section 5.3). Therefore, quetiapine should only be used during pregnancy if the benefits justify the potential risks.

Third trimester

Neonates exposed to antipsychotics (including quetiapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress or feeding disorder. Consequently, newborns should be monitored carefully.

Breast-feeding

Based on very limited data from published reports on quetiapine excretion into human breast milk, excretion of quetiapine at therapeutic doses appears to be inconsistent. Due to lack of robust data, a decision must be made whether to discontinue breast-feeding or to discontinue Seroquel XL therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

The effects of quetiapine on human fertility have not been assessed. Effects related to elevated prolactin levels were seen in rats, although these are not directly relevant to humans (see section 5.3).

4.7 Effects on ability to drive and use machines

Given its primary central nervous system effects, quetiapine may interfere with activities requiring mental alertness. Therefore, patients should be advised not to drive or operate machinery, until individual susceptibility to this is known.

4.8 Undesirable effects

The most commonly reported Adverse Drug Reactions (ADRs) with quetiapine (≥ 10%) are somnolence, dizziness, headache, dry mouth, withdrawal (discontinuation) symptoms, elevations in serum triglyceride levels, elevations in total cholesterol (predominantly LDL cholesterol), decreases in HDL cholesterol, weight gain, decreased haemoglobin and extrapyramidal symptoms.

The incidences of ADRs associated with quetiapine therapy, are tabulated below (Table 1) according to the format recommended by the Council for International Organizations of Medical Sciences (CIOMS III Working Group 1995).

Table 1 ADRs associated with quetiapine therapy

The frequencies of adverse events are ranked according to the following: Very common (≥ 1/10), common (≥ 1/100, <1/10), uncommon (≥ 1/1000, <1/100, rare (≥ 1/10,000, <1/1000), very rare (<1/10,000), and not known (cannot be estimated from the available data).

SOC	Very Common	Common	Uncommon	Rare	Very Rare	Not known
Blood and lymphatic system disorders	Decreased haemoglobin[22]	Leucopenia[1, 28], decreased neutrophil count, eosinophils increased[27]	Neutropenia[1], Thrombocytopenia, Anaemia, platelet count decreased[13]	Agranulocytosis[26]		
Immune system disorders			Hypersensitivity (including allergic skin reactions)		Anaphylactic reaction[5]	
Endocrine disorders		Hyperprolactinaemia[15], decreases in total T_4 [24], decreases in free T_4 [24], decreases in total T_3 [24], increases in TSH[24]	Decreases in free T_3 [24], Hypothyroidism[21]		Inappropriate antidiuretic hormone secretion	
Metabolism and nutritional disorders	Elevations in serum triglyceride levels[10, 30] Elevations in total cholesterol (predominantly LDL cholesterol)[11, 30] Decreases in HDL cholesterol[17, 30], Weight gain[8, 30]	Increased appetite, blood glucose increased to hyperglycaemic levels[6, 30]	Hyponatraemia[19], Diabetes Mellitus[1, 5] Exacerbation of pre-existing diabetes	Metabolic syndrome[29]		
Psychiatric disorders		Abnormal dreams and nightmares, Suicidal ideation and suicidal behaviour[20]		Somnambulism and related reactions such as sleep talking and sleep related eating disorder		
Nervous system disorders	Dizziness[4, 16], somnolence[2,16], headache, Extrapyramidal symptoms[1, 21]	Dysarthria	Seizure[1], Restless legs syndrome, Tardive dyskinesia [1, 5], Syncope[4,16] Confusional state			
Cardiac disorders		Tachycardia[4], Palpitations[23]	QT prolongation [1,12, 18] Bradycardia[32]			cardiomyopathy and myocarditis
Eye disorders		Vision blurred				
Vascular disorders		Orthostatic hypotension[4,16]		Venous thromboembolism[1]		Stroke[33]

Respiratory, thoracic and mediastinal disorder		Dyspnoea[23]	Rhinitis			
Gastrointestinal disorders	Dry mouth	Constipation, dyspepsia, vomiting[25]	Dysphagia[7]	Pancreatitis[1], Intestinal obstruction/Ileus		
Hepato-biliary disorders		Elevations in serum alanine aminotransferase (ALT)[3], Elevations in gamma-GT levels[3]	Elevations in serum aspartate aminotransferase (AST)[3]	Jaundice[5] Hepatitis		
Skin and subcutaneous tissue disorders					Angioedema[5], Stevens-Johnson syndrome[5]	Toxic Epidermal Necrolysis, Erythema Multiforme, Acute Generalized Exanthematous Pustulosis (AGEP), Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), Cutaneous vasculitis
Musculoskeletal and connective tissue disorders					Rhabdomyolysis	
Renal and urinary disorders			Urinary retention			
Pregnancy, puerperium and perinatal conditions						Drug withdrawal syndrome neonatal[31]
Reproductive system and breast disorders			Sexual dysfunction	Priapism, galactorrhoea, breast swelling, menstrual disorder		
General disorders and administration site conditions	Withdrawal (discontinuation) symptoms [1,9]	Mild asthenia, peripheral oedema, irritability, pyrexia		Neuroleptic malignant syndrome[1], hypothermia		
Investigations				Elevations in blood creatine phosphokinase[14]		

(1) See section 4.4.

(2) Somnolence may occur, usually during the first two weeks of treatment and generally resolves with the continued administration of quetiapine.

(3) Asymptomatic elevations (shift from normal to ≥ 3 x ULN at any time) in serum transaminase (ALT, AST) or gamma-GT levels have been observed in some patients administered quetiapine. These elevations were usually reversible on continued quetiapine treatment.

(4) As with other antipsychotics with alpha$_1$ adrenergic blocking activity, quetiapine may commonly induce orthostatic hypotension,

associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period. (see section 4.4).

(5) Calculation of Frequency for these ADR's have only been taken from postmarketing data with the immediate release formulation of quetiapine.

(6) Fasting blood glucose ≥ 126mg/dL (≥ 7.0 mmol/L) or a non-fasting blood glucose ≥ 200mg/dL (≥ 11.1 mmol/L) on at least one occasion.

(7) An increase in the rate of dysphagia with quetiapine vs. placebo was only observed in the clinical trials in bipolar depression.

(8) Based on >7% increase in body weight from baseline. Occurs predominantly during the early weeks of treatment in adults.

(9) The following withdrawal symptoms have been observed most frequently in acute placebo-controlled, monotherapy clinical trials, which evaluated discontinuation symptoms: insomnia, nausea, headache, diarrhoea, vomiting, dizziness, and irritability. The incidence of these reactions had decreased significantly after 1 week post-discontinuation.

(10) Triglycerides ≥ 200 mg/dL (≥ 2.258 mmol/L) (patients ≥ 18 years of age) or ≥ 150 mg/dL (≥ 1.694 mmol/L) (patients <18 years of age) on at least one occasion.

(11) Cholesterol ≥ 240 mg/dL (≥ 6.2064 mmol/L) (patients ≥ 18 years of age) or ≥ 200 mg/dL (≥ 5.172 mmol/L) (patients <18 years of age) on at least one occasion. An increase in LDL cholesterol of ≥ 30 mg/dL (≥ 0.769 mmol/L) has been very commonly observed. Mean change among patients who had this increase was 41.7 mg/dL (≥ 1.07 mmol/L).

(12) See text below.

(13) Platelets ≤ 100 x 10^9/L on at least one occasion.

(14) Based on clinical trial adverse event reports of blood creatine phosphokinase increase not associated with neuroleptic malignant syndrome.

(15) Prolactin levels (patients >18 years of age): >20 µ g/L (>869.56 pmol/L) males; >30 µ g/L (>1304.34 pmol/L) females at any time.

(16) May lead to falls.

(17) HDL cholesterol: <40 mg/dL (1.025 mmol/L) males; <50 mg/dL (1.282 mmol/L) females at any time.

(18) Incidence of patients who have a QTc shift from <450 msec to ≥ 450 msec with a ≥ 30 msec increase. In placebo-controlled trials with quetiapine the mean change and the incidence of patients who have a shift to a clinically significant level is similar between quetiapine and placebo.

(19) Shift from >132 mmol/L to ≤ 132 mmol/L on at least one occasion.

(20) Cases of suicidal ideation and suicidal behaviours have been reported during quetiapine therapy or early after treatment discontinuation (see sections 4.4 and 5.1).

(21) See section 5.1.

(22) Decreased haemoglobin to ≤ 13 g/dL (8.07 mmol/L) males, ≤ 12 g/dL (7.45 mmol/L) females on at least one occasion occurred in 11% of quetiapine patients in all trials including open label extensions. For these patients, the mean maximum decrease in haemoglobin at any time was -1.50 g/dL.

(23) These reports often occurred in the setting of tachycardia, dizziness, orthostatic hypotension and/or underlying cardiac/ respiratory disease.

(24) Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in total T_4, free T_4, total T_3 and free T_3 are defined as <0.8 x LLN (pmol/L) and shift in TSH is >5 mIU/L at any time.

(25) Based upon the increased rate of vomiting in elderly patients (≥ 65 years of age).

(26) Based on shift in neutrophils from > = 1.5 x 10^9/L at baseline to <0.5 x 10^9/L at any time during treatment and based on patients with severe neutropenia (<0.5 x 10^9/L) and infection during all quetiapine clinical trials (see section 4.4).

(27) Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in eosinophils are defined as ≥ 1 x 10^9 cells/L at any time.

(28) Based on shifts from normal baseline to potentially clinically important value at any time post-baseline in all trials. Shifts in WBCs are defined as ≤ 3 x 10^9 cells/L at any time.

(29) Based on adverse event reports of metabolic syndrome from all clinical trials with quetiapine.

(30) In some patients, a worsening of more than one of the metabolic factors of weight, blood glucose and lipids was observed in clinical studies (see section 4.4).

(31) See section 4.6.

(32) May occur at or near initiation of treatment and be associated with hypotension and/or syncope. Frequency based on adverse event reports of bradycardia and related events in all clinical trials with quetiapine.

(33) Based on one retrospective non-randomised epidemiological study.

Cases of QT prolongation, ventricular arrhythmia, sudden unexplained death, cardiac arrest and torsades de pointes have been reported with the use of neuroleptics and are considered class effects.

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in association with quetiapine treatment.

Paediatric population

The same ADRs described above for adults should be considered for children and adolescents. The following table summarises ADRs that occur in a higher frequency category in children and adolescents patients (10-17 years of age) than in the adult population or ADRs that have not been identified in the adult population.

Table 2 ADRs in children and adolescents associated with quetiapine therapy that occur in a higher frequency than adults, or not identified in the adult population

The frequencies of adverse events are ranked according to the following: Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000) and very rare (<1/10,000).

SOC	Very Common	Common
Endocrine disorders	Elevations in prolactin[1]	
Metabolism and nutritional disorders	Increased appetite	
Nervous system disorders	Extrapyramidal symptoms[3, 4]	Syncope
Vascular disorders	Increases in blood pressure[2]	
Respiratory, thoracic and mediastinal disorders		Rhinitis
Gastrointestinal disorders	Vomiting	
General disorders and administration site conditions		Irritability[3]

(1) Prolactin levels (patients < 18 years of age): >20 µ g/L (>869.56 pmol/L) males; >26 µ g/L (>1130.428 pmol/L) females at any time. Less than 1% of patients had an increase to a prolactin level >100 µ g/L.

(2) Based on shifts above clinically significant thresholds (adapted from the National Institutes of Health criteria) or increases >20 mmHg for systolic or >10 mmHg for diastolic blood pressure at any time in two acute (3-6 weeks) placebo-controlled trials in children and adolescents.

(3) Note: The frequency is consistent to that observed in adults, but might be associated with different clinical implications in children and adolescents as compared to adults.

(4) See section 5.1.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

In general, reported signs and symptoms were those resulting from an exaggeration of the active substance's known pharmacological effects, i.e., drowsiness and sedation, tachycardia, hypotension and anti-cholinergic effects.

Overdose could lead to QT-prolongation, seizures, status epilepticus, rhabdomyolysis, respiratory depression, urinary retention, confusion, delirium and/or agitation, coma and death. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose. (see section 4.4, Orthostatic hypotension).

Management of overdose

There is no specific antidote to quetiapine. In cases of severe signs, the possibility of multiple drug involvement should be considered, and intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system.

Based on public literature, patients with delirium and agitation and a clear anti-cholinergic syndrome may be treated with

physostigmine, 1-2 mg (under continuous ECG monitoring). This is not recommended as standard treatment, because of potential negative effect of physostigmine on cardiac conductance. Physostigmine may be used if there are no ECG aberrations. Do not use physostigmine in case of dysrhythmias, any degree of heart block or QRS-widening.

Whilst the prevention of absorption in overdose has not been investigated, gastric lavage can be indicated in severe poisonings and if possible to perform within one hour of ingestion. The administration of activated charcoal should be considered.

In cases of quetiapine overdose refractory hypotension should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. Epinephrine and dopamine should be avoided, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade.

Close medical supervision and monitoring should be continued until the patient recovers.

In case of overdose with extended-release quetiapine there is a delayed peak sedation and peak pulse and prolonged recovery compared with IR Quetiapine overdose.

In case of a quetiapine extended-release overdose gastric bezoar formation has been reported and appropriate diagnostic imaging is recommended to further guide patient management. Routine gastric lavage may not be effective in the removal of the bezoar due to gum like sticky consistency of the mass.

Endoscopic pharmacobezoar removal has been performed successfully in some cases.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics; Diazepines, oxazepines and thiazepines

ATC code: N05A H04

Mechanism of action

Quetiapine is an atypical antipsychotic agent. Quetiapine and the active human plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for brain serotonin ($5HT_2$) and dopamine D_1- and D_2-receptors. It is this combination of receptor antagonism with a higher selectivity for $5HT_2$ relative to D_2-receptors, which is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effect (EPS) liability of Seroquel compared to typical antipsychotics. Quetiapine and norquetiapine have no appreciable affinity at benzodiazepine receptors but high affinity at histaminergic and adrenergic alpha1 receptors and moderate affinity at adrenergic alpha2 receptors. Quetiapine also has low or no affinity for muscarinic receptors, while norquetiapine has moderate to high affinity at several muscarinic receptors, which may explain anti-cholinergic (muscarinic effects). Inhibition of NET and partial agonist action at 5HT1A sites by norquetiapine may contribute to Seroquel XL's therapeutic efficacy as an antidepressant.

Pharmacodynamic effects

Quetiapine is active in tests for antipsychotic activity, such as conditioned avoidance. It also blocks the action of dopamine agonists, measured either behaviourally or electrophysiologically, and elevates dopamine metabolite concentrations, a neurochemical index of D_2-receptor blockade.

In pre-clinical tests predictive of EPS, quetiapine is unlike typical antipsychotics and has an atypical profile. Quetiapine does not produce dopamine D_2-receptor supersensitivity after chronic administration. Quetiapine produces only weak catalepsy at effective dopamine D_2-receptor blocking doses. Quetiapine demonstrates selectivity for the limbic system by producing depolarisation blockade of the mesolimbic but not the nigrostriatal dopamine-containing neurones following chronic administration. Quetiapine exhibits minimal dystonic liability in haloperidol-sensitised or drug-naive Cebus monkeys after acute and chronic administration (see section 4.8).

Clinical efficacy

Schizophrenia

The efficacy of Seroquel XL in the treatment of schizophrenia was demonstrated in one 6-week placebo-controlled trial in patients who met DSM-IV criteria for schizophrenia, and one active-controlled Seroquel IR-to-Seroquel XL switching study in clinically stable outpatients with schizophrenia.

The primary outcome variable in the placebo-controlled trial was change from baseline to final assessment in the PANSS total score. Seroquel XL 400 mg/day, 600 mg/day and 800 mg/day were associated with statistically significant improvements in psychotic symptoms compared to placebo. The effect size of the 600 mg and 800 mg doses was greater than that of the 400 mg dose.

In the 6-week active-controlled switching study the primary outcome variable was the proportion of patients who showed lack of efficacy, i.e. who discontinued study treatment due to lack of efficacy or whose PANSS total score increased 20% or more from randomisation to any visit. In patients stabilised on Seroquel immediate release 400 mg to 800 mg, efficacy was maintained when patients were switched to an equivalent daily dose of Seroquel XL given once daily.

In a long-term study in stable schizophrenic patients who had been maintained on Seroquel XL for 16 weeks, Seroquel XL was more effective than placebo in preventing relapse. The estimated risks of relapse after 6 months treatments was 14.3% for the Seroquel XL treatment group compared to 68.2% for placebo. The average dose was 669 mg. There were no additional safety findings associated with treatment with Seroquel XL for up to 9 months (median 7 months). In particular, reports of adverse events

related to EPS and weight gain did not increase with longer-term treatment with Seroquel XL.

Bipolar disorder

In the treatment of moderate to severe manic episodes, Seroquel demonstrated superior efficacy to placebo in reduction of manic symptoms at 3 and 12 weeks, in two monotherapy trials. The efficacy of Seroquel XL was further demonstrated with significance versus placebo in an additional 3-week study. Seroquel XL was dosed in the range of 400 to 800 mg/day and the mean dose was approximately 600 mg/day. Seroquel data in combination with divalproex or lithium in acute moderate to severe manic episodes at 3 and 6 weeks is limited; however, combination therapy was well tolerated. The data showed an additive effect at week 3. A second study did not demonstrate an additive effect at week 6.

In a clinical trial, in patients with depressive episodes in bipolar I or bipolar II disorder, 300 mg/day Seroquel XL showed superior efficacy to placebo in reduction of MADRS total score.

In 4 additional clinical trials with quetiapine, with a duration of 8 weeks in patients with moderate to severe depressive episodes in bipolar I or bipolar II disorder, Seroquel IR 300 mg and 600 mg was significantly superior to placebo treated patients for the relevant outcome measures: mean improvement on the MADRS and for response defined as at least a 50% improvement in MADRS total score from baseline. There was no difference in magnitude of effect between the patients who received 300 mg Seroquel IR and those who received 600 mg dose.

In the continuation phase in two of these studies, it was demonstrated that long-term treatment, of patients who responded on Seroquel IR 300 or 600 mg, was efficacious compared to placebo treatment with respect to depressive symptoms, but not with regard to manic symptoms.

In two recurrence prevention studies evaluating quetiapine in combination with mood stabilizers, in patients with manic, depressed or mixed mood episodes, the combination with quetiapine was superior to mood stabilizers monotherapy in increasing the time to recurrence of any mood event (manic, mixed or depressed). Quetiapine was administered twice-daily totalling 400 mg to 800 mg a day as combination therapy to lithium or valproate.

In a 6-week, randomised, study of lithium and Seroquel XL versus placebo and Seroquel XL in adult patients with acute mania, the difference in YMRS mean improvement between the lithium add-on group and the placebo add-on group was 2.8 points and the difference in % responders (defined as 50% improvement from baseline on the YMRS) was 11% (79% in the lithium add-on group vs. 68% in the placebo add-on group).

In one long-term study (up to 2 years treatment) evaluating recurrence prevention in patients with manic, depressed or mixed mood episodes quetiapine was superior to placebo in increasing the time to recurrence of any mood event (manic, mixed or depressed), in patients with bipolar I disorder. The number of patients with a mood event was 91 (22.5%) in the quetiapine group, 208 (51.5%) in the placebo group and 95 (26.1%) in the lithium treatment groups respectively. In patients who responded to quetiapine, when comparing continued treatment with quetiapine to switching to lithium, the results indicated that a switch to lithium treatment does not appear to be associated with an increased time to recurrence of a mood event.

Major depressive episodes in MDD

Two short-term (6-week) studies enrolled patients who had shown an inadequate response to at least one antidepressant. Seroquel XL 150 mg and 300 mg/day, given as add-on treatment to ongoing antidepressant therapy (amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline or venlafaxine) demonstrated superiority over antidepressant therapy alone in reducing depressive symptoms as measured by improvement in MADRS total score (LS mean change vs. placebo of 2-3.3 points).

Long-term efficacy and safety in patients with MDD has not been evaluated as add-on therapy, however long-term efficacy and safety has been evaluated in adult patients as monotherapy (see below).

The following studies were conducted with Seroquel XL as monotherapy treatment, however Seroquel XL is only indicated for use as add-on therapy:

In three out of four short term (up to 8-weeks) monotherapy studies, in patients with major depressive disorder, Seroquel XL 50 mg, 150 mg and 300 mg/day demonstrated superior efficacy to placebo in reducing depressive symptoms as measured by improvement in the Montgomery-¯ sberg Depression Rating Scale (MADRS) total score (LS mean change vs. placebo of 2-4 points).

In a monotherapy relapse prevention study, patients with depressive episodes stabilised on open-label Seroquel XL treatment for at least 12 weeks were randomised to either Seroquel XL once daily or placebo for up to 52 weeks. The mean dose of Seroquel XL during the randomised phase was 177 mg/day. The incidence of relapse was 14.2% for Seroquel XL treated patients and 34.4% for placebo-treated patients.

In a short-term (9 week) study non-demented elderly patients (aged 66 to 89 years) with major depressive disorder, Seroquel XL dosed flexibly in the range of 50 mg to 300 mg/day demonstrated superior efficacy to placebo in reducing depressive symptoms as measured by improvement in MADRS total score (LS mean change vs placebo -7.54). In this study patients randomised to Seroquel XL received 50 mg/day on Days 1-3, the dose could be increased to 100 mg/day on Day 4, 150 mg/day on Day 8 and up to 300 mg/day depending on clinical response and tolerability. The mean dose of Seroquel XL was 160 mg/day. Other than the incidence of extrapyramidal symptoms (see section 4.8 and 'Clinical safety' below) the tolerability of Seroquel XL once daily in elderly patients was comparable to that seen in adults (aged 18-65 years). The proportion of randomised patients over 75 years of age was 19%.

Clinical safety

In short-term, placebo-controlled clinical trials in schizophrenia and bipolar mania the aggregated incidence of extrapyramidal symptoms was similar to placebo (schizophrenia: 7.8% for quetiapine and 8.0% for placebo; bipolar mania: 11.2% for quetiapine and 11.4% for placebo). Higher rates of extrapyramidal symptoms were seen in quetiapine treated patients compared to those treated with placebo in short-term, placebo-controlled clinical trials in MDD and bipolar depression. In short-term, placebo-controlled bipolar depression trials the aggregated incidence of extrapyramidal symptoms was 8.9% for quetiapine compared to 3.8% for placebo. In short-term, placebo-controlled monotherapy clinical trials in major depressive disorder the aggregated incidence of extrapyramidal symptoms was 5.4% for Seroquel XL and 3.2% for placebo. In a short-term placebo-controlled monotherapy trial in elderly patients with major depressive disorder, the aggregated incidence of extrapyramidal symptoms was 9.0% for Seroquel XL and 2.3% for placebo. In both bipolar depression and MDD, the incidence of the individual adverse events (e.g. akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) did not exceed 4% in any treatment group.

In short-term, fixed-dose (50 mg/d to 800 mg/d), placebo-controlled studies (ranging from 3 to 8 weeks), the mean weight gain for quetiapine-treated patients ranged from 0.8 kg for the 50 mg daily dose to 1.4 kg for the 600 mg daily dose (with lower gain for the 800 mg daily dose), compared to 0.2 kg for the placebo treated patients. The percentage of quetiapine treated patients who gained ≥ 7% of body weight ranged from 5.3% for the 50 mg daily dose to 15.5% for the 400 mg daily dose (with lower gain for the 600 and 800 mg daily doses), compared to 3.7% for placebo treated patients.

A 6-week, randomised, study of lithium and Seroquel XL versus placebo and Seroquel XL in adult patients with acute mania indicated that the combination of Seroquel XL with lithium leads to more adverse events (63% versus 48% in Seroquel XL in combination with placebo). The safety results showed a higher incidence of extrapyramidal symptoms reported in 16.8% of patients in the lithium add-on group and 6.6% in the placebo add-on group, the majority of which consisted of tremor, reported in 15.6% of the patients in the lithium add-on group and 4.9% in the placebo add-on group. The incidence of somnolence was higher in the Seroquel XL with lithium add-on group (12.7%) compared to the Seroquel XL with the placebo add-on group (5.5%). In addition, a higher percentage of patients treated in the lithium add-on group (8.0%) had weight gain (≥ 7%) at the end of treatment compared to patients in the placebo add-on group (4.7%).

Longer term relapse prevention trials had an open label period (ranging from 4 to 36 weeks) during which patients were treated with quetiapine, followed by a randomised withdrawal period during which patients were randomised to quetiapine or placebo. For patients who were randomised to quetiapine, the mean weight gain during the open label period was 2.56 kg, and by week 48 of the randomised period, the mean weight gain was 3.22 kg, compared to open label baseline. For patients who were randomised to placebo, the mean weight gain during the open label period was 2.39 kg, and by week 48 of the randomised period the mean weight gain was 0.89 kg, compared to open label baseline.

In placebo-controlled studies in elderly patients with dementia-related psychosis, the incidence of cerebrovascular adverse events per 100 patient years was not higher in quetiapine-treated patients than in placebo-treated patients.

In all short-term placebo-controlled monotherapy trials in patients with a baseline neutrophil count ≥ 1.5 x 10^9/L, the incidence of at least one occurrence of a shift to neutrophil count <1.5 x 10^9/L, was 1.9% in patients treated with quetiapine compared to 1.5% in placebo-treated patients. The incidence of shifts to >0.5 - <1.0 x 10^9/L was the same (0.2%) in patients treated with quetiapine as with placebo-treated patients. In all clinical trials (placebo-controlled, open-label, active comparator) in patients with a baseline neutrophil count ≥ 1.5 x 10^9/L, the incidence of at least one occurrence of a shift to neutrophil count <1.5 x 10^9/L was 2.9% and to <0.5 x 10^9/L was 0.21% in patients treated with quetiapine.

Quetiapine treatment was associated with dose-related decreases in thyroid hormone levels. The incidences of shifts in TSH was 3.2 % for quetiapine versus 2.7 % for placebo. The incidence of reciprocal, potentially clinically significant shifts of both T3 or T4 and TSH in these trials were rare, and the observed changes in thyroid hormone levels were not associated with clinically symptomatic hypothyroidism. The reduction in total and free T_4 was maximal within the first six weeks of quetiapine treatment, with no further reduction during long-term treatment. For about 2/3 of all cases, cessation of quetiapine treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment.

Cataracts/lens opacities

In a clinical trial to evaluate the cataractogenic potential of Seroquel (200-800 mg/day) versus risperidone (2-8 mg/day) in patients with schizophrenia or schizoaffective disorder, the percentage of patients with increased lens opacity grade was not higher in Seroquel (4%) compared with risperidone (10%), for patients with at least 21 months of exposure.

Paediatric population

Clinical efficacy

The efficacy and safety of Seroquel was studied in a 3-week placebo controlled study for the treatment of mania (n= 284 patients from the US, aged 10-17). About 45% of the patient population had an additional diagnosis of ADHD. In addition, a 6-week placebo controlled study for the treatment of schizophrenia (n= 222 patients, aged 13-17) was performed. In both studies, patients with known lack of response to Seroquel were excluded. Treatment with Seroquel was initiated at 50 mg/day and on day 2 increased to 100 mg/day; subsequently the dose was titrated to a target dose (mania 400-600 mg/day; schizophrenia 400-800 mg/day) using increments of 100 mg/day given two or three times daily.

In the mania study, the difference in LS mean change from baseline in YMRS total score (active minus placebo) was -5.21 for Seroquel 400 mg/day and -6.56 for Seroquel 600 mg/day. Responder rates (YMRS improvement ≥ 50%) were 64% for Seroquel 400 mg/day, 58% for 600 mg/day and 37% in the placebo arm.

In the schizophrenia study, the difference in LS mean change from baseline in PANSS total score (active minus placebo) was -8.16 for Seroquel 400 mg/day and -9.29 for Seroquel 800 mg/day. Neither low dose (400 mg/day) nor high dose regimen (800 mg/day) quetiapine was superior to placebo with respect to the percentage of patients achieving response, defined as ≥ 30% reduction from baseline in PANSS total score. Both in mania and schizophrenia higher doses resulted in numerically lower response rates.

In a third short-term placebo-controlled monotherapy trial with Seroquel XL in children and adolescent patients (10-17 years of age) with bipolar depression, efficacy was not demonstrated.

No data are available on maintenance of effect or recurrence prevention in this age group.

Clinical safety

In the short-term paediatric trials with quetiapine described above, the rates of EPS in the active arm vs. placebo were 12.9% vs. 5.3% in the schizophrenia trial, 3.6% vs. 1.1% in the bipolar mania trial, and 1.1% vs. 0% in the bipolar depression trial. The rates of weight gain ≥ 7% of baseline body weight in the active arm vs. placebo were 17% vs. 2.5% in the schizophrenia and bipolar mania trials, and 13.7% vs. 6.8% in the bipolar depression trial. The rates of suicide related events in the active arm vs. placebo were 1.4% vs. 1.3% in the schizophrenia trial, 1.0% vs. 0% in the bipolar mania trial, and 1.1% vs. 0% in the bipolar depression trial. During an extended post-treatment follow-up phase of the bipolar depression trial, there were two additional suicide related events in two patients; one of these patients was on quetiapine at the time of the event.

Long-term safety

A 26-week open-label extension to the acute trials (n=380 patients), with Seroquel flexibly dosed at 400-800 mg/day, provided additional safety data. Increases in blood pressure were reported in children and adolescents and increased appetite, extrapyramidal symptoms and elevations in serum prolactin were reported with higher frequency in children and adolescents than in adult patients (see sections 4.4 and 4.8). With respect to weight gain, when adjusting for normal growth over the longer term, an increase of at least 0.5 standard deviation from baseline in Body Mass Index (BMI) was used as a measure of a clinically significant change; 18.3% of patients who were treated with quetiapine for at least 26 weeks met this criterion.

5.2 Pharmacokinetic properties

Absorption

Quetiapine is well absorbed following oral administration. Seroquel XL achieves peak quetiapine and norquetiapine plasma concentrations at approximately 6 hours after administration (T_{max}). Steady-state peak molar concentrations of the active metabolite norquetiapine are 35% of that observed for quetiapine.

The pharmacokinetics of quetiapine and norquetiapine are linear and dose-proportional for doses up to 800 mg administered once daily. When Seroquel XL administered once daily is compared to the same total daily dose of immediate-release quetiapine fumarate (Seroquel immediate release) administered twice daily, the area under the plasma concentration-time curve (AUC) is equivalent, but the maximum plasma concentration (C_{max}) is 13% lower at steady state. When Seroquel XL is compared to Seroquel immediate release, the norquetiapine metabolite AUC is 18% lower.

In a study examining the effects of food on the bioavailability of quetiapine, a high-fat meal was found to produce statistically significant increases in the Seroquel XL C_{max} and AUC of approximately 50% and 20% respectively. It cannot be excluded that the effect of a high fat meal on the formulation may be larger. In comparison, a light meal had no significant effect on the C_{max} or AUC of quetiapine. It is recommended that Seroquel XL is taken once daily without food.

Distribution

Quetiapine is approximately 83% bound to plasma proteins.

Biotransformation

Quetiapine is extensively metabolised by the liver, with parent compound accounting for less than 5% of unchanged drug-related material in the urine or faeces, following the administration of radiolabelled quetiapine.

In vitro investigations established that CYP3A4 is the primary enzyme responsible for cytochrome P450 mediated metabolism of quetiapine. Norquetiapine is primarily formed and eliminated via CYP3A4.

Quetiapine and several of its metabolites (including norquetiapine) were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities in vitro. In vitro CYP inhibition is observed only at concentrations approximately 5 to 50 fold higher than those observed at a dose range of 300 to 800 mg/day in humans. Based on these in vitro results, it is unlikely that co-administration of quetiapine with other drugs will result in clinically significant drug inhibition of cytochrome P450 mediated metabolism of the other drug. From animal studies it appears that quetiapine can induce cytochrome P450 enzymes. In a specific interaction study in psychotic patients, however, no increase in the cytochrome P450 activity was found after administration of quetiapine.

Elimination

The elimination half lives of quetiapine and norquetiapine are approximately 7 and 12 hours, respectively. Approximately 73% of a radiolabelled drug was excreted in the urine and 21% in the faeces with less than 5% of the total radioactivity representing unchanged drug-related material. The average molar dose fraction of free quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine.

Special populations

Gender

The pharmacokinetics of quetiapine does not differ between men and women.

Elderly

The mean clearance of quetiapine in the elderly is approximately 30 to 50% lower than that seen in adults aged 18 to 65 years.

Renal impairment

The mean plasma clearance of quetiapine was reduced by approximately 25% in subjects with severe renal impairment (creatinine clearance less than 30 ml/min/1.73 m^2), but the individual clearance values are within the range for normal subjects.

Hepatic impairment

The mean quetiapine plasma clearance decreases with approximately 25% in persons with known hepatic impairment (stable alcohol cirrhosis). As quetiapine is extensively metabolised by the liver, elevated plasma levels are expected in the population with hepatic impairment. Dose adjustments may be necessary in these patients (see section 4.2).

Paediatric population

Pharmacokinetic data were sampled in 9 children aged 10-12 years old and 12 adolescents, who were on steady-state treatment with 400 mg quetiapine (Seroquel) twice daily. At steady-state, the dose-normalised plasma levels of the parent compound, quetiapine, in children and adolescents (10-17 years of age) were in general similar to adults, though C_{max} in children was at the higher end of the range observed in adults. The AUC and C_{max} for the active metabolite, norquetiapine, were higher, approximately 62% and 49% in children (10-12 years), respectively and 28% and 14% in adolescents (13-17 years), respectively, compared to adults.

No information is available for Seroquel XL in children and adolescents.

5.3 Preclinical safety data

There was no evidence of genotoxicity in a series of in vitro and in vivo genotoxicity studies. In laboratory animals at a clinically relevant exposure level the following deviations were seen, which as yet have not been confirmed in long-term clinical research:

In rats, pigment deposition in the thyroid gland has been observed; in cynomolgus monkeys thyroid follicular cell hypertrophy, a lowering in plasma T_3 levels, decreased haemoglobin concentration and a decrease of red and white blood cell count have been observed; and in dogs lens opacity and cataracts (for cataracts/lens opacities, see section 5.1).

In an embryofoetal toxicity study in rabbits the foetal incidence of carpal/tarsal flexure was increased. This effect occurred in the presence of overt maternal effects such as reduced body weight gain. These effects were apparent at maternal exposure levels similar or slightly above those in humans at the maximal therapeutic dose. The relevance of this finding for humans is unknown.

In a fertility study in rats, marginal reduction in male fertility and pseudopregnancy, protracted periods of diestrus, increased precoital interval and reduced pregnancy rate were seen. These effects are related to elevated prolactin levels and not directly relevant to humans because of species differences in hormonal control of reproduction.

6. Pharmaceutical particulars

6.1 List of excipients

Core

Cellulose, microcrystalline

Sodium citrate

Lactose monohydrate

Magnesium stearate

Hypromellose 2208

Coating

Hypromellose 2910

Macrogol 400

Titanium dioxide (E171)

Iron oxide, yellow (E172) (50 mg, 200 mg, and 300 mg tablets)

Iron oxide, red (E172) (50 mg tablets)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Polychlorotrifluoroethylene and polyvinylchloride with aluminium blister

Tablet Strength	Carton (pack) contents	Blisters
50 mg, 150 mg 200 mg, 300 mg and 400 mg tablets	10 tablets	1 blister of 10 tablets
	30 tablets	3 blisters of 10 tablets
	50 tablets	10 blisters of 5 tablets 5 blisters of 10 tablets
	60 tablets	6 blisters of 10 tablets
	100 tablets	10 blisters of 10 tablets 100 blisters of 1 tablet

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

Luye Pharma Limited

Surrey Technology Centre, 40 Occam Road

Surrey Research Park

Guilford

GU2 7YG

United Kingdom

8. Marketing authorisation number(s)

50 mg:	PL 50827/0006
150 mg:	PL 50827/0007
200 mg:	PL 50827/0008
300 mg:	PL 50827/0009
400 mg:	PL 50827/0010

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation:	10th September 2008 (50 mg, 200 mg, 300 mg, 400 mg)
	12th March 2010 (150 mg)
Date of latest renewal:	23rd November 2015

10. Date of revision of the text

June 2024

Company Contact Details

Luye Pharma Limited

Address

Medical Information e-mail

safety@luyepharma.co.uk

Surrey Technology Centre, 40 Occam Road, Surrey
Research Park, Guildford, GU2 7YG

Risperidone

EMC

Risperidone 1 mg Tablets

Summary of Product Characteristics Updated 17-Jan-2024 | Sandoz Limited

1. Name of the medicinal product

Risperidone 1mg Tablets

2. Qualitative and quantitative composition

Each film-coated tablet contains 1 mg of risperidone

Excipient with known effect:

Each film-coated tablet contains 49.88 mg lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Film-coated tablet

White, oval film-coated tablets with breaking notch and debossed with " 1" on one side.

The tablet can be divided into equal doses.

4. Clinical particulars

4.1 Therapeutic indications

Risperidone is indicated for the treatment of schizophrenia.

Risperidone is indicated for the treatment of moderate to severe manic episodes associated with bipolar disorders.

Risperidone is indicated for the short-term treatment (up to 6 weeks) of persistent aggression in patients with moderate to severe Alzheimer's dementia unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others.

Risperidone is indicated for the short-term symptomatic treatment (up to 6 weeks) of persistent aggression in conduct disorder in children from the age of 5 years and adolescents with sub-average intellectual functioning or mental retardation diagnosed according to DSM-IV criteria, in whom the severity of aggressive or other disruptive behaviours require pharmacologic treatment. Pharmacological treatment should be an integral part of a more comprehensive treatment programme, including psychosocial and educational intervention. It is recommended that risperidone be prescribed by a specialist in child neurology and child and adolescent psychiatry or physicians well familiar with the treatment of conduct disorder of children and adolescents.

4.2 Posology and method of administration

Posology

Schizophrenia

Adults

Risperidone may be given once daily or twice daily. Patients should start with 2 mg/day risperidone. The dosage may be increased on the second day to 4 mg.

Subsequently, the dosage can be maintained unchanged, or further individualised, if needed. Most patients will benefit from daily doses between 4 and 6 mg. In some patients, a slower titration phase and a lower starting and maintenance dose may be appropriate.

Doses above 10 mg/day have not demonstrated superior efficacy to lower doses and may cause increased incidence of extrapyramidal symptoms. Safety of doses above 16 mg/day has not been evaluated and are therefore not recommended.

Elderly

A starting dose of 0.5 mg twice daily is recommended. This dosage can be individually adjusted with 0.5 mg twice daily increments to 1 to 2 mg twice daily.

Paediatric population

Risperidone is not recommended for use in children and adolescents below age 18 with schizophrenia due to a lack of data on efficacy.

Manic episodes in bipolar disorder

Adults

Risperidone should be administered on a once daily schedule, starting with 2 mg risperidone. Dosage adjustments, if indicated, should occur at intervals of not less than 24 hours and in dosage increments of 1 mg per day. Risperidone

can be administered in flexible doses over a range of 1 to 6 mg per day to optimize each patient's level of efficacy and tolerability. Daily doses over 6 mg risperidone have not been investigated in patients with manic episodes.

As with all symptomatic treatments, the continued use of Risperidone must be evaluated and justified on an ongoing basis.

Elderly

A starting dose of 0.5 mg twice daily is recommended. This dosage can be individually adjusted with 0.5 mg twice daily increments to 1 to 2 mg twice daily. Since clinical experience in elderly is limited, caution should be exercised.

Paediatric population

Risperidone is not recommended for use in children and adolescents below age 18 with bipolar mania due to a lack of data on efficacy.

Persistent aggression in patients with moderate to severe Alzheimer's dementia

A starting dose of 0.25 mg* twice daily is recommended. This dosage can be individually adjusted by increments of 0.25 mg* twice daily, not more frequently than every other day, if needed. The optimum dose is 0.5 mg* twice daily for most patients. Some patients, however, may benefit from doses up to 1 mg twice daily.

Risperidone should not be used more than 6 weeks in patients with persistent aggression in Alzheimer's dementia. During treatment, patients must be evaluated frequently and regularly, and the need for continuing treatment reassessed.

* for doses not achievable with Risperidone other risperidone presentations are available

Conduct disorder

Paediatric population: Children and adolescents from 5 to 18 years of age

For subjects ≥ 50 kg, a starting dose of 0.5 mg once daily is recommended. This dosage can be individually adjusted by increments of 0.5 mg once daily not more frequently than every other day, if needed. The optimum dose is 1 mg once daily for most patients. Some patients, however, may benefit from 0.5 mg* once daily while others may require 1.5 mg once daily. For subjects <50 kg, a starting dose of 0.25 mg* once daily is recommended. This dosage can be individually adjusted by increments of 0.25 mg* once daily not more frequently than every other day, if needed. The optimum dose is 0.5 mg once daily for most patients. Some patients, however, may benefit from 0.25 mg* once daily while others may require 0.75 mg* once daily.

* for doses not achievable with Risperidone other risperidone presentations are available

As with all symptomatic treatments, the continued use of Risperidone must be evaluated and justified on an ongoing basis.

Risperidone is not recommended in children less than 5 years of age, as there is no experience in children less than 5 years of age with this disorder.

Renal and hepatic impairment

Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than in adults with normal renal function. Patients with impaired hepatic function have increases in plasma concentration of the free fraction of risperidone.

Irrespective of the indication, starting and consecutive dosing should be halved, and dose titration should be slower for patients with renal or hepatic impairment.

Risperidone should be used with caution in these groups of patients.

Method of administration

Risperidone is for oral use. Food does not affect the absorption of Risperidone. The tablets can be divided into equal doses.

Upon discontinuation, gradual withdrawal is advised. Acute withdrawal symptoms, including nausea, vomiting, sweating, and insomnia have very rarely been described after abrupt cessation of high doses of antipsychotic medicines (see section 4.8). Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinesia) has been reported.

Switching from other antipsychotics.

When medically appropriate, gradual discontinuation of the previous treatment while Risperidone therapy is initiated is recommended. Also, if medically appropriate, when switching patients from depot antipsychotics, initiate Risperidone therapy in place of the next scheduled injection. The need for continuing existing anti-Parkinson medicines should be re-evaluated periodically.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Elderly patients with dementia

Increased mortality in elderly people with dementia

In a meta-analysis of 17 controlled trials of atypical antipsychotics, including risperidone, elderly **patients** with dementia treated with atypical antipsychotics have an increased mortality compared to placebo. In placebo-controlled trials with oral risperidone in this population, the incidence of mortality was 4.0% for risperidone-treated patients compared to 3.1% for placebo-treated patients. The odds ratio (95% exact confidence interval) was 1.21 (0.7, 2.1). The mean age (range) of patients who died was 86 years (range 67-100).

Data from two large observational studies showed that elderly people with dementia who are treated with conventional antipsychotics are also at a small increased risk of death compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

Concomitant use with furosemide

In the risperidone placebo-controlled trials in elderly **patients** with dementia, a higher incidence of mortality was observed in patients treated with furosemide plus risperidone (7.3%; mean age 89 years, range 75-97) when compared to patients treated with risperidone alone (3.1%; mean age 84 years, range 70-96) or furosemide alone (4.1%; mean age 80 years, range 67-90). The increase in mortality in patients treated with furosemide plus risperidone was observed in two of the four clinical trials. Concomitant use of risperidone with other diuretics (mainly thiazide diuretics used in low dose) was not associated with similar findings.

No pathophysiological mechanism has been identified to explain this finding, and no consistent pattern for cause of death observed. Nevertheless, caution should be exercised and the risks and benefits of this combination or co-treatment with other potent diuretics should be considered prior to the decision to use.

There was no increased incidence of mortality among patients taking other diuretics as concomitant treatment with risperidone. Irrespective of treatment, dehydration was an overall risk factor for mortality and should therefore be carefully avoided in elderly **patients** with dementia.

Cerebrovascular Adverse Events (CVAE)

An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomised placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The pooled data from six placebo-controlled studies with risperidone in mainly elderly **patients** (>65 years of age) with dementia showed that CVAEs (serious and non-serious, combined) occurred in 3.3% (33/1009) of patients treated with risperidone and 1.2% (8/712) of patients treated with placebo. The odds ratio (95% exact confidence interval) was 2.96 (1.34, 7.50). The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Risperidone should be used with caution in patients with risk factors for stroke.

The risk of CVAEs was significantly higher in patients with mixed or vascular type of dementia when compared to Alzheimer's dementia. Therefore, patients with other types of dementias than Alzheimer's should not be treated with risperidone.

Physicians are advised to assess the risks and benefits of the use of risperidone in elderly **patients** with dementia, taking into account risk predictors for stroke in the individual patient. Patients/caregivers should be cautioned to immediately report signs and symptoms of potential CVAEs such as sudden weakness or numbness in the face, arms or legs, and speech or vision problems. All treatment options should be considered without delay, including discontinuation of risperidone.

Risperidone should only be used short term for persistent aggression in patients with moderate to severe Alzheimer's dementia to supplement non-pharmacological approaches which have had limited or no efficacy and when there is potential risk of harm to self or others.

Patients should be reassessed regularly, and the need for continuing treatment reassessed.

Orthostatic hypotension

Due to the alpha-blocking activity of risperidone, (orthostatic) hypotension can occur, especially during the initial dose-titration period. Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone and antihypertensive treatment. Risperidone should be used with caution in patients with known cardiovascular disease (e.g., heart failure, myocardial infarction, conduction abnormalities, dehydration, hypovolemia, or cerebrovascular disease), and the dosage should be gradually titrated as recommended (see section 4.2). A dose reduction should be considered if hypotension occurs.

Leukopenia, neutropenia, and agranulocytosis

Events of leucopenia, neutropenia and agranulocytosis have been reported with antipsychotic agents, including risperidone. Agranulocytosis has been reported very rarely (< 1/10,000 patients) during post-marketing surveillance.

Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should be monitored during the first few months of therapy and discontinuation of risperidone

should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1 x 10^9/L) should discontinue risperidone and have their WBC followed until recovery.

Tardive dyskinesia/extrapyramidal symptoms (TD/EPS)

Medicines with dopamine receptor antagonistic properties have been associated with the induction of tardive dyskinesia characterised by rhythmical involuntary movements, predominantly of the tongue and/or face.

The onset of extrapyramidal symptoms is a risk factor for tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear, the discontinuation of all antipsychotics should be considered.

Caution is warranted in patients receiving both, psychostimulants (e.g. methylphenidate) and risperidone concomitantly, as extrapyramidal symptoms could emerge when adjusting one or both medications. Gradual withdrawal of stimulant treatment is recommended (see section 4.5).

Neuroleptic malignant syndrome (NMS)

Neuroleptic Malignant Syndrome, characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels has been reported to occur with antipsychotics. Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. In this event, all antipsychotics, including risperidone, should be discontinued.

Parkinson's disease and dementia with Lewy bodies

Physicians should weigh the risks versus the benefits when prescribing antipsychotics, including risperidone, to patients with Parkinson's Disease or Dementia with Lewy Bodies (DLB). Parkinson's Disease may worsen with risperidone. Both groups may be at increased risk of Neuroleptic Malignant Syndrome as well as having an increased sensitivity to antipsychotic medicinal products; these patients were excluded from clinical trials. Manifestation of this increased sensitivity can include confusion, obtundation, postural instability with frequent falls, in addition to extrapyramidal symptoms.

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, diabetes mellitus and exacerbation of pre-existing diabetes have been reported during treatment with risperidone. In some cases, a prior increase in body weight has been reported which may be a predisposing factor. Association with ketoacidosis has been reported very rarely, and rarely with diabetic coma. Appropriate clinical monitoring is advisable in accordance with utilised antipsychotic guidelines. Patients treated with any atypical antipsychotic, including risperidone, should be monitored for symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus should be monitored regularly for worsening of glucose control.

Weight gain

Significant weight gain has been reported with risperidone use. Weight should be monitored regularly.

Hyperprolactinaemia

Hyperprolactinaemia is a common side-effect of treatment with risperidone. Evaluation of the prolactin plasma level is recommended in patients with evidence of possible prolactin-related side-effects (e.g. gynaecomastia, menstrual disorders, anovulation, fertility disorder, decreased libido, erectile dysfunction, and galactorrhoea).

Tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics has so far been demonstrated in clinical and epidemiological studies, caution is recommended in patients with relevant medical history. Risperidone should be used with caution in patients with pre-existing hyperprolactinaemia and in patients with possible prolactin-dependent tumours.

QT prolongation

QT prolongation has very rarely been reported postmarketing. As with other antipsychotics, caution should be exercised when risperidone is prescribed in patients with known cardiovascular disease, family history of QT prolongation, bradycardia, or electrolyte disturbances (hypokalaemia, hypomagnesaemia), as it may increase the risk of arrhythmogenic effects, and in concomitant use with medicines known to prolong the QT interval.

Seizures

Risperidone should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Priapism

Priapism may occur with risperidone treatment due to its alpha-adrenergic blocking effects.

Body temperature regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicines. Appropriate care is advised when prescribing Risperidone to patients who will be experiencing conditions which may

contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant treatment with anticholinergic activity, or being subject to dehydration.

Antiemetic effect

An antiemetic effect was observed in preclinical studies with risperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdosage with certain medicines or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumour.

Renal and hepatic impairment

Patients with renal impairment have less ability to eliminate the active antipsychotic fraction than adults with normal renal function. Patients with impaired hepatic function have increases in plasma concentration of the free fraction of risperidone (see section 4.2).

Venous thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with risperidone and preventative measures undertaken.

Intraoperative Floppy Iris Syndrome

Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in patients treated with medicines with alpha1a-adrenergic antagonist effect, including risperidone (see section 4.8).

IFIS may increase the risk of eye complications during and after the operation. Current or past use of medicines with alpha1a-adrenergic antagonist effect should be made known to the ophthalmic surgeon in advance of surgery. The potential benefit of stopping alpha1 blocking therapy prior to cataract surgery has not been established and must be weighed against the risk of stopping the antipsychotic therapy.

Paediatric population

Before risperidone is prescribed to a child or adolescent with conduct disorder they should be fully assessed for physical and social causes of the aggressive behaviour such as pain or inappropriate environmental demands.

The sedative effect of risperidone should be closely monitored in this population because of possible consequences on learning ability. A change in the time of administration of risperidone could improve the impact of the sedation on attention faculties of children and adolescents.

Risperidone was associated with mean increases in body weight and body mass index (BMI). Baseline weight measurement prior to treatment and regular weight monitoring are recommended. Changes in height in the long-term open-label extension studies were within expected age-appropriate norms. The effect of long-term risperidone treatment on sexual maturation and height has not been adequately studied. Because of the potential effects of prolonged hyperprolactinaemia on growth and sexual maturation in children and adolescents, regular clinical evaluation of endocrinological status should be considered, including measurements of height, weight, sexual maturation, monitoring of menstrual functioning, and other potential prolactin-related effects.

Results from a small post-marketing observational study showed that risperidone-exposed subjects between the ages of 8-16 years were on average approximately 3.0 to 4.8 cm taller than those who received other atypical anti-psychotic medications. This study was not adequate to determine whether exposure to risperidone had any impact on final adult height, or whether the result was due to a direct effect of risperidone on bone growth, or the effect of the underlying disease itself on bone growth, or the result of better control of the underlying disease with resulting increase in linear growth.

During treatment with risperidone regular examination for extrapyramidal symptoms and other movement disorders should also be conducted.

For specific posology recommendations in children and adolescents see Section 4.2.

Risperidone contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic-related interactions

Medicinal products known to prolong the QT interval

As with other antipsychotics, caution is advised when prescribing risperidone with medicinal products known to prolong the QT interval such as antiarrhythmics (e.g., quinidine, dysopiramide, procainamide, propafenone, amiodarone, sotalol), tricyclic antidepressants (i.e., amitriptyline), tetracyclic antidepressants (i.e., maprotiline), some antihistamines, other antipsychotics, some antimalarials (i.e., quinine and mefloquine), and with medicines causing electrolyte imbalance (hypokalaemia, hypomagnesiaemia), bradycardia, or those which inhibit the hepatic metabolism of risperidone. This list is indicative and not exhaustive.

Centrally-acting medicinal products and alcohol

Risperidone should be used with caution in combination with other centrally-acting substances notably including alcohol, opiates, antihistamines and benzodiazepines due to the increased risk of sedation.

Levodopa and dopamine agonists

Risperidone may antagonise the effect of levodopa and other dopamine agonists. If this combination is deemed necessary, particularly in end-stage Parkinson's disease, the lowest effective dose of each treatment should be prescribed.

Medicinal products with hypotensive effect

Clinically significant hypotension has been observed postmarketing with concomitant use of risperidone and antihypertensive treatment.

Paliperidone

Concomitant use of oral risperidone with paliperidone is not recommended as paliperidone is the active metabolite of risperidone and the combination of the two may lead to additive active antipsychotic fraction exposure.

Psychostimulants

The combined use of psychostimulants (e.g. methylphenidate) with risperidone can lead to extrapyramidal symptoms upon change of either or both treatments (see section 4.4).

Pharmacokinetic-related interactions

Food does not affect the absorption of risperidone.

Risperidone is mainly metabolised through CYP2D6, and to a lesser extent through CYP3A4. Both risperidone and its active metabolite 9-hydroxyrisperidone are substrates of P-glycoprotein (P-gp). Substances that modify CYP2D6 activity, or substances strongly inhibiting or inducing CYP3A4 and/or P-gp activity, may influence the pharmacokinetics of the risperidone active antipsychotic fraction.

Strong CYP2D6 inhibitors

Co-administration of risperidone with a strong CYP2D6 inhibitor may increase the plasma concentrations of risperidone, but less so of the active antipsychotic fraction. Higher doses of a strong CYP2D6 inhibitor may elevate concentrations of the risperidone active antipsychotic fraction (e.g., paroxetine, see below). It is expected that other CYP 2D6 inhibitors, such as quinidine, may affect the plasma concentrations of risperidone in a similar way. When concomitant paroxetine, quinidine, or another strong CYP2D6 inhibitor, especially at higher doses, is initiated or discontinued, the physician should re-evaluate the dosing of risperidone.

CYP3A4 and/or P-gp inhibitors

Co-administration of risperidone with a strong CYP3A4 and/or P-gp inhibitor may substantially elevate plasma concentrations of the risperidone active antipsychotic fraction. When concomitant itraconazole or another strong CYP3A4 and/or P-gp inhibitor is initiated or discontinued, the physician should re-evaluate the dosing of risperidone.

CYP3A4 and/or P-gp inducers

Co-administration of risperidone with a strong CYP3A4 and/or P-gp inducer may decrease the plasma concentrations of the risperidone active antipsychotic fraction. When concomitant carbamazepine or another strong CYP3A4 and/or P-gp inducer is initiated or discontinued, the physician should re-evaluate the dosing of risperidone. CYP3A4 inducers exert their effect in a time-dependent manner, and may take at least 2 weeks to reach maximal effect after introduction. Conversely, on discontinuation, CYP3A4 induction may take at least 2 weeks to decline.

Highly protein-bound medicinal products

When risperidone is taken together with highly protein-bound medicinal products, there is no clinically relevant displacement of either medicinal product from the plasma proteins. When using concomitant medication, the corresponding label should be consulted for information on the route of metabolism and the possible need to adjust dose.

Paediatric population

Interaction studies have only been performed in adults. The relevance of the results from these studies in paediatric patients is unknown.

The combined use of psychostimulants (e.g., methylphenidate) with risperidone in children and adolescents did not alter the pharmacokinetics and efficacy of risperidone.

Examples

Examples of drugs that may potentially interact or that were shown not to interact with risperidone are listed below:

Effect of other medicinal products on the pharmacokinetics of risperidone

Antibacterials:

• Erythromycin, a moderate CYP3A4 inhibitor and P-gp inhibitor, does not change the pharmacokinetics of risperidone

and the active antipsychotic fraction.

• Rifampicin, a strong CYP3A4 inducer and a P-gp inducer, decreased the plasma concentrations of the active antipsychotic fraction.

Anticholinesterases:

• Donepezil and galantamine, both CYP2D6 and CYP3A4 substrates, do not show a clinically relevant effect on the pharmacokinetics of risperidone and the active antipsychotic fraction.

Antiepileptics:

• Carbamazepine, a strong CYP3A4 inducer and a P-gp inducer, has been shown to decrease the plasma concentrations of the active antipsychotic fraction of risperidone. Similar effects may be observed with e.g. phenytoin and phenobarbital which also induce CYP 3A4 hepatic enzyme, as well as P-glycoprotein.

• Topiramate modestly reduced the bioavailability of risperidone, but not that of the active antipsychotic fraction. Therefore, this interaction is unlikely to be of clinical significance.

Antifungals:

• Itraconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 200 mg/day increased the plasma concentrations of the active antipsychotic fraction by about 70%, at risperidone doses of 2 to 8 mg/day.

• Ketoconazole, a strong CYP3A4 inhibitor and a P-gp inhibitor, at a dosage of 200 mg/day increased the plasma concentrations of risperidone and decreased the plasma concentrations of 9-hydroxyrisperidone.

Antipsychotics:

• Phenothiazines may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction.

Antivirals:

• Protease inhibitors: No formal study data are available; however, since ritonavir is a strong CYP3A4 inhibitor and a weak CYP2D6 inhibitor, ritonavir and ritonavir-boosted protease inhibitors potentially raise concentrations of the risperidone active antipsychotic fraction.

Beta blockers:

• Some beta-blockers may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction.

Calcium channel blockers:

• Verapamil, a moderate inhibitor of CYP3A4 and an inhibitor of P-gp, increases the plasma concentration of risperidone and the active antipsychotic fraction.

Gastrointestinal medicinal products:

• H2-receptor antagonists: Cimetidine and ranitidine, both weak inhibitors of CYP2D6 and CYP3A4, increased the bioavailability of risperidone, but only marginally that of the active antipsychotic fraction.

SSRIs and tricyclic antidepressants:

• Fluoxetine, a strong CYP2D6 inhibitor, increases the plasma concentration of risperidone, but less so of the active antipsychotic fraction.

• Paroxetine, a strong CYP2D6 inhibitor, increases the plasma concentrations of risperidone, but, at dosages up to 20 mg/day, less so of the active antipsychotic fraction. However, higher doses of paroxetine may elevate concentrations of the risperidone active antipsychotic fraction.

• Tricyclic antidepressants may increase the plasma concentrations of risperidone but not those of the active antipsychotic fraction. Amitriptyline does not affect the pharmacokinetics of risperidone or the active antipsychotic fraction.

• Sertraline, a weak inhibitor of CYP2D6, and fluvoxamine, a weak inhibitor of CYP3A4, at dosages up to 100 mg/day are not associated with clinically significant changes in concentrations of the risperidone active antipsychotic fraction. However, doses higher than 100 mg/day of sertraline or fluvoxamine may elevate concentrations of the risperidone active antipsychotic fraction.

Effect of risperidone on the pharmacokinetics of other medicinal products

Antiepileptics:

• Risperidone does not show a clinically relevant effect on the pharmacokinetics of valproate or topiramate.

Antipsychotics:

• Aripiprazole, a CYP2D6 and CYP3A4 substrate: Risperidone tablets or injections did not affect the pharmacokinetics of the sum of aripiprazole and its active metabolite, dehydroaripiprazole.

Digitalis glycosides:

• Risperidone does not show a clinically relevant effect on the pharmacokinetics of digoxin.

Lithium:

• Risperidone does not show a clinically relevant effect on the pharmacokinetics of lithium.

Concomitant use of risperidone with furosemide

• See section 4.4 regarding increased mortality in elderly patients with dementia concomitantly receiving furosemide.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of risperidone in pregnant women. Risperidone was not teratogenic in animal studies but other types of reproductive toxicity were seen (see section 5.3). The potential risk for humans is unknown.

Neonates exposed to antipsychotics (including risperidone) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently newborns should be monitored carefully.

Risperidone should not be used during pregnancy unless clearly necessary. If discontinuation during pregnancy is necessary, it should not be done abruptly.

Breast-feeding

In animal studies, risperidone and 9-hydroxy-risperidone are excreted in the milk. It has been demonstrated that risperidone and 9-hydroxy-risperidone are also excreted in human breast milk in small quantities. There are no data available on adverse reactions in breast-fed infants. Therefore, the advantage of breastfeeding should be weighed against the potential risks for the child.

Fertility

As with other medicinal products that antagonize dopamine D2 receptors, risperidone elevates prolactin level. Hyperprolactinaemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients.

There were no relevant effects observed in the non-clinical studies.

4.7 Effects on ability to drive and use machines

Risperidone can have minor or moderate influence on the ability to drive and use machines due to potential nervous system and visual effects (see section 4.8). Therefore, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

4.8 Undesirable effects

The most frequently reported adverse drug reactions (ADRs) (incidence ≥ 10%) are:

Parkinsonism, sedation/somnolence, headache, and insomnia.

The ADRs that appeared to be dose-related included parkinsonism and akathisia.

The following are all the ADRs that were reported in clinical trials and post-marketing experience with risperidone by frequency category estimated from clinical trials. The following terms and frequencies are applied: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1000 to <1/100), rare (≥ 1/10,000 to <1/1000), very rare (<1/10,000), and not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse Drug Reactions (ADRs) by System Organ Class and Frequency		
MedDRA System Organ Class	**Frequency**	**ADRs**
Infections and infestations	**Common**	Pneumonia, Bronchitis, Upper respiratory tract infection, Sinusitis, Urinary tract infection, Ear infection, Influenza
	Uncommon	Respiratory tract infection, Cystitis, Eye infection, Tonsillitis, Onychomycosis, Cellulitis, Localised infection, Viral infection, Acarodermatitis
	Rare	Infection

Blood and lymphatic system disorders	**Uncommon**	Neutropenia, White blood cell count decreased, Thrombocytopenia, Anaemia, Haematocrit decreased, Eosinophil count increased
	Rare	Agranulocytosis[c]
Immune system disorders	**Uncommon**	Hypersensitivity
	Rare	Anaphylactic reaction[c]
Endocrine disorders	**Common**	Hyperprolactinaemia[a]
	Rare	Inappropriate antidiuretic hormone secretion, Glucose urine present
Metabolism and nutrition disorders	**Common**	Weight increased, Increased appetite, Decreased appetite
	Uncommon	Diabetes mellitus[b], Hyperglycaemia, Polydipsia, Weight decreased, Anorexia, Blood cholesterol increased
	Rare	Water intoxication[c] ,Hypoglycaemia, Hyperinsulinaemia[c], Blood triglycerides increased
	Very rare	Diabetic ketoacidosis
Psychiatric disorders	**Very common**	Insomnia[d]
	Common	Sleep disorder, Agitation, Depression, Anxiety
	Uncommon	Mania, Confusional state, Libido decreased, Nervousness, Nightmare
	Rare	Catatonia, Somnambulism, Sleep-related eating disorder, Blunted affect, Anorgasmia
Nervous system disorders	**Very common**	Sedation/Somnolence, Parkinsonism[d], Headache
	Common	Akathisia[d], Dystonia[d], Dizziness, Dyskinesia[d], Tremor,
	Uncommon	Tardive dyskinesia, Cerebral ischaemia, Unresponsive to stimuli, Loss of consciousness, Depressed level of consciousness, Convulsion[d], Syncope, Psychomotor hyperactivity, Balance disorder, Coordination abnormal, Dizziness postural, Disturbance in attention, Dysarthria, Dysgeusia, Hypoaesthesia, Paraesthesia,
	Rare	Neuroleptic malignant syndrome, Cerebrovascular disorder, Diabetic coma, Head titubation
Eye disorders	**Common**	Vision blurred, Conjunctivitis
	Uncommon	Photophobia, Dry eye, Lacrimation increased, Ocular hyperaemia
	Rare	Glaucoma, Eye Movement disorder, Eye rolling, Eyelid margin crusting, Floppy iris syndrome (intraoperative)[c]
Ear and labyrinth disorders	**Uncommon**	Vertigo, Tinnitus, Ear pain
Cardiac disorders	**Common**	Tachycardia
	Uncommon	Atrial fibrillation, Atrioventricular block, Conduction disorder, Electrocardiogram QT prolonged, Bradycardia, Electrocardiogram abnormal, Palpitations
	Rare	Sinus arrhythmia
Vascular disorders	**Common**	Hypertension
	Uncommon	Hypotension, Orthostatic hypotension, Flushing

	Rare	Pulmonary embolism, Venous thrombosis
Respiratory, thoracic and mediastinal disorders	**Common**	Dyspnoea, Pharyngolaryngeal pain, Cough, Epistaxis, Nasal congestion
	Uncommon	Pneumonia aspiration, Pulmonary congestion, Respiratory tract congestion, Rales, Wheezing, Dysphonia, Respiratory disorder
	Rare	Sleep apnea syndrome, Hyperventilation
Gastrointestinal disorders	**Common**	Abdominal pain, Abdominal discomfort, Vomiting, Nausea, Constipation, Diarrhoea, Dyspepsia, Dry mouth, Toothache
	Uncommon	Faecal incontinence, Faecaloma, Gastroenteritis, Dysphagia, Flatulence
	Rare	Pancreatitis, Intestinal obstruction, Swollen tongue, Cheilitis
	Very rare	Ileus
Hepato-biliary disorders	**Uncommon**	Transaminases increased, Gamma-glutamyltransferase increased, Hepatic enzyme increased
	Rare	Jaundice
Skin and subcutaneous tissue disorders	**Common**	Rash, Erythema
	Uncommon	Urticaria, Pruritus, Alopecia, Hyperkeratosis, Eczema, Dry skin, Skin discolouration, Acne, Seborrhoeic dermatitis, Skin disorder, Skin lesion,
	Rare	Drug eruption, Dandruff
	Very rare	Angioedema
	Not known	Stevens-Johnson syndrome/toxic epidermal necrolysis[c]
Musculoskeletal and connective tissue disorders	**Common**	Muscle Spasms, Musculoskeletal pain, Back pain, Arthralgia
	Uncommon	Blood creatine phosphokinase increased, Posture abnormal, Joint stiffness, Joint swelling, Muscular weakness, Neck pain
	Rare	Rhabdomyolysis
Renal and urinary disorders	**Common**	Urinary incontinence
	Uncommon	Pollakiuria, Urinary retention, Dysuria
Pregnancy, puerperium and neonatal conditions	**Rare**	Drug withdrawal syndrome neonatal[c]
Reproductive system and breast disorders	**Uncommon**	Erectile dysfunction, Ejaculation disorder, Amenorrhoea, Menstrual disorder[d], Gynaecomastia, Galactorrhoea, Sexual dysfunction, Breast pain, Breast discomfort, Vaginal discharge
	Rare	Priapism[c], Menstruation delayed, Breast engorgement, Breast enlargement, Breast discharge
General disorders and administration site conditions	**Common**	Oedema[d], Pyrexia, Chest pain, Asthenia, Fatigue, Pain
	Uncommon	Face oedema, Chills, Body temperature increased, Gait abnormal, Thirst, Chest discomfort, Malaise, Feeling abnormal, Discomfort
	Rare	Hypothermia, Body temperature decreased, Peripheral coldness, Drug withdrawal syndrome, Induration[c]
Injury, poisoning and procedural complications	**Common**	Fall

	Uncommon	Procedural pain

[a] Hyperprolactinaemia can in some cases lead to gynaecomastia, menstrual disturbances, amenorrhoea, anovulation, galactorrhea, fertility disorder, decreased libido, erectile dysfunction.

[b] In placebo-controlled trials diabetes mellitus was reported in 0.18% in risperidone-treated subjects compared to a rate of 0.11% in placebo group. Overall incidence from all clinical trials was 0.43% in all risperidone-treated subjects.

[c] Not observed in risperidone clinical studies but observed in post-marketing environment with risperidone.

[d] Extrapyramidal disorder may occur: **Parkinsonism** (salivary hypersecretion, musculoskeletal stiffness, parkinsonism, drooling, cogwheel rigidity, bradykinesia, hypokinesia, masked facies, muscle tightness, akinesia, nuchal rigidity, muscle rigidity, parkinsonian gait, and glabellar reflex abnormal, parkinsonian rest tremor), **akathisia** (akathisia, restlessness, hyperkinesia, and restless leg syndrome), tremor, **dyskinesia** (dyskinesia, muscle twitching, choreoathetosis, athetosis, and myoclonus), dystonia. **Dystonia** includes dystonia, hypertonia, torticollis, muscle contractions involuntary, muscle contracture, blepharospasm, oculogyration, tongue paralysis, facial spasm, laryngospasm, myotonia, opisthotonus, oropharyngeal spasm, pleurothotonus, tongue spasm, and trismus. It should be noted that a broader spectrum of symptoms are included, that do not necessarily have an extrapyramidal origin. **Insomnia** includes: initial insomnia, middle insomnia; **Convulsion** includes: Grand mal convulsion; **Menstrual disorder** includes: Menstruation irregular, oligomenorrhoea; **Oedema** includes: generalised oedema, oedema peripheral, pitting oedema.

Undesirable effects noted with paliperidone formulations

Paliperidone is the active metabolite of risperidone, therefore, the adverse reaction profiles of these compounds (including both the oral and injectable formulations) are relevant to one another. In addition to the above adverse reactions, the following adverse reaction has been noted with the use of paliperidone products and can be expected to occur with risperidone.

Cardiac disorders: Postural orthostatic tachycardia syndrome

Class effects

As with other antipsychotics, very rare cases of QT prolongation have been reported postmarketing with risperidone. Other class-related cardiac effects reported with antipsychotics which prolong QT interval include ventricular arrhythmia, ventricular fibrillation, ventricular tachycardia, sudden death, cardiac arrest and Torsades de Pointes.

Venous thromboembolism

Cases of venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis, have been reported with antipsychotic drugs (frequency unknown). ´

Weight gain

The proportions of risperidone and placebo-treated adult patients with schizophrenia meeting a weight gain criterion of ≥ 7% of body weight were compared in a pool of 6- to 8-week, placebo-controlled trials, revealing a statistically significantly greater incidence of weight gain for risperidone (18%) compared to placebo (9%). In a pool of placebo-controlled 3-week studies in adult patients with acute mania, the incidence of weight increase of ≥ 7% at endpoint was comparable in the risperidone (2.5%) and placebo (2.4%) groups, and was slightly higher in the active-control group (3.5%).

In a population of children and adolescents with conduct and other disruptive behaviour disorders, in long-term studies, weight increased by a mean of 7.3 kg after 12 months of treatment. The expected weight gain for normal children between 5-12 years of age is 3 to 5 kg per year. From 12-16 years of age, this magnitude of gaining 3 to 5 kg per year is maintained for girls, while boys gain approximately 5 kg per year.

Additional information on special populations

Adverse drug reactions that were reported with higher incidence in elderly patients with dementia or paediatric patients than in adult populations are described below:

Elderly patients with dementia

Transient ischaemic attack and cerebrovascular accident were ADRs reported in clinical trials with a frequency of 1.4% and 1.5%, respectively, in elderly patients with dementia. In addition, the following ADRs were reported with a frequency ≥ 5% in elderly patients with dementia and with at least twice the frequency seen in other adult populations: urinary tract infection, peripheral oedema, lethargy, and cough.

Paediatric population

In general, type of adverse reactions in children is expected to be similar to those observed in adults.

The following ADRs were reported with a frequency ≥ 5% in paediatric patients (5 to 17 years) and with at least twice the frequency seen in clinical trials in adults: somnolence/sedation, fatigue, headache, increased appetite, vomiting, upper respiratory tract infection, nasal congestion, abdominal pain, dizziness, cough, pyrexia, tremor, diarrhoea, and

enuresis. The effect of long-term risperidone treatment on sexual maturation and height has not been adequately studied (see section 4.4 subsection " Paediatric population").

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme (www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in Google play or Apple App store.

4.9 Overdose

Symptoms

In general, reported signs and symptoms have been those resulting from an exaggeration of the known pharmacological effects of risperidone. These include drowsiness and sedation, tachycardia and hypotension, and extrapyramidal symptoms. In overdose, QT-prolongation and convulsions have been reported. Torsade de Pointes has been reported in association with combined overdose of risperidone and paroxetine.

In case of acute overdose, the possibility of multiple drug involvement should be considered.

Treatment

Establish and maintain a clear airway and ensure adequate oxygenation and ventilation. Administration of activated charcoal together with a laxative should be considered only when drug intake was less than one hour before. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias.

There is no specific antidote to Risperidone. Therefore, appropriate supportive measures should be instituted. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents. In case of severe extrapyramidal symptoms, an anticholinergic medicinal product should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antipsychotics, ATC-code: N05AX08

Mechanism of action

Risperidone is a selective monoaminergic antagonist with unique properties. It has a high affinity for serotoninergic 5-HT2 and dopaminergic D2 receptors. Risperidone binds also to alpha1-adrenergic receptors, and, with lower affinity, to H1-histaminergic and alpha2 adrenergic receptors. Risperidone has no affinity for cholinergic receptors.

Pharmacodynamic effects

Although risperidone is a potent D2 antagonist, which is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy than classical antipsychotics. Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability and extend the therapeutic activity to the negative and affective symptoms of schizophrenia.

Clinical efficacy and safety

Schizophrenia

The efficacy of risperidone in the short-term treatment of schizophrenia was established in four studies, 4- to 8-weeks in duration, which enrolled over 2500 patients who met DSM-IV criteria for schizophrenia. In a 6-week, placebo-controlled trial involving titration of risperidone in doses up to 10 mg/day administered twice daily, risperidone was superior to placebo on the Brief Psychiatric Rating Scale (BPRS) total score. In an 8- week, placebo-controlled trial involving four fixed doses of risperidone (2, 6, 10, and 16 mg/day, administered twice daily), all four risperidone groups were superior to placebo on the Positive and Negative Syndrome Scale (PANSS) total score. In an 8-week, dose comparison trial involving five fixed doses of risperidone (1, 4, 8, 12, and 16 mg/day administered twice-daily), the 4, 8, and 16 mg/day risperidone dose groups were superior to the 1 mg risperidone dose group on PANSS total score. In a 4-week, placebo-controlled dose comparison trial involving two fixed doses of risperidone (4 and 8 mg/day administered once daily), both risperidone dose groups were superior to placebo on several PANSS measures, including total PANSS and a response measure (>20% reduction in PANSS total score). In a longer-term trial, adult outpatients predominantly meeting DSM-IV criteria for schizophrenia and who had been clinically stable for at least 4 weeks on an antipsychotic medicinal product were randomised to risperidone 2 to 8 mg/day or to haloperidol for 1 to 2 years of observation for relapse. Patients receiving risperidone experienced a significantly longer time to relapse over this time period compared to those receiving haloperidol.

Manic episodes in bipolar disorder

The efficacy of risperidone monotherapy in the acute treatment of manic episodes associated with bipolar I disorder was demonstrated in three double-blind, placebo-controlled monotherapy studies in approximately 820 patients who had bipolar I disorder, based on DSM-IV criteria. In the three studies, risperidone 1 to 6 mg/day (starting dose 3 mg in two studies and 2 mg in one study) was shown to be significantly superior to placebo on the pre-specified primary endpoint,

i.e., the change from baseline in total Young Mania Rating Scale (YMRS) score at Week 3. Secondary efficacy outcomes were generally consistent with the primary outcome. The percentage of patients with a decrease of ≥ 50% in total YMRS score from baseline to the 3-week endpoint was significantly higher for risperidone than for placebo. One of the three studies included a haloperidol arm and a 9-week double-blind maintenance phase. Efficacy was maintained throughout the 9-week maintenance treatment period. Change from baseline in total YMRS showed continued improvement and was comparable between risperidone and haloperidol at Week 12.

The efficacy of risperidone in addition to mood stabilisers in the treatment of acute mania was demonstrated in one of two 3-week double-blind studies in approximately 300 patients who met the DSM-IV criteria for bipolar I disorder. In one 3-week study, risperidone 1 to 6 mg/day starting at 2 mg/day in addition to lithium or valproate was superior to lithium or valproate alone on the pre-specified primary endpoint, i.e., the change from baseline in YMRS total score at Week 3. In a second 3-week study, risperidone 1 to 6 mg/day starting at 2 mg/day, combined with lithium, valproate, or carbamazepine was not superior to lithium, valproate, or carbamazepine alone in the reduction of YMRS total score. A possible explanation for the failure of this study was induction of risperidone and 9-hydroxy-risperidone clearance by carbamazepine, leading to subtherapeutic levels of risperidone and 9-hydroxy-risperidone. When the carbamazepine group was excluded in a post-hoc analysis, risperidone combined with lithium or valproate was superior to lithium or valproate alone in the reduction of YMRS total score.

Persistent aggression in dementia

The efficacy of risperidone in the treatment of Behavioural and Psychological Symptoms of Dementia (BPSD), which includes behavioural disturbances, such as aggressiveness, agitation, psychosis, activity, and affective disturbances was demonstrated in three double-blind, placebo-controlled studies in 1150 elderly patients with moderate to severe dementia. One study included fixed risperidone doses of 0.5, 1, and 2 mg/day. Two flexible-dose studies included risperidone dose groups in the range of 0.5 to 4 mg/day and 0.5 to 2 mg/day, respectively. Risperidone showed statistically significant and clinically important effectiveness in treating aggression and less consistently in treating agitation and psychosis in elderly dementia patients (as measured by the Behavioural Pathology in Alzheimer's Disease Rating Scale [BEHAVE-AD] and the Cohen-Mansfield Agitation Inventory [CMAI]). The treatment effect of risperidone was independent of Mini-Mental State Examination (MMSE) score (and consequently of the severity of dementia); of sedative properties of risperidone; of the presence or absence of psychosis; and of the type of dementia, Alzheimer's, vascular, or mixed. (See also section 4.4)

Paediatric population

Conduct disorder

The efficacy of risperidone in the short-term treatment of disruptive behaviours was demonstrated in two double-blind placebo-controlled studies in approximately 240 patients 5 to 12 years of age with a DSM-IV diagnosis of disruptive behaviour disorders (DBD) and borderline intellectual functioning or mild or moderate mental retardation/learning disorder. In the two studies, risperidone 0.02 to 0.06 mg/kg/day was significantly superior to placebo on the pre-specified primary endpoint, i.e., the change from baseline in the Conduct Problem subscale of the Nisonger-Child Behaviour Rating Form (N-CBRF) at Week 6.

5.2 Pharmacokinetic properties

Risperidone is metabolised to 9-hydroxy-risperidone, which has a similar pharmacological activity to risperidone (see *Biotransformation and elimination*).

Absorption

Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. The absolute oral bioavailability of risperidone is 70% (CV=25%). The relative oral bioavailability of risperidone from a tablet is 94% (CV=10%) compared with a solution. The absorption is not affected by food and thus risperidone can be given with or without meals. Steady-state of risperidone is reached within 1 day in most patients. Steady-state of 9-hydroxy-risperidone is reached within 4-5 days of dosing.

Distribution

Risperidone is rapidly distributed. The volume of distribution is 1-2 l/kg. In plasma, risperidone is bound to albumin and alpha1-acid glycoprotein. The plasma protein binding of risperidone is 90%, that of 9-hydroxyrisperidone is 77%.

Biotransformation and elimination

Risperidone is metabolised by CYP 2D6 to 9-hydroxy-risperidone, which has a similar pharmacological activity as risperidone. Risperidone plus 9-hydroxy-risperidone form the active antipsychotic fraction. CYP 2D6 is subject to genetic polymorphism. Extensive CYP 2D6 metabolisers convert risperidone rapidly into 9-hydroxy-risperidone, whereas poor CYP 2D6 metabolisers convert it much more slowly. Although extensive metabolisers have lower risperidone and higher 9-hydroxy-risperidone concentrations than poor metabolisers, the pharmacokinetics of risperidone and 9-hydroxy-risperidone combined (i.e., the active antipsychotic fraction), after single and multiple doses, are similar in extensive and poor metabolisers of CYP 2D6.

Another metabolic pathway of risperidone is N-dealkylation. In vitro studies in human liver microsomes showed that risperidone at clinically relevant concentration does not substantially inhibit the metabolism of medicines metabolised by cytochrome P450 isozymes, including CYP 1A2, CYP 2A6, CYP 2C8/9/10, CYP 2D6, CYP 2E1, CYP 3A4, and CYP 3A5. One week after administration, 70% of the dose is excreted in the urine and 14% in the faeces. In urine,

risperidone plus 9-hydroxy-risperidone represent 35-45% of the dose. The remainder is inactive metabolites. After oral administration to psychotic patients, risperidone is eliminated with a half-life of about 3 hours. The elimination half-life of 9-hydroxy-risperidone and of the active antipsychotic fraction is 24 hours.

Linearity/non-linearity

Risperidone plasma concentrations are dose-proportional within the therapeutic dose-range.

Elderly, hepatic and renal impairment

A single-dose PK study with oral risperidone showed on average a 43% higher active antipsychotic fraction plasma concentration, a 38% longer half-life and a reduced clearance of the active antipsychotic fraction by 30% in the elderly In adults with moderate renal disease the clearance of the active moiety was ~48% of the clearance in young healthy adults. In adults with severe renal disease the clearance of the active moiety was ~31% of the clearance in young healthy adults. The half-life of the active moiety was 16.7 h in young adults, 24.9 h in adults with moderate renal disease (or ~1.5 times as long as in young adults), and 28.8 h in those with severe renal disease (or ~1.7 times as long as in young adults). Risperidone plasma concentrations were normal in patients with liver insufficiency, but the mean free fraction of risperidone in plasma was increased by 37.1%. The oral clearance and the elimination half-life of risperidone and of the active moiety in adults with moderate and severe liver impairment were not significantly different from those parameters in young healthy adults.

Paediatric population

The pharmacokinetics of risperidone, 9-hydroxy-risperidone and the active antipsychotic fraction in children are similar to those in adults.

Other special populations: Gender, race and smoking habits

A population pharmacokinetic analysis revealed no apparent effect of gender, race or smoking habits on the pharmacokinetics of risperidone or the active antipsychotic fraction.

5.3 Preclinical safety data

In (sub)chronic toxicity studies, in which dosing was started in sexually immature rats and dogs, dose-dependent effects were present in male and female genital tract and mammary gland. These effects were related to the increased serum prolactin levels, resulting from the dopamine D2-receptor blocking activity of risperidone. In addition, tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Risperidone was not teratogenic in rat and rabbit. In rat reproduction studies with risperidone, adverse effects were seen on mating behaviour of the parents, and on the birth weight and survival of the offspring. In rats, intrauterine exposure to risperidone was associated with cognitive deficits in adulthood. Other dopamine antagonists, when administered to pregnant animals, have caused negative effects on learning and motor development in the offspring.

In a toxicity study in juvenile rats, increased pup mortality and a delay in physical development was observed. In a 40-week study with juvenile dogs, sexual maturation was delayed. Based on AUC, long bone growth was not affected in dogs at 3.6-times the maximum human exposure in adolescents (1.5 mg/day); while effects on long bones and sexual maturation were observed at 15 times the maximum human exposure in adolescents.

Risperidone was not genotoxic in a battery of tests. In oral carcinogenicity studies of risperidone in rats and mice, increases in pituitary gland adenomas (mouse), endocrine pancreas adenomas (rat), and mammary gland adenomas (both species) were seen. These tumours can be related to prolonged dopamine D2 antagonism and hyperprolactinaemia. The relevance of these tumour findings in rodents in terms of human risk is unknown. In vitro and in vivo, animal models show that at high doses risperidone may cause QT interval prolongation, which has been associated with a theoretically increased risk of torsade de pointes in patients.

6. Pharmaceutical particulars

6.1 List of excipients

Core

Lactose monohydrate

Microcrystalline cellulose (E 460)

Maize starch Pregelatinised

Colloidal anhydrous silica

Magnesium stearate (E 470b)

Coating

Hypromellose (E 464)

Titanium dioxide (E 171)

Macrogol (4000)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Pack sizes

PVC/COC/PVDC/Al-blister: 6, 10, 20, 30, 50, 60, 100, 100x1 and 250 tablets.

PVC/PE/PVDC/Al-blister: 6, 10, 20, 30, 50, 60, 100, 100x1 and 250 tablets.

HDPE container with PP cap with desiccant: 6, 10, 20, 30, 50, 60, 100 and 250 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7. Marketing authorisation holder

Sandoz Limited

Park View, Riverside Way

Watchmoor Park

Camberley, Surrey

GU15 3YL

United Kingdom

8. Marketing authorisation number(s)

PL 04416/0662

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 13 September 2005

Date of latest renewal:

10. Date of revision of the text

20/12/2023

Company Contact Details

Sandoz Limited

Address

Maxis 1, Western Road, Bracknell, RG12 1RF, UK

WWW

https://pvi1j.solutions.iqvia.com

Medical Information Direct Line

+44 (0)1276 698 101

Adverse event reporting email

adverse.event.uk@sandoz.com

E-mail

mailbox.sandoz-gb@sandoz.com

WWW

http://www.sandoz.uk.com

Telephone

+44 (0) 1276 698020

Medical Information e-mail

mi.uk@sandoz.com

Customer Care direct line

+44 (0)1276 698020

E-mail

sales.sandoz-gb@sandoz.com

Sertindole

EMA

ANNEX I

LIST OF THE INVENTED NAMES, PHARMACEUTICAL FORMS, STRENGTHS OF THE MEDICINAL PRODUCTS, ROUTE OF ADMINISTRATION AND MARKETING AUTHORISATION HOLDERS IN THE MEMBER STATES

SERTINDOLE CONTAINING MEDICINAL PRODUCTS WITH MARKETING AUTHORISATION IN THE EUROPEAN UNION

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration
Austria	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 4 mg Filmtabletten	4 mg	film coated tablet	Oral use
Austria	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 8 mg Filmtabletten	8 mg	film coated tablet	Oral use
Austria	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 12 mg Filmtabletten	12 mg	film coated tablet	Oral use
Austria	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 16 mg Filmtabletten	16 mg	film coated tablet	Oral use
Austria	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 20 mg Filmtabletten	20 mg	film coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration
Austria	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 24 mg Filmtabletten	24 mg	film coated tablet	Oral use
Belgium	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	4 mg	film coated tablet	Oral use
Belgium	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	8 mg	film coated tablet	Oral use
Belgium	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	12 mg	film coated tablet	Oral use
Belgium	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	16 mg	film coated tablet	Oral use
Belgium	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	20 mg	film coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration
Belgium	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	24 mg	film coated tablet	Oral use
Czech Republic	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 4 mg	4 mg	film coated tablet	Oral use
Czech Republic	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 12 mg	12 mg	film coated tablet	Oral use
Czech Republic	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 16 mg	16 mg	film coated tablet	Oral use
Czech Republic	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 20 mg	20 mg	film coated tablet	Oral use
Denmark	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	4 mg	film coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration
Denmark	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	8 mg	film coated tablet	Oral use
Denmark	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	12 mg	film coated tablet	Oral use
Denmark	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	16 mg	film coated tablet	Oral use
Denmark	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	20 mg	film coated tablet	Oral use
Denmark	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	24 mg	film coated tablet	Oral use
Estonia	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	4 mg	tablet	Oral use

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration
Estonia	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	12 mg	tablet	Oral use
Estonia	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	16 mg	tablet	Oral use
Estonia	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	20 mg	tablet	Oral use
Finland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	4 mg	film coated tablet	Oral use
Finland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	8 mg	film coated tablet	Oral use
Finland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	12 mg	film coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration
Finland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	16 mg	film coated tablet	Oral use
Finland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	20 mg	film coated tablet	Oral use
Finland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	24 mg	film coated tablet	Oral use
France	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	4 mg	film coated tablet	Oral use
France	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	8 mg	film coated tablet	Oral use
France	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	12 mg	film coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration
France	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	16 mg	film coated tablet	Oral use
France	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	20 mg	film coated tablet	Oral use
France	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	24 mg	film coated tablet	Oral use
Germany	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Zerdol 4mg	4 mg	film coated tablet	Oral use
Germany	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Zerdol 8mg	8 mg	film coated tablet	Oral use
Germany	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 4mg	4 mg	film coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration
Germany	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 8mg	8 mg	film coated tablet	Oral use
Germany	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 12 mg	12 mg	film coated tablet	Oral use
Germany	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 16mg	16 mg	film coated tablet	Oral use
Germany	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 20 mg	20 mg	film coated tablet	Oral use
Germany	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 24 mg	24 mg	film coated tablet	Oral use
Greece	Lundbeck Hellas Kifisias 64 GR-15125 Marousi Greece	Serdolect	4 mg	film coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration
Greece	Lundbeck Hellas Kifisias 64 GR-15125 Marousi Greece	Serdolect	8 mg	film coated tablet	Oral use
Greece	Lundbeck Hellas Kifisias 64 GR-15125 Marousi Greece	Serdolect	12 mg	film coated tablet	Oral use
Greece	Lundbeck Hellas Kifisias 64 GR-15125 Marousi Greece	Serdolect	16 mg	film coated tablet	Oral use
Greece	Lundbeck Hellas Kifisias 64 GR-15125 Marousi Greece	Serdolect	20 mg	film coated tablet	Oral use
Greece	Lundbeck Hellas Kifisias 64 GR-15125 Marousi Greece	Serdolect	24 mg	film coated tablet	Oral use
Hungary	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	4 mg	Film coated tablet	Oral use
Hungary	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	12 mg	Film coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration
Hungary	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	16 mg	Film coated tablet	Oral use
Hungary	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	20 mg	Film coated tablet	Oral use
Iceland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	4 mg	Film coated tablet	Oral use
Iceland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	8 mg	Film coated tablet	Oral use
Iceland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	12 mg	Film coated tablet	Oral use
Iceland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	16 mg	Film coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration
Iceland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	20 mg	Film coated tablet	Oral use
Iceland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	24 mg	Film coated tablet	Oral use
Ireland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	4 mg	film coated tablet	Oral use
Ireland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	8 mg	film coated tablet	Oral use
Ireland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	12 mg	film coated tablet	Oral use
Ireland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	16 mg	film coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration
Ireland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	20 mg	film coated tablet	Oral use
Ireland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	24 mg	film coated tablet	Oral use
Italy	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	4 mg	film coated tablet	Oral use
Italy	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	8 mg	film coated tablet	Oral use
Italy	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	12 mg	film coated tablet	Oral use
Italy	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	16 mg	film coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration
Italy	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	20 mg	film coated tablet	Oral use
Italy	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	24 mg	film coated tablet	Oral use
Latvia	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 4 mg	4 mg	Film coated tablets	Oral use
Latvia	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 12 mg	12 mg	Film coated tablets	Oral use
Latvia	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 16 mg	16 mg	Film coated tablets	Oral use
Latvia	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 20 mg	20 mg	Film coated tablets	Oral use

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration
Lithuania	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	4 mg	Film coated tablets	Oral use
Lithuania	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	12 mg	Film coated tablets	Oral use
Lithuania	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	16 mg	Film coated tablets	Oral use
Lithuania	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	20 mg	Film coated tablets	Oral use
Luxembourg	Lundbeck S.A. 225 Avenue Molière B – 1050 Brussels Belgium	Serdolect	4 mg	film coated tablet	Oral use
Luxembourg	Lundbeck S.A. 225 Avenue Molière B – 1050 Brussels Belgium	Serdolect	8 mg	film coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration
Luxembourg	Lundbeck S.A. 225 Avenue Molière B – 1050 Brussels Belgium	Serdolect	12 mg	film coated tablet	Oral use
Luxembourg	Lundbeck S.A. 225 Avenue Molière B – 1050 Brussels Belgium	Serdolect	16 mg	film coated tablet	Oral use
Luxembourg	Lundbeck S.A. 225 Avenue Molière B – 1050 Brussels Belgium	Serdolect	20 mg	film coated tablet	Oral use
Luxembourg	Lundbeck S.A. 225 Avenue Molière B – 1050 Brussels Belgium	Serdolect	24 mg	film coated tablet	Oral use
Netherlands	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 4 mg	4 mg	film coated tablet	Oral use
Netherlands	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 8 mg	8 mg	film coated tablet	Oral use
Netherlands	H. Lundbeck A/S	Serdolect 12 mg	12 mg	film coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration
	Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark				
Netherlands	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 16 mg	16 mg	film coated tablet	Oral use
Netherlands	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 20 mg	20 mg	film coated tablet	Oral use
Netherlands	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect 24 mg	24 mg	film coated tablet	Oral use
Norway	H lundbeck A/S Ottiliavej 9 Valby DK-2500 Denmark	Serdolect	4 mg	Film coated tablet	Oral use
Norway	H lundbeck A/S Ottiliavej 9 Valby DK-2500 Denmark	Serdolect	12 mg	Film coated tablet	Oral use
Norway	H lundbeck A/S	Serdolect	16 mg	Film coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration
	Ottiliavej 9 Valby DK-2500 Denmark				
Norway	H lundbeck A/S Ottiliavej 9 Valby DK-2500 Denmark	Serdolect	20 mg	Film coated tablet	Oral use
Poland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	4 mg	Film coated tablet	Oral use
Poland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	12 mg	Film coated tablet	Oral use
Poland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	16 mg	Film coated tablet	Oral use
Poland	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	20 mg	Film coated tablet	Oral use
Portugal	H. Lundbeck A/S	Serdolect	4 mg	Film coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration
	Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark				
Portugal	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	12 mg	Film coated tablet	Oral use
Portugal	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	16 mg	Film coated tablet	Oral use
Portugal	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	20 mg	Film coated tablet	Oral use
Slovakia	H lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen Denmark	Serdolect 4 mg	4 mg	Film coated tablet	Oral use
Slovakia	H lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen Denmark	Serdolect 12 mg	12 mg	Film coated tablet	Oral use
Slovakia	H lundbeck A/S	Serdolect 16 mg	16 mg	Film coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration
	Ottiliavej 9 Valby DK-2500 Copenhagen Denmark				
Slovakia	H lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen Denmark	Serdolect 20 mg	20 mg	Film coated tablet	Oral use
Spain	H. Lundbeck A/S Otillavej 7-9 DK-2500 Köbenhamn Valby Denmark	Serdolect	4 mg	film coated tablet	Oral use
Spain	H. Lundbeck A/S Otillavej 7-9 DK-2500 Köbenhamn Valby Denmark	Serdolect	8 mg	film coated tablet	Oral use
Spain	H. Lundbeck A/S Otillavej 7-9 DK-2500 Köbenhamn Valby Denmark	Serdolect	12 mg	film coated tablet	Oral use
Spain	H. Lundbeck A/S Otillavej 7-9 DK-2500 Köbenhamn Valby Denmark	Serdolect	16 mg	film coated tablet	Oral use
Spain	H. Lundbeck A/S	Serdolect	20 mg	film coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration
	Otillavej 7-9 DK-2500 Köbenhamn Valby Denmark				
Spain	H. Lundbeck A/S Otillavej 7-9 DK-2500 Köbenhamn Valby Denmark	Serdolect	24 mg	film coated tablet	Oral use
Sweden	H. Lundbeck A/S Otillavej 7-9 DK-2500 Köbenhamn Valby Denmark	Serdolect	4 mg	Film coated tablet	Oral use
Sweden	H. Lundbeck A/S Otillavej 7-9 DK-2500 Köbenhamn Valby Denmark	Serdolect	12 mg	Film coated tablet	Oral use
Sweden	H. Lundbeck A/S Otillavej 7-9 DK-2500 Köbenhamn Valby Denmark	Serdolect	16 mg	Film coated tablet	Oral use
Sweden	H. Lundbeck A/S Otillavej 7-9 DK-2500 Köbenhamn Valby Denmark	Serdolect	20 mg	Film coated tablet	Oral use
UK	H. Lundbeck A/S	Serdolect	4 mg	film coated tablet	Oral use

Member State	Marketing Authorisation Holder	Invented Name	Strength	Pharmaceutical Form	Route of administration
	Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark				
UK	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	8 mg	Film coated tablet	Oral use
UK	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	12 mg	film coated tablet	Oral use
UK	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	16 mg	film coated tablet	Oral use
UK	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	20 mg	film coated tablet	Oral use
UK	H. Lundbeck A/S Ottiliavej 9 Valby DK-2500 Copenhagen- Denmark	Serdolect	24 mg	Film coated tablet	Oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS AND CONDITIONS OF THE MARKETING AUTHORISATIONS PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF SERTINDOLE CONTAINING MEDICINAL PRODUCTS (see Annex I)

Sertindole is an atypical antipsychotic agent. It has affinity for dopamine receptors, especially D_2 and for serotinergic receptors: $5HT_{2A}$ and $5HT_{2C}$. It also inhibits α1-adrenergic receptors, but has almost no affinity to histaminergic or cholinergic receptors. Sertindole is metabolised by both CYP 3A4 and CYP 2D6. Sertindole, indicated for the treatment of schizophrenia, was authorised in the UK in May 1996 and then subsequently in other European Member States through the Mutual Recognition procedure.

The cardiac safety of sertindole was first brought into question in 1998, when the reporting rate of sudden unexplained death and cardiac arrhythmia associated with sertindole (through the UK ADROIT database) was noted to be higher than for other atypical antipsychotics. This signal ultimately led the Netherlands to suspend the Marketing Authorisations and to refer the matter to the CHMP under Article 36 of Directive 2001/83/EC, as amended[1].

As an outcome of the Article 36 referral, medicinal products containing sertindole were suspended in the EU on 20 January 2000 and subsequently the suspension was renewed on 22 February 2001, because of concerns regarding the risk of serious cardiovascular adverse reactions such as prolongation of QT interval and sudden deaths.

Further to the suspension and the subsequent renewal of suspension of sertindole, the MAH presented data. In October 2001, the CHMP reached a positive opinion for sertindole and recommended lifting of the suspension of the Marketing Authorisations. The Commission Decision was issued in June 2002, including a revised Summary of Product Characteristics with a limited indication and additional warnings and precautions, and conditions set out in the annex IV of the Commission Decision. Some conditions of the Commission Decision concern a restriction on the marketing and launching activities for sertindole, i.e. patients will only be treated with sertindole in a clinical trial environment.

The MAH requested the CHMP on 29 October 2004 to review the conditions as stated in the Commission Decision of 26 June 2002, specifically in relation to the marketing and launching activities of sertindole in order to make sertindole available for patients outside clinical trials i.e. on normal prescription.

To support this request the MAHs submitted interim data from post-marketing studies previously requested by CHMP. It concerns the post-marketing surveillance study (Study 99823) and the post-marketing, randomised, safety outcome study (Study 99824).

The CHMP reviewed the data submitted by the MAHs mainly from study 99824 (in study 99823 only two patients were enrolled) and concluded that the data do not indicate an excess of overall mortality. There was an excess risk for cardiovascular adverse events but it was agreed that it may be due to the regular ECG monitoring.

The CHMP concluded that the restrictions on the marketing and launching activities could be lifted provided that study 99824 is continued and that the MAHs will provide interim analysis and the final study report as described in the study protocol until ontherwise decided by the CHMP.

The CHMP noted that the patients have been very closely monitored during the study, in particular regarding cardiac events. The CHMP is of the opinion that such a clinical monitoring is much more difficult to ensure in real clinical practice and therefore concluded that the SPC should contain stronger warnings in sections 4.2 and 4.4 of the SPC recommending a periodic cardiac monitoring of

[1] Corresponding to Article 15a of Directive 75/319/EEC, for referrals before 18 December 2001

the patients, with more regular ECGs during therapy. Moreover a Pharmacovigilance Plan and Risk Mitigation Plan should be put in place once it has been agreed with the CHMP.

GROUNDS FOR AMENDMENT OF THE SUMMARIES OF PRODUCT CHARACTERISTICS AND CONDITIONS OF THE MARKETING AUTHORISATIONS

Wheras

- The Committee considered the additional data submitted by the MAHs with regard to the cardiac safety profile of sertindole.

- The Committee considered that the data do not indicate an excess of overall mortality. There was an excess risk for cardiovascular adverse events but it was agreed that it may be due to the regular ECG monitoring.

- The CHMP concluded that the restrictions on the marketing and launching activities could be lifted provided that study 99824 is continued and that the MAHs will provide interim analysis and final study reports as described in the study protocol until ontherwise decided by the CHMP.

- The CHMP concluded that the SPC should contain stronger warnings in sections 4.2 and 4.4 of the SPC recommending a periodic cardiac monitoring of the patients, with more regular ECGs during therapy.

- Moreover the CHMP concluded that a Pharmacovigilance Plan and Risk Mitigation Plan should be implemented once agreed by the CHMP.

As a consequence the CHMP recommends the maintenance of the Marketing Authorisations for which the amended Summary of Product Characteristics and the conditions of the Marketing Authorisations are set out in Annexes III and IV respectively.

ANNEX III

SUMMERY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

{INVENTED NAME} {Strength} {Pharmaceutical form}

[To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<Each <tablet><film-coated tablet> contains <4 mg><8 mg><12 mg><16 mg> <20 mg><24 mg> sertindole

For excipients see section 6.1.

[To be completed nationally]

3. PHARMACEUTICAL FORM

<Tablet> <Film-coated tablet>

[To be completed nationally]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sertindole is indicated for the treatment of schizophrenia.

Due to cardiovascular safety concerns, sertindole should only be used for patients intolerant to at least one other antipsychotic agent.

Sertindole should not be used in emergency situations for urgent relief of symptoms in acutely disturbed patients.

4.2 Posology and method of administration

Sertindole is administered orally once daily with or without meals. In patients where sedation is required, a benzodiazepine may be co-administered.

Note: ECG monitoring is required before and during treatment with sertindole; see section 4.4.
Clinical studies have shown that sertindole prolongs the QT interval to a greater extent than some other antipsychotics. Sertindole should therefore only be used for patients intolerant to at least one other antipsychotic agent.
Prescribing physicians should comply fully with the required safety measures: see section 4.3 and 4.4.

Titration
All patients should be started on sertindole 4 mg/day. The dose should be increased by increments of 4 mg after 4-5 days on each dose until the optimal daily maintenance dose within the range of 12-20 mg is reached. Due to the α_1-blocking activity of sertindole, symptoms of postural hypotension may occur during the initial dose-titration period. A starting dose of 8 mg or a rapid increase in dose carries a significantly increased risk of postural hypotension.

Maintenance
Dependent on individual patient response, the dose may be increased to 20mg/day. Only in exceptional cases should the maximum dose of 24mg be considered, as clinical trials have not demonstrated consistently improved efficacy above 20mg and QT prolongation may be increased at the upper end of the dose range.

The blood pressure of the patients should be monitored during titration and early maintenance treatment.

Elderly
A pharmacokinetic study showed no difference between young and elderly subjects. However, only limited clinical trial data exist for patients greater than 65 years of age. Treatment should only be initiated after a thorough cardiovascular examination. Slower titration and lower maintenance doses may be appropriate in elderly patients (see section 4.4).

Children and adolescents under the age of 18
The safety and efficacy of sertindole in children and adolescents have not been established.

Reduced renal function
Sertindole can be given at the usual dosage to patients with renal impairment (see section 4.3). The pharmacokinetics of sertindole is not affected by haemodialysis.

Reduced hepatic function
Patients with mild/moderate hepatic impairment require slower titration and a lower maintenance dose.

Re-titration of sertindole in patients for whom treatment has previously been discontinued
When restarting sertindole treatment in patients who have had an interval of less than one week without sertindole, re-titration of sertindole is not required and their maintenance dose can be re-introduced. Otherwise the recommended titration schedule should be followed. An ECG should be taken prior to re-titration of sertindole.

Switching from other antipsychotics
Treatment with sertindole can be initiated according to the recommended titration schedule concomitantly with cessation of other oral antipsychotics. For patients treated with depot antipsychotics, sertindole is initiated in place of the next depot injection.

4.3 Contraindications

Hypersensitivity to sertindole or any of the excipients.

Sertindole is contraindicated in patients with known uncorrected hypokalaemia, and those with known uncorrected hypomagnesaemia.

Sertindole is contraindicated in patients with a history of clinically significant cardiovascular disease, congestive heart failure, cardiac hypertrophy, arrhythmia, or bradycardia (<50 beats per minute).

Furthermore, sertindole should not be initiated in patients with congenital long QT syndrome or a family history of this disease, or in patients with known acquired QT interval prolongation (QTc above 450 msec in males and 470 msec in females).

Sertindole is contraindicated in patients receiving drugs known to significantly prolong the QT interval. Relevant classes include:
- class Ia and III antiarrhythmics (e.g., quinidine, amiodarone, sotalol, dofetilide)
- some antipsychotics (e.g., thioridazine)
- some macrolides (e.g., erythromycin)
- some antihistamines (e.g., terfenadine, astemizole)
- some quinolone antibiotics (e.g., gatifloxacin, moxifloxacin)

The above list is not exhaustive and other individual drugs known to significantly increase QT interval (e.g., cisapride, lithium) are also contraindicated.

Co-administration of sertindole is contraindicated with drugs known to potently inhibit hepatic cytochrome P450 3A enzymes (see section 4.5). Relevant classes include:
- systemic treatment with 'azole' antifungal agents (e.g. ketoconazole, itraconazole)
- some macrolide antibiotics (e.g., erythromycin, clarithromycin)
- HIV protease inhibitors (e.g., indinavir)
- Some calcium channel blockers (e.g. diltiazem, verapamil)

The above list is not exhaustive and other individual drugs known to potently inhibit CYP3A enzymes (e.g., cimetidine) are also contraindicated.

Sertindole is contraindicated in patients with severe hepatic impairment.

4.4 Special warnings and special precautions for use

Cardiovascular

Clinical studies have shown that sertindole prolongs the QT interval to a greater extent than some other antipsychotics. The mean QT prolongation is greater at the upper end of the recommended dose range (20 and 24 mg). Prolongation of the QTc interval in some drugs is associated with the ability to cause Torsade de Pointes-type (TdP) arrhythmia (a potentially fatal polymorphic ventricular tachycardia) and sudden death. However, clinical and non-clinical data have been unable to confirm whether sertindole is more arrhythmogenic than other antipsychotics. Sertindole should therefore only be used for patients intolerant to at least one other antipsychotic agent.

Prescribing physicians should comply fully with the required safety measures.

ECG monitoring:
- ECG monitoring is mandatory prior to and during treatment with sertindole.
- Sertindole is contraindicated if a QT_c interval of more than 450 msec in males or 470 msec in females is observed at baseline.
- ECG monitoring should be conducted at baseline, upon reaching steady state after approximately 3 weeks or when reaching 16 mg and again after 3 months of treatment. During maintenance therapy an ECG is required every 3 months.
- During maintenance treatment, ECG measurements should take place prior to and after any increase in dose.
- An ECG is recommended after the addition or increase of dosage of concomitant medication that may increase the sertindole concentration (see section 4.5).
- If a QT_c interval of more than 500 msec is observed during treatment with sertindole, treatment with sertindole should be discontinued.
- For patients with symptoms such as palpitations, convulsions, or syncope that could indicate the occurrence of arrhythmias, the prescriber should initiate urgent evaluation, including an ECG.
- ECG monitoring is ideally conducted in the morning and the Bazett or Fridericia formulae for calculating the QT_c interval are preferred.

The risk of QT prolongation is increased in patients receiving concomitant treatment with drugs that prolong the QTc interval or drugs that inhibit sertindole metabolism (see section 4.3).

Baseline serum potassium and magnesium levels should be measured before commencing treatment with sertindole in patients at risk of significant electrolyte disturbances. Low serum potassium and magnesium should be corrected before proceeding with treatment. Monitoring of serum potassium is recommended for patients experiencing vomiting, diarrhoea, treatment with potassium-depleting diuretics, or other electrolyte disturbances.

Due to the α_1-blocking activity of sertindole, symptoms of postural hypotension may occur during the initial dose-titration period.

Antipsychotic drugs may inhibit the effects of dopamine agonists. Sertindole should be used cautiously in patients with Parkinson's disease.

Some SSRIs, like fluoxetine and paroxetine (potent CYP2D6 inhibitors), may increase the plasma levels of sertindole by a factor of 2 to 3. Sertindole should therefore only be used concomitantly with these drugs with extreme caution, and only if the potential benefit outweighs the risk. A lower maintenance dose of sertindole may be needed and careful ECG monitoring should be undertaken before and after any dose adjustment of these drugs (see section 4.5).

Sertindole should be used with caution in patients, who are known to be poor CYP2D6 metabolisers (see section 4.5).

Use in the elderly
In view of the increased risk of significant cardiovascular disease in the elderly, sertindole should be used with care in patients above 65 years of age. Treatment should only be initiated after a thorough cardiovascular examination (see section 4.2).

Reduced hepatic function
Patients with mild/moderate hepatic dysfunction should be closely observed. Slower titration and a lower maintenance dose are recommended.

Tardive dyskinesia
Tardive dyskinesia is thought to be caused by dopamine receptor hypersensitivity in the basal ganglia as a result of chronic receptor blockade by antipsychotics. A low incidence (comparable to that of placebo) of extrapyramidal symptoms during treatment with sertindole has been seen in clinical studies. However, long-term treatment with antipsychotic compounds (especially at high dosages) is associated with the risk of tardive dyskinesia. If signs of tardive dyskinesia appear, dosage reduction or drug discontinuation should be considered.

Seizures
Sertindole should be used with caution in patients with a history of seizures.

Neuroleptic Malignant Syndrome
A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. The management of NMS should include immediate discontinuation of antipsychotic drugs.

Withdrawal
Acute withdrawal symptoms, including nausea vomiting, sweating, and insomnia have been described after abrupt cessation of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movements disorders (such as akathisia, dystonia and dyskinesia) has been reported. Therefore, gradual withdrawal is advisable.

4.5 Interactions with other medicinal products and other forms of interaction

Increases in the QT interval related to sertindole treatment may be exacerbated by the co-administration of other drugs known to significantly increase the QT interval. Co-administration of such drugs is therefore contraindicated (see section 4.3). Such an interaction may occur e.g. between quinidine and sertindole. In addition to the effects on QT interval prolongation (see section 4.3), CYP2D6 is markedly inhibited by quinidine.

Sertindole is extensively metabolised by the CYP2D6 and CYP3A isozymes of the cytochrome P450 system. CYP2D6 is polymorphic in the population and both isozymes can be inhibited by a variety of psychotropic and other drugs (see section 4.4).

CYP2D6
The plasma concentration of sertindole is increased by a factor of 2-3 in patients concurrently taking fluoxetine or paroxetine (potent CYP2D6 inhibitors), sertindole should therefore only be used concomitantly with these or other CYP2D6 inhibitors with extreme caution. A lower maintenance dose of sertindole may be needed and careful ECG monitoring should be undertaken before and after any dose adjustment of these drugs (see section 4.4).

CYP3A
Minor increases (<25%) in sertindole plasma concentrations have been noted for macrolide antibiotics (e.g., erythromycin, a CYP3A inhibitor) and calcium channel antagonists (diltiazem, verapamil). However, the consequences could be greater in CYP2D6 poor metabolisers (since elimination of sertindole by both CYP2D6 and CYP3A would be affected). Therefore, because it is not possible to routinely identify patients who are poor metabolisers of CYP2D6, the concomitant administration of CYP3A inhibitors and sertindole is contraindicated, as this may lead to significant increases in sertindole levels (see section 4.3).

The metabolism of sertindole may be significantly enhanced by agents known to induce CYP isozymes, notably rifampicin, carbamazepine, phenytoin and phenobarbital, which can decrease the plasma concentrations of sertindole by a factor of 2 to 3. Reduced antipsychotic efficacy in patients receiving these drugs or other inducing agents may require the dose of sertindole to be adjusted to the upper dosage range.

4.6 Pregnancy and lactation

Pregnancy
The safety of sertindole for use during pregnancy has not been established.

Sertindole was not teratogenic in animal reproduction studies. A peri/postnatal study in rats showed a decrease in offspring fertility at a dose within the therapeutic range for humans (see section 5.3).

Consequently, sertindole should not be used during pregnancy.

Lactation
Studies in nursing mothers have not been performed, however, it is expected that sertindole will be excreted in breast milk.

If treatment with sertindole is considered necessary, discontinuation of breast-feeding should be considered.

4.7 Effects on ability to drive and use machines

Sertindole is not sedative, however, patients should be advised not to drive or operate machinery until their individual susceptibility is known.

4.8 Undesirable effects

Side effects
In clinical trials, adverse events with an incidence greater than 1% associated with the use of sertindole and significantly different from placebo were (listed in order of decreasing frequency): rhinitis/nasal congestion, abnormal ejaculation (decreased ejaculatory volume), dizziness, dry mouth, postural hypotension, weight gain, peripheral oedema, dyspnoea, paraesthesia, and prolonged QT interval (see section 4.4).

Extrapyramidal Symptoms (EPS)
The incidences of patients treated with sertindole reporting EPS-related adverse events were similar to those of patients treated with placebo. In addition, in placebo-controlled clinical trials, the percentage of sertindole-treated patients requiring anti-EPS medication was indistinguishable from that of placebo-treated patients.

Some of the adverse drug reactions will appear at the beginning of treatment and disappear with continuous treatment, e.g., postural hypotension.

The table below shows adverse reactions sorted by system organ class and frequency:
Very common (>10%)
Common (1-10%)
Uncommon (0.1-1%)
Rare (0.01-0.1%)
Very rare (<0.01%)

Metabolism and nutritional disorders	
Uncommon	Hyperglycemia
Nervous system disorders	
Common	Dizziness, paraesthesia
Uncommon	Syncope, convulsion, movement disorder (in particular tardive dyskinesia, see section 4.4)
Rare	Cases reported as Neuroleptic Malignant Syndrome (NMS) have been received in association with sertindole (see section 4.4)
Cardiac disorders	
Common	Peripheral oedema
Uncommon	Torsade de Pointes (see section 4.4)
Vascular disorders	
Common	Postural hypotension (see section 4.4)
Respiratory, thoracic and mediastinal disorders	
Very common	Rhinitis/nasal congestion
Common	Dyspnoea
Gastrointestinal disorders	
Common	Dry mouth
Reproductive system and breast disorders	
Common	Abnormal ejaculation (decreased ejaculatory volume)
Investigations	
Common	Weight gain, prolonged QT interval, red blood cells urine positive, white blood cells urine positive

4.9 Overdose

Experience with sertindole in acute overdose is limited. Fatal cases have occurred. However, patients taking estimated dosages up to 840 mg have recovered without sequelae. Reported signs and symptoms of overdose were somnolence, slurred speech, tachycardia, hypotension, and transient prolongation of the QTc interval. Cases of Torsade de Pointes have been observed, often in combination with other drugs known to induce TdP.

Treatment
In case of acute overdose, establishment of an airway and maintenance of adequate oxygenation should be ensured.

Continuous monitoring of ECG and vital signs should commence immediately. If the QTc interval is prolonged, it is recommended that the patient be monitored until the QTc interval has normalised. A half-life of sertindole of 2 to 4 days should be taken into account.

Intravenous access should be established, and the administration of activated charcoal with laxative should be considered. The possibility of multiple drug involvement should be considered.

There is no specific antidote to sertindole, and it is not dialysable, therefore appropriate supportive measures should be instituted. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids. If sympathomimetic agents are used for vascular support, adrenaline and dopamine should be used with caution, since β stimulation combined with α_1 antagonism associated with sertindole may worsen hypotension.

If antiarrhythmic therapy is administered, agents such as quinidine, disopyramide, and procainamide carry a theoretical hazard of QT interval-prolonging effects that might be additive to those of sertindole.

In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: limbic selective antipsychotics, ATC-code: N05A E 03

It has been proposed that the neuropharmacological profile of sertindole, as an antipsychotic drug, is derived from its selective inhibitory effect on mesolimbic dopaminergic neurons and is due to balanced inhibitory effects on central dopamine D_2 and serotonin $5HT_2$ receptors as well as on α_1-adrenergic receptors.

In animal pharmacology studies, sertindole inhibited spontaneously active dopamine neurons in the mesolimbic ventral tegmental area (VTA) with a selectivity ratio of more than 100 compared to dopamine neurons in substantia nigra pars compacta (SNC). Inhibition of SNC activity is thought to be involved in movement side effects (EPS) associated with many antipsychotic drugs.

Antipsychotic drugs are known to increase serum prolactin levels through dopamine blockade. The prolactin levels in patients receiving sertindole remained within normal limits, both in short-term studies and during long-term treatment (one year).

Sertindole has no effect on muscarinic and histaminic H_1 receptors. This is confirmed by the absence of anticholinergic and sedative effects related to those receptors.

5.2 Pharmacokinetic properties

Elimination of sertindole occurs via hepatic metabolism, with a mean terminal half-life of approximately 3 days. The clearance of sertindole decreases with multiple dosing to a mean around 14 l/h (females have approximately 20% lower apparent clearance than males, although lean-mass corrected clearances are comparable). Therefore, upon multiple dosing, accumulation is greater than predicted from a single dose, due to an increase in the systemic bioavailability. However, at steady state, clearance is dose independent and plasma concentrations are proportional to dose. There is moderate inter-subject variability in sertindole pharmacokinetics, due to the polymorphism in the cytochrome P450 2D6 (CYP2D6). Patients who are deficient in this hepatic enzyme have sertindole clearances that are ½ to 1/3 of those who are CYP2D6 extensive metabolisers. These poor metabolisers (up to 10% of the population) will therefore have plasma levels 2-3 times the normal.

Sertindole concentration is not predictive of therapeutic effect for an individual patient; thus, dosing individualisation is best achieved by assessment of therapeutic effect and tolerability.

Absorption
Sertindole is well absorbed with a t_{max} of sertindole after oral administration of approximately 10 hours. Different dose strengths are bioequivalent. Food and aluminium-magnesium antacids have no clinically significant effect on the rate or the extent of sertindole absorption.

Distribution
The apparent volume of distribution (V_β/F) of sertindole after multiple dosing is approximately 20 l/kg. Sertindole is about 99.5% bound to plasma proteins, primarily to albumin and α_1-acid glycoprotein. In patients treated with recommended doses, 90% of the measured concentrations are below 140 ng/ml (~320 nmol/l). Sertindole penetrates into red blood cells with a 1.0 blood/plasma ratio. Sertindole readily penetrates the blood-brain and placental barriers.

Metabolism
Two metabolites have been identified in human plasma: dehydrosertindole (oxidation of the imidazolidinone ring) and norsertindole (N-dealkylation). Concentrations of dehydrosertindole and norsertindole are approximately 80% and 40%, respectively, of the parent compound at steady state. Sertindole activity is primarily due to the parent drug and the metabolites do not appear to have significant pharmacological effects in humans.

Excretion
Sertindole and its metabolites are eliminated very slowly, with a total recovery of 50-60% of a radiolabelled oral dose 14 days after administration. Approximately 4% of the dose is excreted into the urine as parent drug plus metabolites of which less than 1% is present as parent drug. Faecal excretion is the major route of excretion and accounts for the rest of the parent drug and metabolites.

5.3 Preclinical safety data

QT prolongation on the ECG, possibly due to inhibition of the delayed rectifier potassium channel (I_{Kr} , HERG), has been observed in animal studies. However, sertindole shows absence of early after-depolarisations in cardiac rabbit and dog purkinje fibres. Early after-depolarisations are considered essential to trigger Torsade de Pointes. Sertindole did not induce Torsade de Pointes ventricular arrhythmias in atrio-ventricular node ablated rabbit hearts, despite experimental introduction of severe hypokalaemia (1.5 mmol) and bradycardia. However, the extrapolation of animal findings to humans with regard to QT prolongation and arrhythmia must be undertaken with caution as significant inter-species differences may exist.

The acute toxicity of sertindole is low. In chronic toxicity studies in the rat and dog (3-5 times clinical exposure), several effects were observed. These effects are in line with the pharmacological properties of the drug.

Animal reproduction studies have not given evidence of teratogenic effects. A peri/postnatal study in rats showed a decrease in offspring fertility at a dose within the therapeutic range for humans (0.2 mg/kg/day), and at higher dosages, a decreased pup survival in the early lactation period, reduced weight gain, and delayed development of pups in doses producing maternal toxicity.

Mating and fertility were affected in adult male rats at dosages of 0.14 mg/kg/day and above. The adult fertility impairment, which was reversible, was ascribed to the pharmacological profile of sertindole.

Sertindole was not toxic in a battery of *in vitro* and *in vivo* genotoxicity studies. Carcinogenicity studies conducted in the mouse and rat did not indicate any development of tumours relevant to the clinical use of sertindole.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[To be completed nationally]

6.2 Incompatibilities

[To be completed nationally]

6.3 Shelf life

[To be completed nationally]

6.4 Special precautions for storage

[To be completed nationally]

6.5 Nature and contents of container

[To be completed nationally]

6.6 Instructions for use and handling

[To be completed nationally]

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATIONS

Conditions of the Marketing Authorisations

1. The MAHs commit to continue the post-marketing randomised safety outcome study (study 99824), until otherwise decided by CHMP. The MAHs will provide the CHMP with the interim analysis and the final study report of study 99824 as described in the study protocol.

2. The MAHs commit to semi-annual study updates to the Reference Member State on the progress of the study.

3. Periodic Safety Update Reports are submitted every six month to the Reference Member State until otherwise decided by the Reference Member State.

4. Promotional and educational material is reviewed and agreed by the individual National Competent Authorities.

5. The “Dear Doctor Letter” agreed by CHMP is used in the Member States when sertindole is reintroduced on the EU market.

6. The MAHs commit to implement the Pharmacovigilance Plan and Risk Mitigation Plan once agreed by the CHMP.

Xanomeline and Trospium Chloride

FDA

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use COBENFY safely and effectively. See full prescribing information for COBENFY.

COBENFY™ (xanomeline and trospium chloride) capsules, for oral use
Initial U.S. Approval: 2024

----------INDICATIONS AND USAGE----------

COBENFY is a combination of xanomeline, a muscarinic agonist, and trospium chloride, a muscarinic antagonist, indicated for the treatment of schizophrenia in adults. (1)

----------DOSAGE AND ADMINISTRATION----------

- Assess liver enzymes and bilirubin prior to initiating treatment with COBENFY and as clinically indicated during treatment. (2.1)
- Assess heart rate at baseline and as clinically indicated during treatment with COBENFY. (2.1)
- Recommended starting dosage of COBENFY is 50 mg/20 mg orally twice daily for at least two days, then increase the dosage to 100 mg/20 mg twice daily for at least five days. (2.2)
- Dosage may be increased to 125 mg/30 mg orally twice daily based on patient tolerability and response. (2.2)
- See the full prescribing information for the recommended titration and maximum recommended dosage. (2.2)
- Take at least 1 hour before a meal or at least 2 hours after a meal. Do not open capsules. (2.2)
- Geriatric patients: Recommended starting dosage of COBENFY is 50 mg/20 mg orally twice daily. Consider a slower titration. The maximum recommended dosage is 100 mg/20 mg twice daily. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Capsules (xanomeline/trospium chloride): 50 mg/20 mg, 100 mg/20 mg, 125 mg/30 mg (3)

----------CONTRAINDICATIONS----------

COBENFY is contraindicated in:

- urinary retention (4)
- moderate or severe hepatic impairment (4)
- gastric retention (4)
- history of hypersensitivity to COBENFY or trospium chloride (4)
- untreated narrow-angle glaucoma (4)

----------WARNINGS AND PRECAUTIONS----------

- Risk of Urinary Retention: COBENFY can cause urinary retention. Geriatric patients and patients with bladder outlet obstruction and incomplete bladder emptying are at increased risk. Monitor patients for symptoms of acute urinary retention. (5.1)
- Risk of Use in Patients with Hepatic Impairment: COBENFY is contraindicated in patients with moderate to severe hepatic impairment and is not recommended in patients with mild hepatic impairment. (5.2)
- Risk of Use in Patients with Biliary Disease: Assess liver enzymes and bilirubin prior to initiating COBENFY and as clinically indicated. Discontinue COBENFY in the presence of signs or symptoms of substantial liver injury. (5.3)
- Decreased Gastrointestinal Motility: COBENFY may decrease gastrointestinal motility. Use with caution in patients with gastrointestinal obstructive disorders because of the risk of gastric retention. (5.4)
- Risk of Angioedema: Angioedema of the face, lips, tongue and/or larynx has been reported with COBENFY. (5.5)
- Risk of Use in Patients with Narrow-angle Glaucoma: Use COBENFY only if the potential benefits outweigh the risks and with careful monitoring. (5.6)
- Increases in Heart Rate: COBENFY may increase heart rate. Assess heart rate at baseline and as clinically indicated during treatment with COBENFY. (5.7)
- Anticholinergic Adverse Reactions in Patients with Renal Impairment: COBENFY is not recommended for use in patients with moderate and severe renal impairment. Anticholinergic adverse reactions are expected to be greater in these patients. (5.8)
- Central Nervous System Effects: COBENFY may be associated with CNS effects. Advise patients not drive or operate heavy machinery until they know how COBENFY affects them. (5.9)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence ≥ 5% and at least twice placebo) were nausea, dyspepsia, constipation, vomiting, hypertension, abdominal pain, diarrhea, tachycardia, dizziness, and gastrointestinal reflux disease. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol Myers-Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Drugs Eliminated by Active Tubular Secretion: Monitor for increased frequency and/or severity of adverse reactions related to COBENFY and to drugs eliminated by active tubular secretion. (7.1)
- Strong CYP2D6 Inhibitors: Monitor for increased frequency and/or severity of COBENFY-related adverse reactions. (7.1)
- Sensitive Substrates of CYP3A4 or P-glycoprotein: Monitor for increased frequency and/or severity of adverse reactions from these substrates. (7.1)
- Antimuscarinic Drugs: Monitor for increased frequency or severity of anticholinergic adverse reactions. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- Moderate or Severe Renal Impairment: Not recommended. (8.6)
- Mild Hepatic Impairment: Not recommended. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 9/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

COBENFY is indicated for the treatment of schizophrenia in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Testing and Monitoring Prior to Initiation and During Treatment with COBENFY

- Assess liver enzymes and bilirubin prior to initiating COBENFY and as clinically indicated during treatment *[see Contraindications (4) and Warnings and Precautions (5.2, 5.3)]*.
- Assess heart rate at baseline and as clinically indicated during treatment *[see Warnings and Precautions (5.7)]*.

2.2 Recommended Dosage and Administration

The recommended dosage of COBENFY is as follows:

- The recommended starting dosage is one 50 mg/20 mg capsule (contains 50 mg of xanomeline and 20 mg of trospium chloride) orally twice daily for at least two days.
- Increase the dosage to one 100 mg/20 mg capsule (contains 100 mg of xanomeline and 20 mg of trospium chloride) orally twice daily for at least five days.
- The dosage may be increased to one 125 mg/30 mg capsule (contains 125 mg of xanomeline and 30 mg of trospium chloride) orally twice daily based on patient tolerability and response *[see Clinical Studies (14)]*.
- Maximum recommended dosage is 125 mg/30 mg orally twice daily.

Administer COBENFY orally at least one hour before a meal or at least two hours after a meal *[see Clinical Pharmacology (12.3)]*. Do not open the capsules.

2.3 Dosage Recommendations in Geriatric Patients

The recommended starting dosage of COBENFY in geriatric patients is one 50 mg/20 mg capsule orally twice daily. Consider a slower titration for geriatric patients. The maximum recommended dosage in geriatric patients is one 100 mg/20 mg capsule twice daily *[see Warnings and Precautions (5.1, 5.8) and Use in Specific Populations (8.5)]*.

3 DOSAGE FORMS AND STRENGTHS

COBENFY is available as:

- 50 mg/20 mg (xanomeline/trospium chloride): Buff capsules imprinted with Karuna 50/20 mg
- 100 mg/20 mg (xanomeline/trospium chloride): Brown capsules imprinted with Karuna 100/20 mg

- 125 mg/30 mg (xanomeline/trospium chloride): Swedish Orange capsules imprinted with Karuna 125/30 mg

4 CONTRAINDICATIONS

COBENFY is contraindicated in patients with:

- urinary retention *[see Warnings and Precautions (5.1)]*.
- moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment *[see Warnings and Precautions (5.2)]*.
- gastric retention *[see Warnings and Precautions (5.4)]*.
- history of hypersensitivity to COBENFY or trospium chloride. Angioedema has been reported with COBENFY and trospium chloride *[see Warnings and Precautions (5.5)]*.
- untreated narrow-angle glaucoma *[see Warnings and Precautions (5.6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Urinary Retention

COBENFY can cause urinary retention *[see Adverse Reactions (6.1)]*. Geriatric patients and patients with clinically significant bladder outlet obstruction and incomplete bladder emptying (e.g., patients with benign prostatic hyperplasia (BPH), diabetic cystopathy) may be at increased risk of urinary retention *[see Use in Specific Populations (8.5)]*.

COBENFY is contraindicated in patients with pre-existing urinary retention *[see Contraindications (4)]* and is not recommended in patients with moderate or severe renal impairment *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

In patients taking COBENFY, monitor for symptoms of urinary retention, including urinary hesitancy, weak stream, incomplete bladder emptying, and dysuria. Instruct patients to be aware of the risk and promptly report symptoms of urinary retention to their healthcare provider. Urinary retention is a known risk factor for urinary tract infections. In patients with symptoms of urinary retention, consider reducing the dose of COBENFY, discontinuing COBENFY, or referring patients for urologic evaluation as clinically indicated.

5.2 Risk of Use in Patients with Hepatic Impairment

Patients with hepatic impairment have higher systemic exposures of xanomeline, a component of COBENFY, compared to patients with normal hepatic function, which may result in increased incidence of COBENFY-related adverse reactions *[see Clinical Pharmacology (12.3)]*.

COBENFY is contraindicated in patients with moderate or severe hepatic impairment *[see Contraindications (4)]*. COBENFY is not recommended in patients with mild hepatic impairment *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

Assess liver enzymes prior to initiating COBENFY and as clinically indicated during treatment.

5.3 Risk of Use in Patients with Biliary Disease

In clinical studies with COBENFY, transient increases in liver enzymes with rapid decline occurred, consistent with transient biliary obstruction due to biliary contraction and possible gallstone passage *[see Adverse Reactions (6.1)]*.

COBENFY is not recommended for patients with active biliary disease such as symptomatic gallstones. Assess liver enzymes and bilirubin prior to initiating COBENFY and as clinically indicated during treatment. The occurrence of symptoms such as dyspepsia, nausea, vomiting, or upper abdominal pain should prompt assessment for gallbladder disorders, biliary disorders, and pancreatitis, as clinically indicated.

Discontinue COBENFY in the presence of signs or symptoms of substantial liver injury such as jaundice, pruritus, or alanine aminotransferase levels more than five times the upper limit of normal or five times baseline values.

5.4 Decreased Gastrointestinal Motility

COBENFY contains trospium chloride. Trospium chloride, like other antimuscarinic agents, may decrease gastrointestinal motility. Administer COBENFY with caution in patients with gastrointestinal obstructive disorders because of the risk of gastric retention *[see Contraindications (4)]*. Use COBENFY with caution in patients with conditions such as ulcerative colitis, intestinal atony, and myasthenia gravis.

5.5 Risk of Angioedema

Angioedema of the face, lips, tongue, and/or larynx has been reported with COBENFY and trospium chloride, a component of COBENFY *[see Adverse Reactions (6.2)]*. In one case, angioedema occurred after the first dose of trospium chloride. Angioedema associated with upper airway swelling may be life-threatening. If involvement of the tongue, hypopharynx, or larynx occurs, discontinue COBENFY and initiate appropriate therapy and/or measures necessary to ensure a patent airway. COBENFY is contraindicated in patients with a history of hypersensitivity to trospium chloride.

5.6. Risk of Use in Patients with Narrow-angle Glaucoma

Pupillary dilation may occur due to the anticholinergic effects of COBENFY. This may trigger an acute angle closure attack in patients with anatomically narrow angles. In patients known to have anatomically narrow angles, COBENFY should only be used if the potential benefits outweigh the risks and with careful monitoring *[see Contraindications (4)]*.

5.7. Increases in Heart Rate

COBENFY can increase heart rate *[see Adverse Reactions (6.1)]*. Assess heart rate at baseline and as clinically indicated during treatment with COBENFY *[see Dosage and Administration (2.1)]*.

5.8 Anticholinergic Adverse Reactions in Patients with Renal Impairment

Trospium chloride, a component of COBENFY, is substantially excreted by the kidney. COBENFY is not recommended in patients with moderate or severe renal impairment (estimated glomerular filtration rate (eGFR) <60 mL/min). Systemic exposure of trospium chloride is higher in patients with moderate and severe renal impairment *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*. Therefore, anticholinergic adverse reactions (including dry mouth, constipation, dyspepsia, urinary tract infection, and urinary retention) are expected to be greater in patients with moderate and severe renal impairment.

5.9 Central Nervous System Effects

Trospium chloride, a component of COBENFY, is associated with anticholinergic central nervous system (CNS) effects *[see Adverse Reactions (6.1)]*. A variety of CNS anticholinergic effects have been reported with trospium chloride, including dizziness, confusion, hallucinations, and somnolence. Monitor patients for signs of anticholinergic CNS effects, particularly after beginning treatment or increasing the dose. Advise patients not to drive or operate heavy machinery until they know how COBENFY affects them. If a patient experiences anticholinergic CNS effects, consider dose reduction or drug discontinuation.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Risk of Urinary Retention *[see Warnings and Precautions (5.1)]*
- Risk of Use in Patients with Hepatic Impairment *[see Warnings and Precautions (5.2)]*
- Risk of Use in Patients with Biliary Disease *[see Warnings and Precautions (5.3)]*
- Decreased Gastrointestinal Motility *[see Warnings and Precautions (5.4)]*
- Risk of Angioedema *[see Warnings and Precautions (5.5)]*
- Risk of Use in Patients with Narrow-angle Glaucoma *[see Warnings and Precautions (5.6)]*
- Increases in Heart Rate *[see Warnings and Precautions (5.7)]*
- Anticholinergic Adverse Reactions in Patients with Renal Impairment *[see Warnings and Precautions (5.8)]*
- Central Nervous System Effects *[see Warnings and Precautions (5.9)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

COBENFY was evaluated for safety in a total of 1,594 subjects exposed to one or more doses, including 1,135 adult patients with schizophrenia and 389 healthy subjects. A total of 347

COBENFY-treated patients had at least 6 months of exposure and 150 patients had at least 1 year of exposure (defined as ≥ 50 weeks) from open-label studies.

The adverse reaction findings are based on two pooled 5-week, placebo-controlled, flexible-dose studies in 504 adult patients with schizophrenia in which COBENFY or placebo was started at an initial dose of 50 mg/20 mg twice daily for the first 2 days followed by 100 mg/20 mg twice daily for the remainder of Week 1 (Days 3 to 7). On Day 8, dosing was titrated to 125 mg/30 mg twice daily unless the patient could not tolerate it. All patients had the option to return to 100 mg/20 mg twice daily for the remainder of the treatment period *[see Clinical Studies (14)]*.

In the 5-week placebo-controlled studies, 6% of patients treated with COBENFY and 4% of placebo-treated patients discontinued participation due to adverse reactions. Adverse reactions that led to study discontinuation in ≥1% of patients treated with COBENFY include nausea (2%) and vomiting (1%).

The most common adverse reactions (≥5% and at least twice placebo) were nausea, dyspepsia, constipation, vomiting, hypertension, abdominal pain, diarrhea, tachycardia, dizziness, and gastroesophageal reflux disease.

Adverse reactions reported with COBENFY at an incidence of at least 2% in patients exposed to COBENFY and greater than the rate of placebo are shown in Table 1.

Table 1: Adverse Reactions Reported in ≥2% of COBENFY-Treated Patients and Greater than Rate of Placebo in Two 5-week Schizophrenia Trials

	COBENFY (N=251)	Placebo (N=253)
Nausea	19%	4%
Dyspepsia[a]	18%	5%
Constipation	17%	7%
Vomiting	15%	1%
Hypertension[b]	11%	2%
Abdominal Pain[c]	8%	4%
Diarrhea	6%	2%
Tachycardia[d]	5%	2%
Dizziness	5%	2%
Gastroesophageal reflux disease	5%	<1%
Dry mouth	4%	2%
Somnolence	3%	2%
Vision blurred	3%	0%
Salivary hypersecretion	2%	0%
Orthostatic hypotension	2%	1%
Cough[e]	2%	1%
Extrapyramidal symptoms (EPS), non-akathisia[f]	2%	<1%

[a] Dyspepsia includes dyspepsia, esophageal discomfort
[b] Hypertension includes hypertension, blood pressure increased, labile hypertension, orthostatic hypertension
[c] Abdominal Pain includes abdominal discomfort, abdominal pain upper, abdominal pain, abdominal pain lower, abdominal tenderness
[d] Tachycardia includes tachycardia, heart rate increased, sinus tachycardia
[e] Cough: includes cough, productive cough
[f] EPS (non-akathisia) includes dyskinesia, drooling, dystonia, extrapyramidal disorder, muscle contraction involuntary, muscle spasms

Increases in Heart Rate

In a dedicated 8-week clinical study, 24-hour ambulatory blood pressure monitoring (ABPM) was conducted in 133 patients with schizophrenia. A total of 95 patients had acceptable ABPM recordings at both baseline and Week 8. In that group, there was a mean change in 24-hour heart rate of 9.8 beats per minute (bpm) (95% CI 7.5, 12.2) from baseline to Week 8.

In the two placebo-controlled schizophrenia studies, COBENFY was associated with increases in heart rate compared to placebo, with peak elevation occurring on Day 8 of study treatment (13.5 bpm in the COBENFY group and 4.0 bpm in the placebo group), partially attenuating with continued dosing (11.4 bpm in the COBENFY group and 5.5 bpm in the placebo group at Week 5).

Liver Enzyme Elevations

In the 5-week, placebo-controlled schizophrenia studies, the proportions of patients with ALT or AST elevations of ≥3 times the upper limits of the normal reference range were 2.8% (6/214) for

COBENFY-treated patients compared to 0.4% (1/224) of placebo-treated patients. Twenty-five (1.6%) of the total 1,594 subjects exposed to COBENFY had elevated liver enzymes. The majority of liver enzyme elevations occurred within the first month of treatment and resolved with continued COBENFY use, suggestive of liver adaptation; some cases required treatment interruption, and one was associated with an increase in bilirubin.

Urinary Retention
In the 5-week, placebo-controlled studies, urinary retention (urinary hesitation, dysuria, and urinary retention) was reported in 0.8% of COBENFY-treated patients and 0.4% on placebo. In the long-term, open-label studies, urinary retention was reported in 3.5% of COBENFY-treated patients. Urinary retention was more common in males, geriatric patients, and those with certain risk factors *[see Warnings and Precautions (5.1)]*. Urinary retention occurred at all doses but was predominately observed at the maximum COBENFY dose. In the long-term, open-label studies, urinary tract infections were reported in 2.3% of COBENFY-treated patients and were more commonly reported in females than males. Of the total 1,594 subjects exposed to COBENFY (including healthy volunteers and patients with schizophrenia or other conditions), four subjects required a Foley catheter, including one with elevated serum creatinine and one with urinary tract infections. Four subjects with urinary retention required reduction of COBENFY dose, four discontinued COBENFY, and four received medications for the treatment of benign prostatic hyperplasia (BPH).

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of trospium chloride, one of the components of COBENFY. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Cardiovascular* – chest pain, hypertensive crisis, palpitations, supraventricular tachycardia, syncope
- *Gastrointestinal* – gastritis
- *General* – rash
- *Musculoskeletal* – rhabdomyolysis
- *Nervous System* – confusion, delirium, dizziness, hallucinations, somnolence, vision abnormal
- *Skin and subcutaneous tissue disorders* – angioedema, anaphylactic reaction, Stevens-Johnson syndrome

7 DRUG INTERACTIONS

7.1 Clinically Significant Drug Interactions with COBENFY

Table 2 displays clinically significant drug interactions with COBENFY.

Table 2: Clinically Significant Drug Interactions with COBENFY

Strong Inhibitors of CYP2D6	
Clinical Implication:	CYP2D6 contributes significantly to the metabolism of xanomeline, a component of COBENFY. Concomitant use of COBENFY with strong CYP2D6 inhibitors may increase plasma concentrations of xanomeline, which may increase the frequency and/or severity of adverse reactions from COBENFY *[see Clinical Pharmacology (12.3)]*.
Prevention or Management:	Monitor patients for increased frequency and/or severity of adverse reactions related to COBENFY in patients taking COBENFY with strong inhibitors of CYP2D6.
Drugs Eliminated by Active Tubular Secretion	
Clinical Implication:	Concomitant use of COBENFY with drugs that are eliminated by active tubular secretion may increase plasma concentrations of trospium a component of COBENFY, and/or the concomitantly used drug due to competition for this elimination pathway, which may increase the frequency and/or severity of adverse reactions from COBENFY or the drug eliminated by active tubular secretion *[see Clinical Pharmacology (12.3)]*.
Prevention or Management:	Monitor patients for increased frequency and/or severity of adverse reactions related to COBENFY and adverse reactions related to drugs eliminated by active tubular secretion in patients concomitantly receiving such drugs.
Oral Drugs That Are Sensitive Substrates of CYP3A4	
Clinical Implication:	Xanomeline, a component of COBENFY, transiently inhibits CYP3A4 locally in the gut but not systemically. Concomitant use of COBENFY with oral drugs that are sensitive substrates of CYP3A4 may result in increased plasma concentrations of the oral drugs that are sensitive substrates of CYP3A4. This may increase the frequency and/or severity of adverse reactions from such substrates *[see Clinical Pharmacology (12.3)]*.
Prevention or Management:	Monitor patients for increased frequency and/or severity of adverse reactions related to oral drugs that are sensitive substrates of CYP3A4 in patients taking COBENFY with such substrates.
Oral Drugs That Are Substrates of P-glycoprotein	
Clinical Implication:	Xanomeline, a component of COBENFY, transiently inhibits P-glycoprotein locally in the gut but not systemically. Concomitant use of COBENFY with oral drugs that are substrates of P-glycoprotein may result in increased plasma concentrations of the oral drugs that are substrates of P-glycoprotein, which may increase the frequency and/or severity of adverse reactions from such substrates *[see Clinical Pharmacology (12.3)]*.
Prevention or Management:	Monitor patients for increased frequency and/or severity of adverse reactions related to oral drugs that are narrow therapeutic index substrates of P-glycoprotein in patients taking COBENFY with such substrates.

7.2 Other Antimuscarinic Drugs

Concomitant use of COBENFY with other antimuscarinic drugs that produce anticholinergic adverse reactions (e.g., dry mouth, constipation) may increase the frequency and/or severity of such effects. Monitor patients for increased frequency and/or severity of anticholinergic adverse reactions when COBENFY is used concomitantly with other antimuscarinic drugs.

7.3 Effects on Absorption of Drugs

COBENFY may potentially alter the absorption of some concomitantly administered drugs due to anticholinergic effects on gastrointestinal motility. Dosage adjustment of concomitant medications may be necessary based on clinical response and tolerability.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors outcomes in women exposed to psychiatric medications, including COBENFY, during pregnancy. Healthcare providers are encouraged to advise patients to register by calling 1-866-961-2388 or visiting online at https://womensmentalhealth.org/research/pregnancyregistry/atypicalantipsychotic/.

Risk Summary

There are no available data on COBENFY use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes. There are risks to the mother associated with untreated schizophrenia *(see Clinical Considerations)*. In animal reproduction studies, oral administration of xanomeline alone or in combination with trospium chloride during the period of organogenesis or during pregnancy and lactation caused maternal toxicities of adverse clinical signs, decreased body weight, weight gain and food consumption, and/or maternal death. At these maternally toxic doses, embryofetal and developmental toxicities included decreased fetal and neonatal weight, stillborn pups, and/or neonatal deaths. The no observed adverse effect level (NOAEL) of xanomeline or xanomeline/trospium chloride combination for maternal, embryofetal, and/or developmental toxicity is equal to or higher than the xanomeline and trospium chloride dose at the maximum recommended human dose (MRHD) of 250/60 mg xanomeline/trospium chloride, based on mg/m^2 body surface area (BSA) *(see Data)*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of major birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryofetal risk

There is a risk to the pregnant patient from untreated schizophrenia, including increased risk of relapse, hospitalization, and suicide. Schizophrenia is associated with adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.

Data

Animal Data

Pregnant rats were orally treated during the period of organogenesis with 150 mg/kg/day xanomeline alone, 100 mg/kg/day trospium chloride alone, or xanomeline/trospium chloride combination at 30/25, 75/50, and 150/100 mg/kg/day, respectively. Xanomeline alone and the high dose combination caused maternal toxicities of decreased body weight, weight gain, and food consumption. At these maternally toxic doses, fetal weights were decreased. The NOAEL for maternal and embryofetal toxicity is 75/50 mg/kg/day for the combination, which is approximately 3 and 8 times the xanomeline and trospium chloride dose, respectively, at the MRHD of 250/60 mg xanomeline/trospium chloride, based on BSA. No fetal malformation was observed. Trospium chloride alone did not cause maternal or embryofetal toxicity.

Pregnant rabbits were orally treated during the period of organogenesis with120 mg/kg/day xanomeline alone, 80 mg/kg/day trospium chloride alone, or xanomeline/trospium chloride combination at 30/20, 60/40, and 120/80 mg/kg/day, respectively. Xanomeline alone and the high dose combination caused maternal toxicities of decreased body weight, weight gain, and food consumption, and/or early abortion. At these maternally toxic doses, decreased fetal weight and decreased fetal viability (increased resorption and post-implantation loss) were observed. The NOAEL for maternal and embryofetal toxicity is 60/40 mg/kg/day for the xanomeline/trospium chloride combination, which is 5 and 13 times the xanomeline and trospium chloride dose, respectively at the MRHD, based on BSA. No fetal malformation was observed. Trospium chloride alone did not cause maternal or embryofetal toxicity.

Rats were orally treated during pregnancy and lactation with 30, 75, and 150 mg/kg/day xanomeline alone, 100 mg/kg/day trospium chloride alone, or xanomeline/trospium chloride combination at 30/25, 75/50, and 150/100 mg/kg/day, respectively. Xanomeline alone at ≥ 75 mg/kg/day or in combination with trospium chloride at ≥ 75/50 mg/kg/day caused maternal toxicity of adverse clinical signs, decreased body weight, weight gain, food consumption, and maternal death. At these maternally toxic doses, developmental toxicity was observed in the offspring, including growth suppression (decreased body weight and weight gain), delayed developmental landmarks, stillborn pups, and neonatal deaths. No drug effect was observed on the neurobehavioral function, including learning and memory, or the reproductive capacity of the offspring. The NOAEL for maternal and developmental toxicity is 30/25 mg/kg/day for the xanomeline/trospium chloride combination, which is approximately 1 and 4 times the xanomeline and trospium chloride dose, respectively at the MRHD, based on BSA. Trospium chloride alone did not cause maternal or developmental toxicity.

Pregnant rats were treated during the period of organogenesis with trospium chloride at doses up to 200 mg/kg/day. No malformation or fetal toxicity was observed up to 200 mg/kg/day, which is approximately 32 times the trospium chloride dose at the MRHD of 250/60 mg xanomeline/trospium chloride based on BSA.

Pregnant rabbits were treated during the period of organogenesis with trospium chloride at doses up to 200 mg/kg/day. Maternal toxicity (reduced feces, hunched posture, and diarrhea) was observed at 200 mg/kg/day. The NOAEL for maternal toxicity is 20 mg/kg/day, which is approximately 3 times the trospium chloride dose at the MRHD based on BSA.

Rats were orally treated during pregnancy and lactation with trospium chloride at doses up to 200 mg/kg/day. Maternal toxicity (death, irregular breathing, increased excitability) and neonatal deaths were observed at 200 mg/kg/day, which is approximately 32 times the MRHD, based on BSA. The NOAEL for maternal and developmental toxicity is 20 mg/kg/day, which is approximately 3 times the trospium chloride dose at the MRHD, based BSA.

8.2 Lactation

Risk Summary

There are no data on the presence of xanomeline or trospium in human milk, the effects on the breastfed infant, or the effects on milk production. Xanomeline and trospium are present in animal milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for COBENFY and any potential adverse effects on the breastfed infant from COBENFY or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of COBENFY in pediatric patients have not been established.

8.5 Geriatric Use

Controlled clinical studies of COBENFY did not include patients older than 65 years of age to determine whether they respond differently from younger adult patients.

Because COBENFY can increase the risk of urinary retention in geriatric patients, including older males with bladder outlet obstruction due to benign prostatic hyperplasia (BPH), a slower titration and lower maximum dosage is recommended in geriatric patients *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.

8.6 Renal Impairment

Patients with mild renal impairment (eGFR 60 to <90 mL/min) showed higher systemic exposures to trospium chloride and xanomeline, the components of COBENFY, compared to subjects with normal renal function. However, in the adequate and well-controlled clinical studies, the safety profiles in patients with mild renal impairment were similar to those observed in patients with normal renal function (eGFR ≥90 mL/min). Therefore, the recommended dosage in patients with

mild renal impairment is the same as the recommended dosage for patients with normal renal function.

Use of COBENFY is not recommended in patients with moderate or severe renal impairment (eGFR<60 mL/min) *[see Warnings and Precautions (5.1, 5.8) and Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Patients with mild to moderate hepatic impairment (Child-Pugh Class A and B, respectively) have higher xanomeline exposures compared to patients with normal hepatic function *[see Clinical Pharmacology (12.3)]*. The pharmacokinetics of COBENFY were not studied in patients with severe hepatic impairment (Child-Pugh Class C).

Use of COBENFY is contraindicated in patients moderate or severe hepatic impairment *[see Contraindications (4) and Warnings and Precautions (5.2)]*. It is not recommended in patients with mild hepatic impairment.

10 OVERDOSAGE

Overdose of COBENFY may produce cholinergic, anticholinergic or a combination of cholinergic and anticholinergic signs and symptoms:

- Cholinergic Signs and Symptoms: seizures, vomiting, diarrhea, abdominal pain, hyperhidrosis, salivary hypersecretion, and hypotension possibly preceded by hypertension.
- Anticholinergic Signs and Symptoms (geriatric patients may be more susceptible): delirium, agitation, garbled speech, dizziness, hypertension, tachycardia, dry mouth and eyes, ileus, blurred vision, and urinary retention.

Consider calling the Poison Help Line 1-800-222-1222 or a medical toxicologist for specific treatment recommendations.

11 DESCRIPTION

COBENFY is a combination of xanomeline, a muscarinic agonist, and trospium chloride, a muscarinic antagonist.

The chemical name of xanomeline tartrate is pyridine, 3-[4-(hexyloxy)-1,2,5-thiadiazol-3-yl]-1,2,5,6-tetrahydro-1-methyl-, (2R,3R)-2,3-dihydroxybutanedioate (1:1). Its molecular formula is $C_{14}H_{23}N_3OS.C_4H_6O_6$ and its molecular weight is 431.51 g/mol. Xanomeline tartrate is a white to slightly tan crystalline solid. Xanomeline tartrate is highly soluble in protic solvents, such as methanol and water, and in polar organic solvents such as DMF and dimethyl sulfoxide (DMSO). It is poorly soluble in lipophilic organic solvents, such as hexane or octanol.

The chemical structure of xanomeline tartrate is:

Trospium chloride is a quaternary ammonium compound with the chemical name of spiro[8-azoniabicyclo[3.2.1]octane-8,1′-pyrrolidinium], 3-[(2-hydroxy-2,2-diphenylacetyl)oxy]-, chloride (1:1), (1α,3β,5α). The molecular formula of trospium chloride is $C_{25}H_{30}NO_3.Cl$ and its molecular weight is 427.96 g/mol. Trospium chloride is a fine, colorless to slightly yellow, crystalline solid. Trospium chloride is highly soluble in water, freely soluble in methanol, and practically insoluble in methylene chloride.

The chemical structure of trospium chloride is:

COBENFY (xanomeline and trospium chloride) is for oral administration and is available in capsules in the following strengths:

- 50 mg/20 mg (equivalent to 76.7 mg xanomeline tartrate and 18.3 mg trospium).
- 100 mg/20 mg (equivalent to 153.3 mg xanomeline tartrate and 18.3 mg trospium).
- 125 mg/30 mg (equivalent to 191.7 mg xanomeline tartrate and 27.5 mg trospium).

COBENFY capsules contain a combination of pellets of xanomeline and pellets of trospium chloride.

Inactive ingredients: The xanomeline tartrate pellets contain ascorbic acid, microcrystalline cellulose, and talc.

The trospium chloride pellets contain lactose monohydrate, microcrystalline cellulose, and talc.

The capsules, printed with black ink, contain black iron oxide (only 100 mg/20 mg), hypromellose, red iron oxide, titanium dioxide, and yellow iron oxide (only 50 mg/20 mg and 100 mg/20 mg).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of xanomeline in the treatment of schizophrenia is unclear; however, its efficacy is thought to be due to its agonist activity at M1 and M4 muscarinic acetylcholine receptors in the central nervous system.

Trospium chloride is a muscarinic antagonist. Trospium chloride antagonizes the muscarinic receptors primarily in the peripheral tissues.

12.2 Pharmacodynamics

Xanomeline binds to muscarinic receptors M1 to M5 with comparable affinity (Ki=10, 12, 17, 7, and 22 nM for the M1, M2, M3, M4, and M5 receptors, respectively) and exhibits higher agonist activity at the M1 and M4 receptors.

Trospium chloride antagonizes the muscarinic receptors primarily in peripheral tissues.

Cardiac Electrophysiology

At the maximum recommended dosage of 125 mg/30 mg twice daily, COBENFY does not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Following COBENFY administration, xanomeline area under the plasma concentration-time curve during a 12-hour dosing interval (AUC_{0-12}) at steady state and maximum concentration (C_{max}) increased 50% when the COBENFY dose increased from 100 mg/20 mg twice daily to 125 mg/30 mg twice daily. Trospium exposures increase dose-proportionally over the COBENFY dosage range of 100 mg/20 mg twice daily to 125 mg/30 mg twice daily.

Pharmacokinetic properties of COBENFY are provided in Table 3.

Table 3: Pharmacokinetic Properties of COBENFY

Parameter	Xanomeline	Trospium
General Information		
Dose proportionality	Greater than proportional	Proportional
Accumulation[a]	2 to 3-fold	2 to 3-fold

Time to steady state		3 to 5 days	3 to 5 days
Absorption			
T_{max}		2 hours	1 hour
Effect of food: PK in fed state (compared to fasted state)			
High fat meal[b]	C_{max}	Unchanged	Reduced 70% to 75%
	AUC	Increased 30%	Reduced 85% to 90%
Low fat meal[b]	C_{max}	Unchanged	Reduced 70% to 75%
	AUC	Unchanged	Reduced 85% to 90%
Distribution			
Central volume of distribution (oral)		10,800 Liters	531 Liters
Plasma protein binding		Approximately 95%	Approximately 80%
Elimination			
Half-life ($t_{1/2}$)		5 hours	6 hours
Apparent clearance		1950 Liters/hour	796 Liters/hour
Renal clearance		0.085 Liters/hour	21 Liters/hour
Metabolism			
Primary metabolic pathways	CYP450	2D6, 2B6, 1A2, 2C9, and 2C19	Unlikely
	Other	Flavin monooxygenases (FMO1 and FMO3)	Ester hydrolysis and glucuronic acid conjugation (not fully characterized)
Excretion			
Urine	Total	78%[d]	Unknown
	Unchanged	Less than 0.01%[d]	85-90%[d]
	Tubular secretion	Unknown	Yes
Feces	Total	12%	Unknown
	Unchanged	Unknown	Unknown

Abbreviations: AUC = Area under the time-concentration curve; C_{max} = Maximum concentration; T_{max} =Time to C_{max}

.[a]Dose-normalized accumulation at steady state

[b] High-fat high-calorie meal is 800-1000 calories, 50% from fat; a low-fat meal is 400-500 calories, 25% from fat

Specific Populations

Geriatric Patients

Population pharmacokinetic analysis suggests that AUC_{0-12h} and C_{max} of trospium at steady state were 60% higher and 36% higher, respectively, in subjects 65 years and older compared to subjects younger than 65 years old. The exposures (AUC_{0-12h} and C_{max}) of xanomeline at steady state were not different between subjects 65 years and older and subjects younger than 65 years old *[see Dosage and Administration (2.3) and Use in Specific Populations (8.5)]*.

Male and Female Patients

Plasma concentrations of xanomeline and trospium are similar between females and males.

Racial or Ethnic Groups
Most subjects in clinical studies were Black.
Xanomeline and trospium exposure did not differ between Black and non-Black subjects. Studies have included too few subjects of Asian descent to evaluate comparisons.

Patients with Renal Impairment
The effect of renal impairment on xanomeline and trospium exposure was assessed in a dedicated study that enrolled healthy subjects and subjects with mild, moderate, or severe renal impairment. Estimated glomerular filtration rate (eGFR) was determined by the MDRD equation.

Plasma concentrations of xanomeline and trospium increased with increasing renal dysfunction *[see Use in Specific Populations (8.6)].* For xanomeline, compared to subjects with normal renal function (eGFR: ≥90 mL/min), the steady-state C_{max} and $AUC_{0\text{-}12h}$ were 2.1 and 1.9 times higher in subjects with mild renal impairment (eGFR: 60 to <90 mL/min), 2.4 and 2.1 times higher in subjects with moderate renal impairment (eGFR: 30 to <60 mL/min), and 2.6 and 2.4 times higher in subjects with severe renal impairment (eGFR: <30 mL/min). For trospium, compared to subjects with normal renal function, the steady-state C_{max} and $AUC_{0\text{-}12h}$ were 1.6 and 1.6 times higher in subjects with mild renal impairment, 2.7 and 2.2 times higher in subjects with moderate renal impairment, and 2.9 and 2.9 times higher in subjects with severe renal impairment.

Patients with Hepatic Impairment
The effect of hepatic impairment on xanomeline and trospium in combination was assessed in a dedicated study that enrolled healthy subjects and subjects with mild or moderate hepatic impairment as determined by their Child-Pugh score.

Plasma concentrations of xanomeline increased with increasing hepatic dysfunction *[see Use in Specific Populations (8.7)].* In subjects with mild hepatic impairment (Child-Pugh Class A), the steady-state C_{max} and $AUC_{0\text{-}12h}$ of xanomeline was 2.8 and 2.6 times that in subjects with normal hepatic function. Mild and moderate hepatic impairment did not substantially affect trospium exposure, but significantly impacted xanomeline exposures. In subjects with moderate hepatic impairment (Child-Pugh Class B), the steady-state C_{max} and $AUC_{0\text{-}12h}$ of xanomeline was at least 7 times that in subjects with normal hepatic function *[see Contraindications (4) and Warnings and Precautions (5.2)]*.

The effect of severe hepatic impairment on xanomeline and trospium exposure was not evaluated.

Body Weight
Compared to subjects weighing 70 kg, xanomeline exposures were 30 to 35% lower and trospium exposures were 20 to 35% lower in subjects weighing 120 kg. The lower exposures observed in subjects weighing 120 kg are expected to be clinically not meaningful.

Drug Interaction Studies
Drugs Eliminated by Active Tubular Secretion
Active tubular excretion is a major elimination pathway for trospium. Trospium has the potential for pharmacokinetic interactions with other drugs that are eliminated by active tubular secretion. Coadministration of COBENFY with these drugs may increase plasma concentrations of trospium

and/or the coadministered drug due to competition for this elimination pathway *[see Drug Interactions (7.1)]*.

Metformin
A drug interaction study was conducted in which extended-release trospium chloride 60 mg once daily was coadministered with metformin hydrochloride 500 mg twice daily under steady-state conditions in 44 healthy subjects. Co-administration of 500 mg metformin immediate-release tablets twice daily reduced the steady-state systemic exposure of trospium by approximately 29% for mean AUC_{0-24} and by 34% for mean C_{max}. The steady-state pharmacokinetics of metformin were comparable when administered with or without 60 mg extended-release trospium chloride once daily under fasted conditions. The effect of metformin at higher doses on trospium pharmacokinetics is unknown.

Drugs That Inhibit CYP2D6
CYP2D6 is a significant contributor to the metabolism of xanomeline. Drugs that are inhibitors of CYP2D6 may increase xanomeline concentrations in plasma *[see Drug Interactions (7.1)].*

Drugs That Are Substrates of P-glycoprotein
In vitro data suggest that xanomeline does not inhibit P-glycoprotein systemically, but it may transiently inhibit P-glycoprotein locally in the intestine after dosing. COBENFY may increase plasma concentrations of coadministered P-gp substrates *[see Drug Interactions (7.1)]*.

Drugs That Are Substrates of CYP3A4
In vitro data suggest that xanomeline does not inhibit CYP3A4 systemically, but it may transiently inhibit CYP3A4 locally in the intestine after dosing. COBENFY may increase plasma concentrations of coadministered CYP3A4 substrates *[see Drug Interactions (7.1)]*.

12.5 Pharmacogenomics

CYP2D6 is a significant contributor to the metabolism of xanomeline. The gene encoding CYP2D6 has polymorphisms that impact protein function. Based on a population pharmacokinetic analysis, compared to subjects with normal CYP2D6 function, the median C_{max} and median AUC_{0-12h} of xanomeline were estimated to increase by 28% and 15% in CYP2D6 intermediate metabolizers (N=84) and decrease by 43% in both parameters for ultrarapid metabolizers (N=12)**.** The pharmacokinetics of xanomeline have not been adequately characterized in subjects who are poor metabolizers.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Xanomeline
Xanomeline was administered to rats in the diet at doses of 9, 37, and 134 mg/kg/day in males and 11, 46, and 170 mg/kg/day in females, respectively, for two years. Biliary hyperplasia was observed in all groups with increased incidence and/or severity at ≥ 37 and 46 mg/kg/day in males

and females, respectively, relative to controls. There was no increase in the incidence of tumors at doses up to 37 and 46/mg/kg/day in males and females, respectively; these doses are 1.4 to 1.8 times higher than the xanomeline dose at the MRHD of 250/60 mg xanomeline/trospium, based on mg/m^2 BSA. The high doses of 134 and 170 mg/kg/day in males and females exceeded the maximum tolerated dose (MTD), precluding an adequate assessment for carcinogenic effect at this dose.

Xanomeline was administered to mice in the diet at doses of 52, 174, and 559 mg/kg/day for 21 months in both sexes. Xanomeline did not increase the incidence of tumors in mice at doses up to 174 mg/kg/day, which is approximately 3 times the xanomeline dose at the MRHD, based on BSA. The high dose of 559 mg/kg/day exceeded the MTD, precluding an adequate assessment for carcinogenic effect at this dose.

Trospium chloride
Trospium chloride did not increase the incidence of tumors in rats treated for 104 weeks at doses up to 200 mg/kg/day, which is approximately 32 times the trospium chloride dose at the MRHD, based on BSA.

Trospium chloride did not increase the incidence of tumors in mice treated for 78 weeks at doses up to 200 mg/kg/day, which is approximately 16 times the trospium chloride dose at the MRHD, based on BSA.

Mutagenesis

Xanomeline
Xanomeline was not mutagenic in the in vitro bacterial reverse mutation (Ames assay) or mouse lymphoma assay. Xanomeline did not induce unscheduled DNA synthesis in rat hepatocytes and was not clastogenic in the in vitro chromosome aberration assay or in the in vivo mouse bone marrow micronucleus assay.

Trospium chloride
Trospium chloride was not mutagenic nor genotoxic in tests *in vitro* in bacteria (Ames assay) and mammalian cells (L5178Y mouse lymphoma and CHO cells) or *in vivo* in the rat micronucleus test.

Impairment of Fertility

Xanomeline
Xanomeline did not affect fertility when orally administered to male rats via the diet at doses of 15, 44, and 150 mg/kg/day. The NOAEL for male fertility is 150 mg/kg/day, which is approximately 6 times the xanomeline dose at the MRHD of 250/60 mg xanomeline/trospium, based on BSA.

Xanomeline did not affect fertility when administered subcutaneously to male and female rats at doses of 1, 5, and 25 mg/kg/day. The NOAEL for male and female fertility is 25 mg/kg/day, which is equal to the xanomeline dose at the MRHD, based on BSA.

Trospium chloride
Trospium chloride did not affect fertility in rats at doses up to 200 mg/kg/day which is approximately 32 times the trospium chloride dose at the MRHD, based on BSA.

13.2 Animal Toxicology and/or Pharmacology

In the 2-year dietary study in rats, biliary cysts and/or biliary/biliary ductule dilatation were observed at xanomeline doses equal to or greater than the MRHD of 250/60 mg xanomeline/trospium chloride, based on BSA.

14 CLINICAL STUDIES

The efficacy of COBENFY for the treatment of schizophrenia in adults was evaluated in two placebo-controlled studies with identical designs (N = 470). Study 1 (NCT04659161) and Study 2 (NCT04738123) were five-week, randomized, double-blind, placebo-controlled, multi-center studies in adult patients with a diagnosis of schizophrenia according to the DSM-5 criteria.

In Study 1 and Study 2, patients randomized to COBENFY were started on an initial dose of 50 mg/20 mg orally twice daily for the first 2 days and if tolerated, followed by 100 mg/20 mg orally twice daily for the remainder of Week 1 (Days 3 to 7). On Day 8, dosing was titrated upwards to 125 mg/30 mg orally twice daily unless the patient could not tolerate it. All patients could return to 100 mg/20 mg orally twice daily for the remainder of the treatment period.

Demographic and baseline disease characteristics were similar for the COBENFY and placebo groups. Median age was 46 years (range 19 to 65 years). Twenty-five percent of patients were female, 31% were White, 68% were Black or African American, and 1% were Other (or not reported).

The primary efficacy measure was the change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score at Week 5. The PANSS is a 30-item scale that measures symptoms of schizophrenia. Each item is rated by a clinician on a seven-point scale. A score of 1 indicates the absence of symptoms, and a score of 7 indicates extremely severe symptoms. The PANSS total score may range from 30 to 210 with higher scores reflecting greater overall symptom severity.

In Study 1 and Study 2, patients randomized to COBENFY showed a statistically significant reduction from baseline to Week 5 in the PANSS Total Score compared to the placebo group. The results of Studies 1 and 2 are shown in Table 4. A secondary endpoint, the change from baseline to Week 5 on the Clinical Global Impression–Severity (CGI-S) score, was statistically significant for COBENFY compared to placebo in Study 1. The CGI-S is a validated clinician-rated scale that measures the patient's current illness state and overall clinical state on a 1 (normal, not at all ill) to 7-point (extremely ill) scale.

Examination of subgroups by age, sex, and race did not suggest differences in response in the study (there were no patients over 65 years of age).

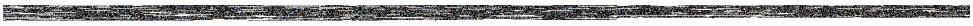
Table 4: Primary Efficacy Results for Change from Baseline in PANSS Total Score at Week 5 in Adults with Schizophrenia (Studies 1 and 2)

Study Number	Treatment Group	N	Primary Efficacy Endpoint: PANSS Total Score		
			Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference (95% CI) [a]
1	COBENFY	117	98.2 (8.9)	-21.2 (1.7)	-9.6 (-13.9, -5.2)*
	Placebo	119	97.7 (9.4)	-11.6 (1.6)	
2	COBENFY	114	96.9 (8.8)	-20.6 (1.6)	-8.4 (-12.4, -4.3)*
	Placebo	120	96.5 (8.8)	-12.2 (1.6)	

The PANSS Total Score may range from 30 to 210; higher scores reflect greater symptom severity.
SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval.
[a] Difference (drug minus placebo) in LS mean change from baseline.
*Statistically significantly superior to placebo.

The change from baseline in PANSS total score to Week 5 is summarized in Figure 1.

Figure 1: Change from Baseline in PANSS Total Score by Week in Adults with Schizophrenia (Study 1)



Error bars represent standard error. LS=least squares; SE=standard error

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

COBENFY is available as:

- 50 mg/20 mg (xanomeline/trospium chloride): Buff capsules imprinted with Karuna 50/20 mg
- 100 mg/20 mg (xanomeline/trospium chloride): Brown capsules imprinted with Karuna 100/20 mg
- 125 mg/30 mg (xanomeline/trospium chloride): Swedish Orange capsules imprinted with Karuna 125/30 mg

COBENFY capsules are packaged as described in Table 5.

Table 5: COBENFY Packaging Configurations

Capsule Strength	Total Package Count	Package Configuration	Package Components	NDC Code
50 mg/20 mg	60	Bottle	N/A	0003-0050-60
100 mg/20 mg	60	Bottle	N/A	0003-0100-60
125 mg/30 mg	60	Bottle	N/A	0003-0125-60
50 mg/20 mg (4) 100 mg/20 mg (52)	56	Starter Pack for 100 mg/20 mg dose	1 Mixed Blister Wallet: four (4) 50 mg/20 mg capsules and ten (10) 100 mg/20 mg capsules and 3 Wallets: fourteen (14) 100 mg/20 mg capsules in each wallet	0003-5200-56

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Risk of Urinary Retention

Inform patients that COBENFY may cause urinary retention and that the risk of urinary retention is greater in some patients, including geriatric patients and those with bladder outlet obstruction

(e.g., due to BPH) and patients with other causes of reduced bladder emptying (e.g., diabetic cystopathy). Urinary retention may occur at any time during treatment with COBENFY and is more likely when taking higher doses.

Advise patients to monitor for symptoms of urinary retention, such as urinary hesitancy, weak urinary stream, incomplete bladder emptying and pain with urination, and to promptly report these symptoms to their healthcare provider. Inform patients that urinary retention may increase the risk of urinary tract infection. Advise patients to seek immediate medical attention if they are unable to urinate *[see Warnings and Precautions (5.1)]*.

Risk of Use in Patients with Hepatic Impairment
Instruct patients to report signs of hepatic impairment (e.g., skin and eyes that appear yellowish, abdominal pain and swelling, itchy skin, dark urine color) and symptoms of hepatic injury (e.g., biliary spasm, pancreatitis, and cholangitis) to their healthcare provider *[see Warnings and Precautions (5.2)]*.

Risk of Use in Patients with Biliary Disease
Inform patients that COBENFY can increase liver enzymes and about the need for specific monitoring, including liver enzymes and bilirubin levels. Inform patients to report symptoms such as dyspepsia, nausea, vomiting, or upper abdominal pain to their healthcare provider *[see Warnings and Precautions (5.3)]*.

Decreased Gastrointestinal Motility
Inform patients that COBENFY can delay or slow emptying of food in their stomach. Advise patients to inform their healthcare provider about the presence of or symptoms of gastrointestinal obstructive disorders and conditions such as ulcerative colitis, intestinal atony, and myasthenia gravis *[see Warnings and Precautions (5.4)]*.

Risk of Angioedema
Advise patients that hypersensitivity reactions to COBENFY could and occur and result in life-threatening airway obstruction. Instruct patients to seek medical attention if they experience edema of the tongue, edema of the laryngopharynx, or difficulty breathing occurs, discontinue COBENFY, and seek immediate medical attention *[see Warnings and Precautions (5.5)].*

Risk of Use in Patients with Narrow-angle Glaucoma
Inform patients pupillary dilation may occur with COBENFY use and in susceptible individuals, can lead to an episode of angle closure glaucoma *[see Warnings and Precautions (5.6)].*

Increases in Heart Rate
Inform patients that COBENFY can increase heart rate *[see Warnings and Precautions (5.7)]*.

Anticholinergic Adverse Reactions in Patients with Renal Impairment
Inform patients that COBENFY is associated with anticholinergic adverse reactions such as dry mouth, constipation, dyspepsia, urinary tract infection, and urinary retention and the effects are expected to be greater in patients with renal impairment *[see Warnings and Precautions (5.8)]*.

Central Nervous System Effects
Advise patients that COBENFY is associated with central nervous system effects such as dizziness, confusion, hallucinations, and somnolence. Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that COBENFY therapy does not adversely affect their ability to engage in such activities *[see Warnings and Precautions (5.9)]*.

Administration Information
Instruct patients to take COBENFY twice daily at least one hour before a meal or at least 2 hours after a meal and not to open the capsules *[see Dosage and Administration (2.2)]*.

Concomitant Medications
Advise patients to inform their health care providers of any changes to their current prescription or over-the-counter medications because there may be a potential for interactions *[see Drug Interactions (7)]*.

Pregnancy
Advise patients to notify their healthcare provider with a known or suspected pregnancy. Advise pregnant women that there is a pregnancy exposure registry that monitors outcomes in females exposed to COBENFY during pregnancy *[see Use in Specific Populations (8.1)]*.

Marketed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
COBENFY is a trademark of Karuna Therapeutics, Inc., a Bristol-Myers Squibb company.

PATIENT INFORMATION
COBENFY™ (co-BEN-fee)
(xanomeline and trospium chloride)
capsules

What is COBENFY?

COBENFY is a prescription medicine used to treat schizophrenia in adults.

It is not known if COBENFY is safe and effective in children.

Do not take COBENFY if you:

- have urinary retention problems that cause your bladder to not empty completely or not empty at all
- have moderate or severe liver problems (impairment)
- have gastric retention problems that cause your stomach to empty slowly
- are allergic to COBENFY, xanomeline, or trospium chloride, or any of the ingredients in COBENFY. See the end of this Patient Information leaflet for a complete list of ingredients in COBENFY.
- have an eye problem called untreated narrow-angle glaucoma

Before taking COBENFY, tell your healthcare provider about all of your medical conditions, including if you:

- have an enlarged prostate, problems passing urine, or a blockage in your urinary bladder
- have liver problems
- have or had gallstones or problems with your bile ducts or pancreas
- have stomach or intestinal problems including constipation, ulcerative colitis, slow emptying of your stomach, or myasthenia gravis
- have an eye condition called narrow-angle glaucoma
- have kidney problems
- are pregnant or plan to become pregnant. It is not known if COBENFY may harm your unborn baby. Tell your healthcare provider if you become pregnant or think you are pregnant during treatment with COBENFY.
  - There is a pregnancy exposure registry for women who take COBENFY during pregnancy. The purpose of this registry is to collect information about the health of women exposed to COBENFY and their baby. If you become pregnant during treatment with COBENFY, your healthcare provider will register you by calling 1-866-961-2388 or online at https://womensmentalhealth.org/research/pregnancyregistry/atypicalantipsychotic/.
- are breastfeeding or plan to breastfeed. It is not known if COBENFY passes into your breast milk or if it can harm your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking COBENFY with certain other medicines may increase your risk of side effects from COBENFY or the other medicine and may affect the way COBENFY or the other medicine works. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take COBENFY?

- Take COBENFY exactly as your healthcare provider tells you. **Do not** change the dose or stop taking COBENFY without first talking to your healthcare provider.
- Take 1 COBENFY capsule 2 times each day.
- Take COBENFY by mouth at least 1 hour before a meal or at least 2 hours after a meal.
- **Do not** open the capsules.
- If you take too much COBENFY, call your healthcare provider or Poison Help Line at 1-800-222-1222, or go to the nearest hospital emergency room right away.

What should I avoid while taking COBENFY?

Do not drive, operate heavy machinery, or do other dangerous activities until you know how COBENFY affects you. COBENFY may cause dizziness, confusion, seeing or hearing things that are not real (hallucinations), and sleepiness.

What are the possible side effects of COBENFY?

COBENFY may cause serious side effects, including:

- **Problems with emptying your bladder (urinary retention)**. See **"Do not take COBENFY if you:"** COBENFY may cause your bladder to not empty completely or not empty at all. You are at increased risk for urinary retention if you are elderly, have a blockage in your bladder, have an enlarged prostate called benign prostatic hyperplasia (BPH), have bladder emptying problems from diabetes, or are taking higher doses of COBENFY. Urinary retention may increase your risk for getting a urinary tract infection. Call your healthcare provider or get emergency help right away if you get any signs or symptoms of urinary retention during treatment with COBENFY, including:
  - difficulty urinating
  - urination in a weak stream or drips
  - urinating frequently
  - full bladder and difficulty emptying your bladder
  - pain when you urinate

- **Risks in people with liver problems.** See **"Do not take COBENFY if you:"** It is not recommended that people with mild liver problems (impairment) take COBENFY because they have an increased risk of getting side effects from COBENFY. Your healthcare provider will check the liver enzyme levels in your blood before starting treatment and as needed during treatment with COBENFY. Tell your healthcare provider if you get any signs or symptoms of liver problems during treatment with COBENFY, including:
  - yellowing of your skin or the white part of your eyes
  - dark urine
  - pain and swelling in the upper right part of your stomach (abdomen)
  - stomach pain that spreads to your back or to below your right shoulder
  - itching
  - nausea or vomiting
  - loss of appetite
  - fever
  - chills
  - light colored stools
  - tiredness
- **Risks in people with bile duct and gallbladder problems (biliary disease).** COBENFY may cause a blockage in your bile ducts that could lead to gallstones, pancreatitis, and increases in your liver enzymes. Your healthcare provider will check your liver enzyme and bilirubin levels in your blood before starting treatment and as needed during treatment with COBENFY. Tell your healthcare provider if you get any signs or symptoms of biliary disorders during treatment with COBENFY, including:
  - stomach upset or burning (dyspepsia)
  - nausea
  - vomiting
  - pain in the upper right part of your stomach
- **Slow emptying of your stomach (decreased gastrointestinal motility)**. See **"Do not take COBENFY if you:"** You are at increased risk for getting decreased gastrointestinal motility if you have ulcerative colitis, already have problems with slow stomach emptying, and have myasthenia gravis. Tell your healthcare provider if you get any signs and symptoms of decreased gastrointestinal motility during treatment with COBENFY, including:
  - constipation
  - vomiting
  - nausea
  - stomach (abdominal) bloating
  - stomach (abdominal) pain
  - a feeling of fullness after eating just a few bites
  - acid reflux
- **Serious allergic reactions (angioedema)**. Angioedema may happen during treatment with COBENFY and can be life threatening. Stop taking COBENFY and call your healthcare provider or get emergency help right away if you get any of the following signs or symptoms of a serious allergic reaction during treatment with COBENFY, including:
  - hives
  - swelling of your face, lips, mouth, or tongue
  - swelling of your throat
  - hoarseness or difficulty speaking
  - breathing problems
- **An eye problem called narrow-angle glaucoma.** See **"Do not take COBENFY if you:"** If you already have narrow angles in your eyes, COBENFY may cause a sudden attack (acute angle closure) of glaucoma. Tell your healthcare provider if you get any signs or symptoms of narrow-angle glaucoma during treatment with COBENFY, including:
  - red eyes
  - blurred vision
  - seeing halos or bright colors around lights
  - eye pain or discomfort
  - nausea or vomiting
  - severe headache
- **Increases in heart rate.** COBENFY may increase your heart (pulse) rate. Your healthcare provider should check your heart rate before you start treatment and during treatment as needed. Tell your healthcare provider if you get a racing or pounding feeling in your chest during treatment with COBENFY.
- **Side effects in people with kidney problems.** People with kidney problems may have an increased risk of getting dry mouth, constipation, stomach upset or burning, urinary tract infection, and urinary retention during treatment with COBENFY.
- **Central nervous system problems.** See "**What should I avoid while taking COBENFY?"**

The most common side effects of COBENFY include:

- nausea
- stomach upset or burning (dyspepsia)
- constipation
- vomiting
- high blood pressure
- stomach (abdominal) pain
- diarrhea
- increased heart rate
- dizziness
- heartburn (gastrointestinal reflux disease)

Your healthcare provider may lower your dose or stop treatment with COBENFY if you get certain side effects.
These are not all of the possible side effects of COBENFY.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store COBENFY?

- Store COBENFY at room temperature between 68°F to 77°F (20°C to 25°C).

Keep COBENFY and all medicines out of the reach of children.

General information about the safe and effective use of COBENFY.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use COBENFY for a condition for which it was not prescribed. Do not give your COBENFY to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about COBENFY that is written for health professionals.

What are the ingredients in COBENFY?

Active ingredients: xanomeline and trospium chloride

Inactive ingredients: ascorbic acid, lactose monohydrate, microcrystalline cellulose, and talc

The capsule shell contains black iron oxide (only 100 mg/20 mg), hypromellose, red iron oxide, titanium dioxide, and yellow iron oxide (only 50 mg/20 mg and 100 mg/20 mg).

Marketed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

For more information, go to www.COBENFY.com or call 1-800-721-5072.

This Patient Information has been approved by the U.S. Food and Drug Administration. Issued: 9/2024

Ziprasidone

HPRA

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Geodon 20mg capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains ziprasidone hydrochloride monohydrate equivalent to 20 mg, of ziprasidone

Excipient(s) with known effects:
Each 20 mg capsule contains 66.1 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard
20 mg-No 4, blue/white capsules, marked "Pfizer" and ZDX 20

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ziprasidone is indicated for the treatment of schizophrenia in adults

Ziprasidone is indicated for the treatment of manic or mixed episodes of moderate severity in bipolar disorder in adults, children and adolescents aged 10-17 years (prevention of episodes of bipolar disorder has not been established - see section 5.1).

4.2 Posology and method of administration

Posology
Adults
The recommended dose, in acute treatment of schizophrenia and bipolar mania, is 40 mg twice daily taken with food. Daily dosage may subsequently be adjusted on the basis of individual clinical status up to a maximum of 80 mg twice daily. If indicated, the maximum recommended dose may be reached as early as day 3 of treatment.

It is of particular importance not to exceed the maximum dose as the safety profile above 160 mg/day has not been confirmed and ziprasidone is associated with dose-related prolongation of the QT interval (see sections 4.3 and 4.4).

In maintenance treatment of schizophrenia patients, ziprasidone should be administered at the lowest effective dose; in many cases, a dose of 20 mg twice daily may be sufficient.

Elderly
A lower starting dose is not routinely indicated but should be considered for those 65 and over when clinical factors warrant.

Patients with renal impairment
No dose adjustment is required in patients with impaired renal function (see section 5.2).

Patients with hepatic impairment
In patients with hepatic insufficiency, lower doses should be considered (see sections 4.4 and 5.2).

Paediatric Population
Bipolar mania

The recommended dose, in acute treatment of bipolar mania, in paediatric patients (age 10 to 17 years) is a single dose of 20 mg on day 1, with food. Ziprasidone should subsequently be administered with food in two daily divided doses, and should be titrated over 1-2 weeks to a target range of 120-160 mg/day for patients weighing ≥45 kg, or to a target range of 60-80 mg/day for patients weighing <45 kg. Subsequent dosing should be adjusted on the basis of individual clinical status within the range of 80-160 mg/day for patients weighing ≥45 kg, or 40-80 mg/day for patients weighing <45 kg. Asymmetric dosing, with morning doses 20 mg or 40 mg less than evening doses, was permitted in the clinical trial. (see sections 4.4, 5.1 and 5.2).

It is of particular importance not to exceed the weight-based maximum dose as the safety profile above the maximum dose (160 mg/day for children ≥45 kg and 80 mg/day for children <45 kg has not been confirmed and ziprasidone is associated with dose-related prolongation of the QT interval (see sections 4.3 and 4.4).

Schizophrenia
The safety and efficacy of ziprasidone in paediatric patients with schizophrenia have not been established (see sections 4.4 and 5.1).

Method of administration
For oral use.

Capsules should be taken with food and swallowed whole without chewing, crushing or opening beforehand because it may affect the absorption of the medication.

4.3 Contraindications

Hypersensitivity to the active substance or any of the excipients listed in section 6.1. Known QT-interval prolongation. Congenital long QT syndrome. Recent acute myocardial infarction. Uncompensated heart failure. Arrhythmias treated with class IA and III antiarrhythmic medicinal products.

Concomitant treatment with medicinal products that prolong the QT interval, such as Class IA and III antiarrhythmics, arsenic trioxide, halofantrine, levomethadyl acetate, mesoridazine, thioridazine, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, dolasetron mesilate, mefloquine, sertindole or cisapride (see sections 4.4 and 4.5).

4.4 Special warnings and precautions for use

A medical history, including assessment of family history, and physical examination should be undertaken to identify patients for whom ziprasidone treatment is not recommended (see section 4.3).

QT interval
Ziprasidone causes a mild to moderate dose-related prolongation of the QT-interval (see sections 4.8 and 5.1).

Ziprasidone should not be given together with medicinal products that are known to prolong the QT-interval (see sections 4.3 and 4.5). Caution is advised in patients with significant bradycardia. Electrolyte disturbances such as hypokalaemia and hypomagnesaemia increase the risk for malignant arrhythmias and should be corrected before treatment with ziprasidone is started. If patients with stable cardiac disease are treated, an ECG review should be considered before treatment is started.

If cardiac symptoms, such as palpitations, vertigo, syncope or seizures occur, then the possibility of a malignant cardiac arrhythmia should be considered and a cardiac evaluation including an ECG should be performed. If the QTc interval is > 500 msec, then it is recommended that the treatment should be stopped (see section 4.3).

There have been rare post-marketing reports of torsade de pointes in patients with multiple confounding risk factors taking ziprasidone.

Paediatric population
Safety and efficacy of ziprasidone in the treatment of schizophrenia in children and adolescents have not been established (see Section 5.1).

Neuroleptic malignant syndrome (NMS)

NMS is a rare but potentially fatal complex that has been reported in association with antipsychotic medicinal products, including ziprasidone. The management of NMS should include immediate discontinuation of all antipsychotic medicinal products.

Severe Cutaneous Adverse Reactions
Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported with ziprasidone exposure. DRESS consists of a combination of three or more of the following:
cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, lymphadenopathy and one or more systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and pericarditis.

Other severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, have been reported with ziprasidone exposure.

Severe cutaneous adverse reactions are sometimes fatal. Discontinue ziprasidone if severe cutaneous adverse reactions occur.

Tardive dyskinesia
There is a potential for ziprasidone to cause tardive dyskinesia and other tardive extrapyramidal syndromes after long-term treatment. Patients with bipolar disorder are known to be particularly vulnerable to this category of symptoms. This is more frequent with increased duration of treatment and increasing age. If signs and symptoms of tardive dyskinesia appear, dose reduction or discontinuation of ziprasidone should be considered.

Falls
Ziprasidone may cause somnolence, dizziness, postural hypotension, gait disturbance, which may lead to falls. Caution should be taken when treating patients at higher risk, and a lower starting dose should be considered (e.g. elderly or debilitated patients) (see section 4.2).

Seizures
Caution is recommended when treating patients with a history of seizures.

Hepatic Impairment
There is a lack of experience in patients with severe hepatic insufficiency and ziprasidone should be used with caution in this group (see sections 4.2 and 5.2).

Medicinal products containing lactose
As the capsule contains the excipient lactose (see section 6.1), patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Geodon contains sodium
Geodon contains less than 1 mmol sodium (23 mg) per capsule. Patients on low sodium diets can be informed that this medicinal product is essentially 'sodium free'.

Increased risk of cerebrovascular accidents in the dementia population
An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomised placebo-controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Geodon should be used with caution in patients with risk factors for stroke.

Increased Mortality in Elderly people with Dementia
Data from two large observational studies showed that elderly people with dementia who are treated with antipsychotics are at a small increased risk of death and/or potentially,cerebrovascular adverse events compared with those who are not treated. There are insufficient data to give a firm estimate of the precise magnitude of the risk and the cause of the increased risk is not known.

Geodon is not licensed for the treatment of dementia-related behavioural disturbances.

Venous Thromboembolism
Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with ziprasidone and preventive measures undertaken.

Priapism
Cases of priapism have been reported with antipsychotic use, including ziprasidone. This adverse reaction, as with other psychotropic drugs, did not appear to be dose-dependent and did not correlate with the duration of treatment.

Hyperprolactinemia
As with other drugs that antagonize dopamine D2 receptors, ziprasidone may elevate prolactin levels. Disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic and pharmacodynamic studies between ziprasidone and other medicinal products that prolong the QT interval have not been performed. An additive effect of ziprasidone and these medicinal products cannot be excluded, therefore ziprasidone should not be given with medicinal products that prolong the QT interval, such as Class IA and III antiarrhythmics, arsenic trioxide, halofantrine, levomethadyl acetate, mesoridazine, thioridazine, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, dolasetron mesilate, mefloquine, sertindole or cisapride (see section 4.3).

No studies on the interaction of ziprasidone with other medicinal products have been performed in children.

CNS medicinal products/alcohol
Given the primary effects of ziprasidone, caution should be used when it is taken in combination with other centrally acting medicinal products and alcohol.

Effect of ziprasidone on other medicinal products
An *in vivo* study with dextromethorphan showed no marked inhibition of CYP2D6 at plasma concentrations 50% lower than those obtained after 40 mg ziprasidone twice daily. *In vitro* data indicated that ziprasidone may be a modest inhibitor of CYP2D6 and CYP3A4. However, it is unlikely that ziprasidone will affect the pharmacokinetics of medicinal products metabolised by these cytochrome P450 isoforms to a clinically relevant extent.

Oral contraceptives – Ziprasidone administration resulted in no significant change to the pharmacokinetics of oestrogen (ethinyl oestradiol, a CYP3A4 substrate) or progesterone components.

Lithium - Co-administration of ziprasidone had no effect on the pharmacokinetics of lithium.
As ziprasidone and lithium are associated with cardiac conduction changes, the combination may pose a risk for pharmacodynamic interactions including arrhythmias, however, in controlled clinical trials, the combination of ziprasidone plus lithium has not demonstrated an increased clinical risk, compared to lithium alone.

There are limited data on co-medication with the mood stabiliser carbamazepine.
A pharmacokinetic interaction of ziprasidone with valproate is unlikely due to the lack of common metabolic pathways for the two drugs. In a study in patients, the co-administration of ziprasidone and valproate showed that the mean concentrations of valproate were within the therapeutic range as compared to valproate administered with placebo.

Effects of other medicinal products on ziprasidone
The CYP3A4 inhibitor ketoconazole (400 mg/day), which also inhibits p-gp, increased the serum concentrations of ziprasidone by <40%. The serum concentrations of S-methyl-dihydroziprasidone and ziprasidone sulphoxide, at the expected Tmax of ziprasidone, were increased by 55% and 8% respectively. No additional QTc prolongation was observed. Changes in pharmacokinetics due to co-administration of potent CYP3A4 inhibitors are unlikely to be of clinical importance, therefore no dosage adjustment is required. *In vitro* and animal data suggest that ziprasidone may be a P-glycoprotein (p-gp) substrate. The *in vivo* relevance for humans remains unknown. Since ziprasidone is a substrate of CYP3A4 and induction of CYP3A4 and P-gp is related, co-administration with inducers of CYP3A4 and p-gp such as carbamazepine, rifampin and St John´s Wort could cause decreased concentrations of ziprasidone.

Carbamazepine therapy, 200 mg b.i.d for 21 days, resulted in a decrease of approximately 35% in the exposure to ziprasidone.

Antacid - multiple doses of aluminium and magnesium containing antacid or cimetidine have no clinically significant effect onthe pharmacokinetics of ziprasidoneunder fed conditions.

Serotonergic medicinal products

In isolated cases, there have been reports of serotonin syndrome temporally associated with the therapeutic use of ziprasidone in combination with other serotonergic medicinal products such as SSRIs (see section 4.8). The features of serotonin syndrome can include confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea.

Protein binding
Ziprasidone extensively binds to plasma proteins. The in vitro plasma protein binding of ziprasidone was not altered by warfarin or propranolol, two highly protein-bound drugs, nor did ziprasidone alter the binding of these drugs in human plasma. Thus, the potential for drug interactions with ziprasidone due to displacement is unlikely.

4.6 Fertility, pregnancy and lactation

Reproductive toxicity studies have shown undesirable effects on the reproductive process, at doses associated with maternal toxicity and/or sedation. There was no evidence of teratogenicity (see section 5.3).

Pregnancy
No studies have been conducted in pregnant women. As human experience is limited, administration of ziprasidone is not recommended during pregnancy unless the expected benefit to the mother outweighs the potential risk to the foetus.

Antipsychotic class labelling
Neonates exposed to antipsychotics (including ziprasidone) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully. Geodon should not be used during pregnancy unless clearly necessary. If discontinuation during pregnancy is necessary, it should not be done abruptly.

Breast-feeding
There are no adequate and well-controlled studies in lactating women. A single case report found that ziprasidone was detectable in breast milk. Patients should be advised not to breastfeed if they are receiving ziprasidone. If treatment is necessary, breast-feeding should be discontinued.

Fertility
There are no adequate and well-controlled studies in women and men exposed to ziprasidone.

Contraception - Women of childbearing potential receiving ziprasidone should be advised to use an appropriate method of contraception.

4.7 Effects on ability to drive and use machines

Ziprasidone may cause somnolence and may influence on the ability to drive and use machines. Patients likely to drive or operate machines should be cautioned appropriately.

4.8 Undesirable effects

Oral ziprasidone has been administered in clinical trials (see section 5.1) to approximately 6500 adult subjects. The most common adverse drug reactions in schizophrenia clinical trials were insomnia, somnolence, headache and agitation. In bipolar mania clinical trials, the most common adverse drug reactions were sedation, headache and somnolence.

The table below contains adverse drug reactions based on controlled schizophrenia and bipolar mania studies.

All adverse drug reactions are listed by class and frequency: *very common* (≥ 1/10); *common* (≥ 1/100 to < 1/10); *uncommon* (≥ 1/1,000 to < 1/100); *rare* (≥ 1/10,000 to < 1/1,000); *very rare (< 1/10,000);not known (cannot be estimated from the available data).*

The adverse reactions listed below may also be associated with the underlying disease and/or concomitant medications.

System Organ Class	**Very Common**	**Common ≥ 1/100 to <**	**Uncommon ≥ 1/1,000 to**	**Rare ≥ 1/10,000 to**	**Frequency not known (cannot be estimated from available**

	≥ 1/10	1/10	< 1/100	< 1/1,000	data)
Immune system disorders			Hypersensitivity	Anaphylactic reaction	
Infections and infestations		Rhinitis			
Blood and lymphatic system disorders				Lymphopenia, eosinophil count increased	
Endocrine disorders			Hyperprolactinaemia		
Metabolism and nutrition disorders			Increased appetite	Hypocalcaemia	
Psychiatric disorders	Insomnia	Mania, agitation, anxiety, restlessness	Panic attack, nightmare, nervousness, depressive symptom, libido decreased	Hypomania, bradyphrenia, anorgasmia, flat affect	
Nervous system disorders	Somnolence, headache	Dystonia, extrapyramidal disorder, parkinsonism, tardive dyskinesia, dyskinesia, hypertonia, akathisia, tremor, dizziness, sedation	Syncope, grand mal convulsion, ataxia, akinesia, restless legs syndrome, gait disturbance, drooling, paraesthesia, hypoaesthesia, dysarthria, disturbance in attention, hypersomnia, lethargy	Neuroleptic malignant syndrome, serotonin syndrome, facial droop, paresis,	
Eye disorders		Vision blurred, visual impairment	Oculogyric crisis, photophobia, dry eye	Amblyopia, eye pruritus	
Ear and labyrinth disorders			Vertigo, tinnitus, ear pain		
Cardiac disorders		Tachycardia	Palpitations	Torsade de pointes	
Vascular disorders		Hypertension	Hypertensive crisis, orthostatic hypotension, hypotension	Systolic hypertension, diastolic hypertension, labile blood pressure	Embolism venous
Respiratory, thoracic and mediastinal disorders			Throat tightness, dyspnoea, oropharyngeal pain	Laryngospasm, hiccups	
Gastrointestinal disorders		Vomiting, diarrhoea, nausea, constipation, salivary hypersecretion, dry mouth, dyspepsia	Dysphagia, gastritis, gastro-oesophageal reflux disease, abdominal discomfort, tongue disorder, flatulence	Loose stools	

Skin and subcutaneous tissue disorders		Rash	Urticaria, rash maculo-papular, acne, alopecia	Drug reaction with eosinophilia and systemic symptoms (DRESS), psoriasis, angioedema, dermatitis allergic, swelling face, erythema, rash papular, skin irritation	
Musculoskeletal and connective tissue disorders		Muscle rigidity	Torticollis, muscle spasms, pain in extremity, musculoskeletal discomfort, joint stiffness	Trismus	
Renal and urinary disorders			Urinary incontinence, dysuria	Urinary retention, enuresis	
Pregnancy, puerperium and perinatal conditions				Drug withdrawal syndrome neonatal	
Reproductive system and breast disorders		Male sexual dysfunction	Galactorrhoea, gynaecomastia, amenorrhea	Priapism, erection increased, Erectile dysfunction	
General disorders and administration site conditions		Pyrexia, pain, asthenia, fatigue	Chest discomfort, thirst	Feeling hot	
Investigations		Weight decreased, weight increased	Electrocardiogram QT prolonged, liver function test abnormal	Blood lactate dehydrogenase increased	

In short-term and long-term ziprasidone schizophrenia and bipolar mania clinical trials, the incidence of tonic clonic seizures and hypotension was uncommon, occurring in less than 1% of ziprasidone treated patients.

Ziprasidone causes a mild to moderate dose-related prolongation of the QT interval (see section 5.1). In schizophrenia clinical trials, an increase of 30 to 60 msec was seen in 12.3% (976/7941)of ECG tracings from ziprasidone-treated and 7.5% (73/975) ofECG tracings from placebo-treated patients. A prolongation of >60 msec was seen in 1.6% (128/7941)and 1.2% (12/975)of tracings from ziprasidone and placebo-treated patients, respectively. The incidence of QTc interval prolongation above 500 msec was 3 in a total of 3266 (0.1%)in ziprasidone treated patients and 1 in a total of 538 (0.2%)in placebo treated patients. Comparable findings were observed in bipolar mania clinical trials.
In long term maintenance treatment in schizophrenia clinical trials, prolactin levels in patients treated with ziprasidone were sometimes elevated, but, in most patients, returned to normal ranges without cessation of treatment. In addition, potential clinical manifestations
(e.g. gynaecomastia and breast enlargement) were rare.

Paediatricpopulation

In placebo-controlled bipolar disorder trials (ages 10-17 years), the most frequent adverse reactions (reported with a frequency>10%) were sedation, somnolence, headache, fatigue, nausea, dizziness, vomiting, decreased appetite and

extrapyramidal disorder. In a placebo-controlled schizophrenia trial (ages 13-17 years), the most frequent adverse reactions (reported with a frequency >10%) were somnolence and extrapyramidal disorder. The paediatric safety profile of ziprasidone was generally similar to the adult profile. However high incidence of sedation and somnolence was observed in paediatric studies.
Ziprasidone was associated with a similar mild to moderate dose-related prolongation of the QT interval in paediatric clinical trials similar to that seen in the adult population. Tonic clonic seizures and hypotension were not reported in the placebo-controlled paediatric bipolar clinical trials.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

Experience with ziprasidone in overdose is limited. The largest confirmed single ingestion of ziprasidone is 12,800 mg. In this case, extrapyramidal symptoms and a QTc interval of 446 msec (with no cardiac sequelae) were reported. In general, the most commonly reported symptoms following overdose are, extrapyramidal symptoms, somnolence, tremor and anxiety.

The possibility of obtundation, seizures or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. There is no specific antidote to ziprasidone.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group*:* Antipsychotic, indole derivatives, ATC code NO5A E04.

Ziprasidone has a high affinity for dopamine type 2 (D_2) receptors and substantially higher affinity for serotonin type 2_A ($5HT_{2A}$) receptors. Receptor blockade, 12 hours after a single dose of 40 mg, was greater than 80% for serotonin type 2_A and greater than 50% for D_2 using positron emission tomography (PET). Ziprasidone also interacts with serotonin $5HT_{2C}$, $5HT_{1D}$ and $5HT_{1A}$ receptors where its affinities for these sites are equal to or greater than its affinity for the D_2 receptor. Ziprasidone has moderate affinity for neuronal serotonin and norepinephrine transporters. Ziprasidone demonstrates moderate affinity for histamine H(1)- and alpha(1)-receptors. Ziprasidone demonstrates negligible affinity for muscarinic M(1)-receptors.

Ziprasidone has been shown to be an antagonist at both serotonin type 2_A ($5HT_{2A}$) and dopamine type 2 (D_2) receptors. It is proposed that the therapeutic activity is mediated, in part, through this combination of antagonist activities. Ziprasidone is also a potent antagonist at $5HT_{2C}$ and $5HT_{1D}$ receptors, a potent agonist at the $5HT_{1A}$ receptor and inhibits neuronal reuptake of norepinephrine and serotonin.

Further information on clinical trials

Schizophrenia
In a 52 week study, ziprasidone was effective in maintaining the clinical improvement during continuation therapy in patients who showed an initial treatment response: there was no clear evidence for a dose-response relationship amongst the ziprasidone groups. In this study, which included patients with both positive and negative symptoms, ziprasidone's efficacy was demonstrated in both positive and negative symptoms.

The incidence of body weight gain, reported as an adverse event in short term (4-6 week) schizophrenia studies was low and identical in ziprasidone-treated and placebo-treated patients (both 0.4%). In a one-year placebo-controlled study a median weight loss of 1-3 kg was observed in ziprasidone-treated patients compared to a 3 kg median loss in placebo-treated patients.

In a double-blind comparative schizophrenia study, metabolic parameters including weight and fasting levels of insulin, total cholesterol and triglycerides and an insulin resistance (IR) index were measured. In patients receiving ziprasidone no significant changes from baseline were observed in any of these metabolic parameters.

Results of a large post-marketing safety study

A randomised post-approval study of 18,239 schizophrenic patients with observational follow-up for 1 year was conducted to determine whether ziprasidone´s effect on the QTc interval is associated with an increased risk of non-suicide mortality. This study, which was conducted in naturalistic clinical practice settings, showed no difference in the rate of over-all non-suicide mortality between ziprasidone and olanzapine treatments (primary end-point). The study also showed no difference in secondary end-points of all-cause mortality, mortality due to suicide, mortality due to sudden death, however, a non-significant numerically higher incidence of cardiovascular mortality was observed in the ziprasidone group. A statistically significantly higher incidence of all-cause hospitalisation, mainly due to differences in the number of psychiatric hospitalisations, was also observed in the ziprasidone group.

Bipolar mania
The efficacy of ziprasidone in adults with mania was established in two placebo controlled, double blind, 3 week studies which compared ziprasidone with placebo and one double blind, 12 week study which compared ziprasidone to haloperidol and placebo. These studies included approximately 850 patients meeting DSM-IV criteria for bipolar I disorder with an acute manic or mixed episode, with or without psychotic features. The baseline presence of psychotic features in the studies was 49.7%, 34.7% or 34.9%. Efficacy was assessed using the Mania Rating Scale (MRS). The Clinical Global Impression-Severity (CGI-S) scale was either a co-primary or key secondary efficacy variable in these studies. Ziprasidone treatment (40-80 mg BID, mean daily dose 120 mg) resulted in statistically significantly greater improvement in both MRS and CGI-S scores at Last Visit (3 weeks) compared with placebo. In the 12 week study, haloperidol treatment (mean daily dose 16 mg) produced significantly greater reductions in MRS scores compared with ziprasidone (mean daily dose 121 mg). Ziprasidone demonstrated comparable efficacy to haloperidol in terms of the proportion of patients maintaining a response to treatment from week 3 to week 12.

The efficacy of ziprasidone in the treatment of Bipolar I Disorder in paediatric patients
(10 to 17 years of age) was evaluated in one four-week placebo-controlled trial (n=237) of inpatients or outpatients who met DSM-IV criteria for Bipolar I Disorder manic or mixed episodes with or without psychotic features and had a Y-MRS score ≥17 at baseline. This double-blind, placebo-controlled trial compared flexibly-dosed oral ziprasidone (80-160 mg/day (40-80 mg BID) in two divided doses for patients weighing ³45 kg; 40-80 mg/day (20-40 mg BID) for patients weighing <45 kg) to placebo. Ziprasidone was administered as a single dose of 20 mg on the first day, then titrated over 1-2 weeks, in two daily doses, to a target range of 120-160 mg/day for patients weighing ³45 kg, or 60-80 mg/day for patients weighing <45 kg. Asymmetric dosing, with morning doses 20 mg or 40 mg less than evening doses, was permitted. Ziprasidone was superior to placebo in change from baseline to week 4 on the Y-MRS total score. In this clinical trial, the mean daily doses administered were 119 mg and 69 mg in the patients weighing ³45 kg and <45 kg, respectively.

There are no long-term clinical studies in adult patients investigating the efficacy of ziprasidone in the prevention of recurrence of manic/depressive symptoms.

Paediatric Studies

Bipolar Mania
Ziprasidone has been evaluated for safety in 237 paediatric patients (age 10 to 17 years) who participated in multiple-dose, clinical trials in bipolar mania; a total of 31 paediatric patients with Bipolar I Disorder were dosed with oral ziprasidone for at least 180 days.

In a 4-week trial in paediatric patients (10-17 years) with bipolar mania, there were no differences between ziprasidone and placebo patients in the mean change from baseline in body weight fasting glucose, total cholesterol, LDL cholesterol, or triglyceride levels.

The efficacy of ziprasidone in the treatment of Bipolar I Disorder was evaluated in a post marketing study in paediatric patients (n = 171 [safety population]; n = 168 [ITT population]) who met DSM-5 criteria for Bipolar I Disorder (manic or mixed) at baseline. The study compared flexibly-dosed oral ziprasidone (80-160 mg/day [40-80 mg BID] for patients weighing ≥45 kg; 40-80 mg/day [20-40 mg BID] for patients weighing <45 kg) to placebo over a 4-week period. The study demonstrated that ziprasidone was superior to placebo in change from baseline to week 4 on the Y-MRS total score. The study did not observe any relevant differences between ziprasidone and placebo patients in the mean change from baseline in body weight fasting glucose, total cholesterol, LDL cholesterol, or triglyceride levels.

There are no long-term double-blind clinical studies investigating the efficacy and tolerability of ziprasidone in children and adolescents.

There are no long-term clinical studies in paediatric patients investigating the efficacy of ziprasidone in the prevention of recurrence of manic/depressive symptoms.

Schizophrenia
The paediatric schizophrenia program was a short-term, 6-week, placebo-controlled trial (A1281134), followed by a 26-week open-label extension study (A1281135) that was designed to provide information on the efficacy, safety and tolerability of oral ziprasidone (40-80 mg BID with meals) during its long-term administration in adolescent subjects aged 13 to 17 years (inclusive) with schizophrenia. The Geodon paediatric study in schizophrenia was terminated by Pfizer due to lack of efficacy (see section 4.2).

5.2 Pharmacokinetic properties

Absorption
Following oral administration of multiple doses of ziprasidone with food, peak serum concentrations typically occur 6 to 8 hours post-dose. The absolute bioavailability of a 20 mg dose is 60% in the fed state. Pharmacokinetic studies have demonstrated that the bioavailability of ziprasidone is increased by up to 100% in the presence of food. It is therefore recommended that ziprasidone should be taken with food.

Distribution
The volume of distribution is approximately 1.1 L/kg. Ziprasidone is more than 99% protein bound in serum.

Biotransformation and elimination
The mean terminal half-life of ziprasidone after oral administration is 6.6 hours. Steady state is reached within 1-3 days. Mean clearance of ziprasidone administered intravenously is 5 ml/min/kg. Approximately 20% of the dose is excreted in urine, and approximately 66% is eliminated in faeces.

Ziprasidone demonstrates linear kinetics over the therapeutic dose range of 40 to 80 mg twice daily in fed subjects.

Ziprasidone is extensively metabolised after oral administration with only a small amount excreted in urine (<1%) or faeces (<4%) as unchanged ziprasidone. Ziprasidone is primarily cleared via three proposed metabolic routes to yield four major circulating metabolites, benzisothiazole piperazine (BITP) sulphoxide, BITP sulphone, ziprasidone sulphoxide and S-methyldihydroziprasidone. Unchanged ziprasidone represents about 44% of total drug-related material in serum.

Ziprasidone is primarily metabolised by two pathways: reduction and methylation to generate S-methyldihydroziprasidone which accounts for approximately two-thirds of the metabolism, and oxidative metabolism accounting for the other third. *In vitro* studies using human liver subcellular fractions indicate that S-methyldihydroziprasidone is generated in two steps. These studies indicate that the first step is mediated primarily by chemical reduction by glutathione as well as by enzymatic reduction by aldehyde oxidase. The second step is methylation mediated by thiol methyltransferase. *In vitro* studies indicate that CYP3A4 is the major cytochrome P450 catalysing the oxidative metabolism of ziprasidone with a potential minor contribution of CYP1A2.

Ziprasidone, S-methyldihydroziprasidone, and ziprasidone sulphoxide, when tested *in vitro*, share properties which may predict a QTc-prolonging effect. S-methyldihydroziprasidone is mainly eliminated in faeces by biliary excretion with a minor contribution by CYP3A4 catalysed metabolism. Ziprasidone sulphoxide is eliminated through renal excretion and by secondary metabolism catalysed by CYP3A4.

Special populations
Pharmacokinetic screening of patients has not revealed any significant pharmacokinetic differences between smokers and non-smokers.

No clinically significant age- or gender-differences in the pharmacokinetics of ziprasidone has been observed. The pharmacokinetics of ziprasidone in paediatric patients 10 to17 years of age were similar to those in adults after correcting for the differences in body weights.

Consistent with the fact that renal clearance contributes very little to its overall clearance, no progressive increases in ziprasidone exposure were noted when ziprasidone was administered to subjects with varying degrees of renal function. Exposures in subjects with mild (creatinine clearance 30-60 ml/min), moderate (creatinine clearance 10-29 ml/min) and severe impairment (requiring dialysis) were 146%, 87% and 75% those of healthy subjects (creatinine clearance >70 ml/min) following oral administration of 20 mg BID for seven days. It is unknown whether serum concentrations of the metabolites are increased in these patients.

In mild to moderate impairment of liver function (Child Pugh A or B) caused by cirrhoses, the serum concentrations after oral administration were 30% higher and the terminal half-life was about 2 hours longer than in normal patients. The effect of liver impairment on the serum concentrations of the metabolites is unknown.

5.3 Preclinical safety data

Preclinical safety data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity and carcinogenic potential. In reproductive studies in rats and rabbits, ziprasidone has shown no evidence of teratogenicity. Undesirable effects on fertility and decreased pup weights were observed at doses causing maternal toxicity such as decreased body weight gain. Increased perinatal mortality and delayed functional development of offspring occurred at maternal plasma concentrations extrapolated to be similar to the maximal concentrations in humans given therapeutic doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Contents:
Lactose monohydrate
Pregelatinised maize starch
Magnesium stearate.

Capsule shell:
Gelatin
Titanium dioxide (E171)
Sodium laurilsulfate (sodium dodecylsulfate)
Indigotin (E132, only in 20 mg, 40 mg, 80 mg capsules)

Printing ink:
Shellac
Propylene glycol (E1520)
Ammonium hydroxide (E527)
Potassium hydroxide (E525)
Black iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

Blister
Ziprasidone capsules are presented in aluminium PVC/PVA blisters with aluminium foil lids, in cartons containing 14, 20, 30, 50, 56, 60 or 100 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Upjohn EESV
Rivium Westlaan 142
2909 LD Capelle aan den IJssel
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA23055/015/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 10 June 1998
Date of last renewal: 01 August 2010

10 DATE OF REVISION OF THE TEXT

January 2023