Summary of Product Characteristics

Index

Amisulpride

EMC

Amisulpride 100mg Tablets

Summary of Product Characteristics Updated 17-Feb-2025 | Rivopharm UK Ltd

1. Name of the medicinal product

Amisulpride 100 mg tablets

2. Qualitative and quantitative composition

Each tablet contains:

100 mg amisulpride

Excpient:

50 mg lactose monohydrate

For the full list of excipients, see Section 6.1.

3. Pharmaceutical form

Tablet.

Amisulpride 100 mg tablets are white and round with break line on one side and embossed with A100 on the other side.

The tablets can be divided into equal halves.

4. Clinical particulars

4.1 Therapeutic indications

Amisulpride is indicated for the treatment of acute and chronic schizophrenic disorders, in which positive symptoms (such as delusions, hallucinations, thought disorders) and/or negative symptoms (such as blunted affect, emotional and social withdrawal) are prominent, including patients characterised by predominant negative symptoms.

4.2 Posology and method of administration

Posology

For acute psychotic episodes, oral doses between 400 mg/day and 800 mg/day are recommended.

In individual cases, the daily dose may be increased up to 1200 mg/day. Doses above 1200 mg/day have not been extensively evaluated for safety and therefore should not be used. No specific titration is required when initiating the treatment with Amisulpride. Doses should be adjusted according to individual response.

For patients with mixed positive and negative symptoms, doses should be adjusted to obtain optimal control of positive symptoms.

Maintenance treatment should be established individually with the minimally effective dose.

For patients characterised by predominant negative symptoms, oral doses between 50 mg/day and 300 mg/day are recommended. Doses should be adjusted individually.

Amisulpride can be administered once daily at oral doses up to 300 mg, higher doses should be administered bid.

The minimum effective dose should be used.

Elderly: The safety of amisulpride has been examined in a limited number of elderly patients. Amisulpride should be used with particular caution because of a possible risk of hypotension and sedation. Reduction in dosage may also be required because of renal insufficiency.

Children: The efficacy and safety of amisulpride from puberty to the age of 18 years have not been established. There are limited data available on the use of amisulpride in adolescents in schizophrenia. Therefore, the use of amisulpride from puberty to the age of 18 years is not recommended; in children up to puberty amisulpride is contraindicated, as its safety has not yet been established (see section 4.3 contraindications).

Renal insufficiency: Amisulpride is eliminated by the renal route. In renal insufficiency, the dose should be reduced to half in patients with creatinine clearance (CR_{CL}) between 30-60 ml/min and to a third in patients with CR_{CL} between 10-30 ml/min.

As there is no experience in patients with severe renal impairment (CR_{CL} < 10 ml/min) particular care is recommended in these patients (see section 4.4 special warnings and special precautions for use).

Hepatic insufficiency: since the drug is weakly metabolised a dosage reduction should not be necessary.

Method of administration

Oral

4.3 Contraindications

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

Concomitant prolactin-dependent tumours (e.g. pituitary gland prolactinomas and breast cancer) (see section 4.4 and section 4.8).

Phaeochromocytoma.

Children up to puberty.

Combination with levodopa (see section 4.5 Interactions with other medicinal products and other forms of interactions).

4.4 Special warnings and precautions for use

As with other neuroleptics, Neuroleptic Malignant Syndrome, a potentially fatal complication, characterized by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated CPK, may occur. In the event of hyperthermia, particularly with high daily doses, all antipsychotic drugs, including Amisulpride should be discontinued.

Hyperglycaemia has been reported in patients treated with some atypical antipsychotic agents, including amisulpride, therefore patients with an established diagnosis of diabetes mellitus or with risk factors for diabetes who are started on amisulpride, should get appropriate glycemic monitoring.

Amisulpride is eliminated by the renal route. In cases of renal insufficiency, the dose should be decreased or intermittent treatment could be considered (see section 4.2 Posology and method of administration).

Severe liver toxicity has been reported with Amisulpride use. Patients should be instructed to report immediately signs such as asthenia, anorexia, nausea, vomiting, abdominal pain or icterus to a physician. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately (see section 4.8)

Amisulpride may lower the seizure threshold. Therefore patients with a history of epilepsy should be closely monitored during Amisulpride therapy.

In elderly patients, Amisulpride, like other neuroleptics, should be used with particular caution because of a possible risk of hypotension and sedation. Reduction in dosage may also be required because of renal insufficiency.

As with other antidopaminergic agents, caution should be also exercised when prescribing Amisulpride to patients with Parkinson's disease since it may cause worsening of the disease.

Amisulpride should be used only if neuroleptic treatment cannot be avoided.

Prolongation of the QT interval.

Caution should be exercised when Amisulpride is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and concomitant use with neuroleptics should be avoided.

Stroke:

In randomized clinical trials versus placebo performed in a population of elderly patients with dementia and treated with certain atypical antipsychotic drugs, a 3-fold increase of the risk of cerebrovascular events has been observed. The mechanism of such risk increase is not known. An increase in the risk with other antipsychotic drugs, or other populations of patients cannot be excluded. Amisulpride should be used with caution in patients with stroke risk factors.

Withdrawal symptoms including nausea, vomiting and insomnia have very rarely been described after abrupt cessation of high therapeutic doses of antipsychotic drugs. Recurrence of psychotic symptoms may also occur, and the emergence of involuntary movement disorders (such as akathisia, dystonia and dyskinsia) has been reported with amisulpride. Therefore, gradual withdrawal of amisulpride is advisable.

Leukopenia, neutropenia and agranulocytosis have been reported with antipsychotics, including amisulpride. Unexplained infections or fever may be evidence of blood dyscrasia (see Section 4.8), and requires immediate haematological investigation.

Elderly patients with dementia:

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-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 trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death in clinical trials with atypical antipsychotics were varied, most of the deaths appeared to be either cardiovascular (e.g., hearth failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality.

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.

Amisulpride 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 Amisulpride and preventative measures undertaken.

Benign pituitary tumour:

Amisulpride may increase prolactin levels. Cases of benign pituitary tumours such as prolactinoma have been observed during amisulpride therapy. In case of very high levels of prolactin or clinical signs of pituitary tumour (such as visual field defect and headache), pituitary imaging should be performed. If the diagnosis of pituitary tumour is confirmed, the treatment with amisulpride must be stopped.

Breast cancer:

Amisulpride may increase prolactin levels. Therefore, caution should be exercised and patients with a history or a family history of breast cancer should be closely monitored during Amisulpride therapy.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption should not take this medicine

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

4.5 Interaction with other medicinal products and other forms of interaction

CONTRAINDICATED COMBINATIONS

Levodopa: reciprocal antagonism of effects between levodopa and neuroleptics.

COMBINATIONS NOT RECOMMENDED

Amisulpride may enhance the central effects of alcohol.

COMBINATIONS TO BE TAKEN INTO ACCOUNT

CNS depressants including narcotics, anaesthetics, analgesics, sedative H1 antihistamines, barbiturates, benzodiazepines and other anxiolytics, clonidine and derivatives.

Antihypertensive drugs and other hypotensive medications.

Co-administration of amisulpride and clozapine may lead to an increase in plasma levels of amisulpride.

Caution is advised when prescribing amisulpride with medicines known to prolong the QT interval, e.g., class IA antiarrythmics (e.g., quinidine, disopyramide) and class III antiarrhythmics (e.g. amiodarone, sotalol), some antihistaminics, some other antipsychotics and antimalarials (e.g., mefloquine) (see Section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are only limited data available from the use of amisulpride in pregnant women. The safety of amisulpride during human pregnancy has not been established.

Amisulpride crosses the placenta.

Studies in animals have shown reproductive toxicity (see section 5.3).

The use of amisulpride is not recommended during pregnancy and in women of childbearing potential not using effective contraception, unless the benefits justify the potential risks.

Neonates exposed to antipsychotics (including Amisulpride) 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 (see section 4.8). There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Breast feeding

Amisulpride is excreted into breastmilk in rather large amounts above the accepted value of 10% of the maternal weight-adjusted dosage in some cases, but blood concentrations in breastfed infants have not been evaluated. There is insufficient information on the effects of amisulpride in newborns/infants.

A decision must be made whether to discontinue breast-feeding or to abstain from amisulpride therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility

A decrease in fertility linked to the pharmacological effects of the drug (prolactin-mediated effect) was observed in treated animals.

4.7 Effects on ability to drive and use machines

Even when used as recommended, Amisulpride may cause somnolence and blurred vision so that the ability to drive vehicles or operate machinery can be impaired (see section 4.8 Undesirable Effects)

4.8 Undesirable effects

Adverse effects have been ranked under headings of frequency using the following convention (≥1/10); common (≥1/100; <1/10); uncommon (≥1/1,000;<1/100); rare (≥1/10,000;<1/1,000); very rare (<1/10,000), frequency not known (cannot be estimated from the available data).

● **Blood and lymphatic system disorders:**

Uncommon: leukopenia, neutropenia (see Section 4.4).

Rare: agranulocytosis.

● **Immune system disorders:**

Uncommon: allergic reaction

● **Endocrine disorders:**

Common: amisulpride causes an increase in plasma prolactin levels which is reversible after drug discontinuation. This may result in galactorrhoea, amenorrhoea, gynaecomastia, breast pain, and erectile dysfunction.

Rare: benign pituitary tumour such as prolactinoma (see Section 4.4).

● **Metabolism and nutrition disorders:**

Uncommon: hyperglycemia, hypertriglyceridemia and hypercholesterolemia.

Rare: hyponatraemia, syndrome of inappropriate antidiuretic hormone secretion (SIADH).

● Psychiatric disorders:

Common: insomnia, anxiety, agitation, orgasmic dysfunction.

Uncommon: confusion.

● **Nervous system disorders:**

Very common: extrapyramidal symptoms may occur: tremor, rigidity, hypokinesia, hypersalivation, akathisia, dyskinesia. These symptoms are generally mild at optimal dosages and partially reversible without discontinuation of amisulpride upon administration of antiparkinsonian medication. The incidence of extrapyramidal symptoms which is dose related, remains very low in the treatment of patients with predominantly negative symptoms with doses of 50-300 mg/day.

Common: acute dystonia (spasm torticollis, oculogyric crisis, trismus) may appear. This is reversible without discontinuation of amisulpride upon treatment with an antiparkinsonian agent. Somnolence.

Uncommon: tardive dyskinesia characterized by rhythmic, involuntary movements primarily of the tongue and/or face have been reported, usually after long term administration. Antiparkinsonian medication is ineffective or may induce aggravation of the symptoms.

Seizures.

Rare: Neuroleptic Malignant Syndrome (see Section 4.4), which is a potentially fatal complication.

Not known: restless legs syndrome.

● **Eye disorders:**

Common: blurred vision.

● **Cardiac disorders:**

Uncommon: bradycardia.

Rare: QT interval prolongation, ventricular arrhythmias such as torsade de pointes, ventricular tachycardia, ventricular fibrillation, cardiac arrest, sudden death (see Section 4.4).

● **Vascular disorders:**

Common: hypotension.

Uncommon: increase in blood pressure.

Rare: venous thromboembolism, including pulmonary embolism, sometimes fatal, and deep vein thrombosis

● **Respiratory, thoracic and mediastinal disorders:**

Uncommon: nasal congestion, aspiration pneumonia (mainly in association with other antipsychotics and CNS depressants).

● **Gastrointestinal disorders:**

Common:constipation, nausea, vomiting, dry mouth.

● **Hepatobilary disorders:**

Uncommon: hepatocellular injury

● **Skin and subcutaneous tissue disorders:**

Rare: angioedema, urticaria.

Not known: photosensitivity reaction

● **Musculoskeletal and connective tissue disorders:**

Uncommon: osteopenia, osteoporosis.

● **Renal and urinary disorders:**

Uncommon: urinary retention

● **Pregnancy, puerperium and perinatal conditions**

Frequency not known: drug withdrawal syndrome neonatal (see Section 4.6)

● **Injury, poisoning and procedural complications**

Not Known: Fall as a consequence of adverse reactions compromising body balance

● **Investigations:**

Common: weight gain.

Uncommon: elevations of hepatic enzymes, mainly transaminases.

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 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

Experience with amisulpride in overdosage is limited. Exaggeration of the known pharmacological effects of the drug have been reported. These include drowsiness and sedation, coma, hypotension and extrapyramidal symptoms. Fatal outcomes have been reported mainly in combination with other psychotropic agents.

In cases of acute overdosage, the possibility of multiple drug intake should be considered.

Since Amisulpride is weakly dialysed, hemodialysis should not be used to eliminate the drug.

There is no specific antidote to Amisulpride.

Appropriate supportive measures should therefore be instituted with close supervision of vital functions including continuous cardiac monitoring due to the risk of prolongation of the QT interval.

If severe extrapyramidal symptoms occur, anticholinergic agents should be administered.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics, ATC Code N05A L05

Amisulpride binds selectively with a high affinity to human dopaminergic D_2/D_3 receptor subtypes whereas it is devoid of affinity for D_1, D_4 and D_5 receptor subtypes.

Unlike classical and atypical neuroleptics, amisulpride has no affinity for serotonin, α-adrenergic, histamine H1 and cholinergic receptors. In addition, amisulpride does not bind to sigma sites.

In animals, at high doses, amisulpride blocks post-synaptic D_2 receptors located in the limbic structures in preference to those in the striatum.

Unlike classical neuroleptics it does not induce catalepsy and hypersensitivity of D_2 dopamine receptors does not develop after repeated treatment. At low doses it preferentially blocks pre-synaptic D_2/D_3 receptors, producing dopamine release responsible for its disinhibitory effects.

This pharmacological profile explains the clinical efficacy of amisulpride against both negative and positive symptoms of schizophrenia.

5.2 Pharmacokinetic properties

In man, amisulpride shows two absorption peaks: one which is attained rapidly, one hour post-dose and a second between 3 and 4 hours after administration. Corresponding plasma concentrations are 39 ± 3 and 54 ± 4 ng/ml after a 50 mg dose.

The volume of distribution is 5.8 l/kg. As plasma protein binding is low (16%) drug interactions are unlikely.

Absolute bioavailability is 48%.

Amisulpride is weakly metabolised: two inactive metabolites, accounting for approximately 4% of the dose, have been identified. There is no accumulation of amisulpride and its pharmacokinetics remain unchanged after the administration of repeated doses. The elimination half-life of amisulpride is approximately 12 hours after an oral dose.

Amisulpride is eliminated unchanged in the urine. Fifty percent of an intravenous dose is excreted via the urine, of which 90% is eliminated in the first 24 hours. Renal clearance is in the order of 20 l/h or 330 ml/min.

A carbohydrate rich meal (containing 68% fluids) significantly decreases the AUC_s, Tmax and Cmax of amisulpride but no changes were seen after a high fat meal. However, the significance of these findings in routine clinical use is not known.

Hepatic insufficiency: Since the drug is weakly metabolised a dosage reduction should not be necessary in patients with hepatic insufficiency.

Renal insufficiency: The elimination half-life is unchanged in patients with renal insufficiency while systemic clearance is reduced by a factor of 2.5 to 3. The AUC of amisulpride in mild renal failure increased two fold and almost tenfold in moderate renal failure (see section 4.2 for dosing recommendations). Experience is however limited and there is no data with doses greater than 50 mg.

Amisulpride is very weakly dialysed.

Limited pharmacokinetic data in elderly subjects (> 65 years) show that a 10-30% rise occurs in Cmax, T1/2 and AUC after a single oral dose of 50 mg. No data are available after repeat dosing.

5.3 Preclinical safety data

An overall review of the completed safety studies indicates that amisulpride is devoid of any general, organ-specific, teratogenic, mutagenic or carcinogenic risk. Changes observed in rats and dogs at doses below the maximum tolerated dose are either pharmacological effects or are devoid of major toxicological significance under these conditions. Compared with the maximum recommended dosages in man, maximum tolerated doses are 2 and 7 times greater in the rat (200 mg/kg/day) and dog (120 mg/kg/day) respectively in terms of AUC. No carcinogenic risk, relevant to man, was identified in the rat at up to 1.5 - 4.5 times the expected human AUC.

A mouse carcinogenicity study (120 mg/kg/d) and reproductive studies (160, 300 and 500 mg/kg/d respectively in rat, rabbit and mouse) were performed. The exposure of the animals to amisulpride during these latter studies was not evaluated.

In animal trials amisulpride elicited an effect on foetal growth and development at doses corresponding to Human Equivalent Dose of 2000 mg/day and upwards for a 50-kg patient. There was no evidence for a teratogenic potential of amisulpride.

Studies on the impact of amisulpride on the behaviour of the offspring have not been conducted.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose monohydrate

Methylcellulose

Sodium starch glycolate (Type A)

Microcrystalline cellulose

Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

PVC/aluminium foil blister packs containing 60 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

Rivopharm UK Limited

100 Bishopsgate

London

EC2N 4AG

United Kingdom

8. Marketing authorisation number(s)

PL 33155/0087

9. Date of first authorisation/renewal of the authorisation

11/02/2025

10. Date of revision of the text

11/02/2025

Company Contact Details

Rivopharm UK Ltd

Address

Rivopharm UK Ltd, 100 Bishopsgate, London, EC2N 4AG

Telephone

+44 (0)207 864 1677

Medical Information e-mail

pv.sanoswiss@biomapas.com

WWW

https://www.rivopharm.co.uk

Medical Information Direct Line

+44 (0)2034328085

Stock Availability

+44 (0)7831 690 243

Aripiprazole

EMA

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 5 mg tablets
ABILIFY 10 mg tablets
ABILIFY 15 mg tablets
ABILIFY 30 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ABILIFY 5 mg tablets
Each tablet contains 5 mg of aripiprazole.
Excipient with known effect
63.65 mg lactose (as monohydrate) per tablet

ABILIFY 10 mg tablets
Each tablet contains 10 mg of aripiprazole.
Excipient with known effect
59.07 mg lactose (as monohydrate) per tablet

ABILIFY 15 mg tablets
Each tablet contains 15 mg of aripiprazole.
Excipient with known effect
54.15 mg lactose (as monohydrate) per tablet

ABILIFY 30 mg tablets
Each tablet contains 30 mg of aripiprazole.
Excipient with known effect
177.22 mg lactose (as monohydrate) per tablet

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

ABILIFY 5 mg tablets
Rectangular and blue, engraved with "A-007" and "5" on one side.

ABILIFY 10 mg tablets
Rectangular and pink, engraved with "A-008" and "10" on one side.

ABILIFY 15 mg tablets
Round and yellow, engraved with "A-009" and "15" on one side.

ABILIFY 30 mg tablets
Round and pink, engraved with "A-011" and "30" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ABILIFY is indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older.

ABILIFY is indicated for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment (see section 5.1).

ABILIFY is indicated for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older (see section 5.1).

4.2 Posology and method of administration

Posology

Adults

Schizophrenia: the recommended starting dose for ABILIFY is 10 mg/day or 15 mg/day with a maintenance dose of 15 mg/day administered on a once-a-day schedule without regard to meals. ABILIFY is effective in a dose range of 10 mg/day to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 15 mg has not been demonstrated although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Manic episodes in Bipolar I Disorder: the recommended starting dose for ABILIFY is 15 mg administered on a once-a-day schedule without regard to meals as monotherapy or combination therapy (see section 5.1). Some patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Recurrence prevention of manic episodes in Bipolar I Disorder: for preventing recurrence of manic episodes in patients, who have been receiving aripiprazole as monotherapy or combination therapy, continue therapy at the same dose. Adjustments of daily dosage, including dose reduction should be considered on the basis of clinical status.

Paediatric population

Schizophrenia in adolescents aged 15 years and older: the recommended dose for ABILIFY is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using ABILIFY oral solution 1 mg/mL) for 2 days, titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg. When appropriate, subsequent dose increases should be administered in 5 mg increments without exceeding the maximum daily dose of 30 mg (see section 5.1). ABILIFY is effective in a dose range of 10 mg/day to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated although individual patients may benefit from a higher dose.
ABILIFY is not recommended for use in patients with schizophrenia below 15 years of age due to insufficient data on safety and efficacy (see sections 4.8 and 5.1).

Manic episodes in Bipolar I Disorder in adolescents aged 13 years and older: the recommended dose for ABILIFY is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using ABILIFY oral solution 1 mg/mL) for 2 days, titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg. The treatment duration should be the minimum necessary for symptom control and must not exceed 12 weeks. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated, and a daily dose of 30 mg is associated with a substantially higher incidence of significant adverse reactions including EPS related events, somnolence, fatigue and weight gain (see section 4.8). Doses higher than 10 mg/day should therefore only be used in exceptional cases and with close clinical monitoring (see sections 4.4, 4.8 and 5.1). Younger patients are at increased risk of experiencing adverse events associated with aripiprazole. Therefore, ABILIFY is not recommended for use in patients below 13 years of age (see sections 4.8 and 5.1).

Irritability associated with autistic disorder: the safety and efficacy of ABILIFY in children and adolescents aged below 18 years have not yet been established. Currently available data are described

in section 5.1 but no recommendation on a posology can be made.

Tics associated with Tourette's disorder: the safety and efficacy of ABILIFY in children and adolescents 6 to 18 years of age have not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Special population

Hepatic impairment
No dosage adjustment is required for patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In these patients dosing should be managed cautiously. However, the maximum daily dose of 30 mg should be used with caution in patients with severe hepatic impairment (see section 5.2).

Renal impairment
No dosage adjustment is required in patients with renal impairment.

Elderly
The safety and efficacy of ABILIFY in the treatment of schizophrenia or manic episodes in Bipolar I Disorder in patients aged 65 years and older has not been established. Owing to the greater sensitivity of this population, a lower starting dose should be considered when clinical factors warrant (see section 4.4).

Gender
No dosage adjustment is required for female patients as compared to male patients (see section 5.2).

Smoking status
According to the metabolic pathway of aripiprazole no dosage adjustment is required for smokers (see section 4.5).

Dose adjustments due to interactions
When concomitant administration of strong CYP3A4 or CYP2D6 inhibitors with aripiprazole occurs, the aripiprazole dose should be reduced. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased (see section 4.5).
When concomitant administration of strong CYP3A4 inducers with aripiprazole occurs, the aripiprazole dose should be increased. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced to the recommended dose (see section 4.5).

Method of administration

ABILIFY is for oral use.

Orodispersible tablets or oral solution may be used as an alternative to ABILIFY tablets for patients who have difficulty swallowing ABILIFY tablets (see section 5.2).

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

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

Suicidality

The occurrence of suicidal behaviour is inherent in psychotic illnesses and mood disorders and in

some cases has been reported early after initiation or switch of antipsychotic treatment, including treatment with aripiprazole (see section 4.8). Close supervision of high-risk patients should accompany antipsychotic treatment.

Cardiovascular disorders

Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medicinal products) or hypertension, including accelerated or malignant. 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 aripiprazole and preventive measures undertaken.

QT prolongation

In clinical trials of aripiprazole, the incidence of QT prolongation was comparable to placebo. Aripiprazole should be used with caution in patients with a family history of QT prolongation (see section 4.8).

Tardive dyskinesia

In clinical trials of one year or less duration, there were uncommon reports of treatment emergent dyskinesia during treatment with aripiprazole. If signs and symptoms of tardive dyskinesia appear in a patient on aripiprazole, dose reduction or discontinuation should be considered (see section 4.8). These symptoms can temporally deteriorate or can even arise after discontinuation of treatment.

Other extrapyramidal symptoms

In paediatric clinical trials of aripiprazole akathisia and Parkinsonism were observed. If signs and symptoms of other EPS appear in a patient taking aripiprazole, dose reduction and close clinical monitoring should be considered.

Neuroleptic Malignant Syndrome (NMS)

NMS is a potentially fatal symptom complex associated with antipsychotics. In clinical trials, rare cases of NMS were reported during treatment with aripiprazole. 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. However, elevated creatine phosphokinase and rhabdomyolysis, not necessarily in association with NMS, have also been reported. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotics, including aripiprazole, must be discontinued.

Seizure

In clinical trials, uncommon cases of seizure were reported during treatment with aripiprazole. Therefore, aripiprazole should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures (see section 4.8).

Elderly patients with dementia-related psychosis

Increased mortality
In three placebo-controlled trials (n = 938; mean age: 82.4 years; range: 56 to 99 years) of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease, patients treated with

aripiprazole were at increased risk of death compared to placebo. The rate of death in aripiprazole-treated patients was 3.5 % compared to 1.7 % in the placebo group. Although the causes of deaths were varied, most of the deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia) in nature (see section 4.8).

Cerebrovascular adverse reactions
In the same trials, cerebrovascular adverse reactions (e.g. stroke, transient ischaemic attack), including fatalities, were reported in patients (mean age: 84 years; range: 78 to 88 years). Overall, 1.3 % of aripiprazole-treated patients reported cerebrovascular adverse reactions compared with 0.6 % of placebo-treated patients in these trials. This difference was not statistically significant. However, in one of these trials, a fixed-dose trial, there was a significant dose response relationship for cerebrovascular adverse reactions in patients treated with aripiprazole (see section 4.8).

Aripiprazole is not indicated for the treatment of patients with dementia-related psychosis.

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including aripiprazole. Risk factors that may predispose patients to severe complications include obesity and family history of diabetes. In clinical trials with aripiprazole, there were no significant differences in the incidence rates of hyperglycaemia-related adverse reactions (including diabetes) or in abnormal glycaemia laboratory values compared to placebo. Precise risk estimates for hyperglycaemia-related adverse reactions in patients treated with aripiprazole and with other atypical antipsychotics are not available to allow direct comparisons. Patients treated with any antipsychotics, including aripiprazole, 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 (see section 4.8).

Hypersensitivity

Hypersensitivity reactions, characterised by allergic symptoms, may occur with aripiprazole (see section 4.8).

Weight gain

Weight gain is commonly seen in schizophrenic and bipolar mania patients due to co-morbidities, use of antipsychotics known to cause weight gain, poorly managed life-style, and might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed aripiprazole. When seen, it is usually in those with significant risk factors such as history of diabetes, thyroid disorder or pituitary adenoma. In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain in adults (see section 5.1). In clinical trials of adolescent patients with bipolar mania, aripiprazole has been shown to be associated with weight gain after 4 weeks of treatment. Weight gain should be monitored in adolescent patients with bipolar mania. If weight gain is clinically significant, dose reduction should be considered (see section 4.8).

Dysphagia

Oesophageal dysmotility and aspiration have been associated with the use of antipsychotics, including aripiprazole. Aripiprazole should be used cautiously in patients at risk for aspiration pneumonia.

Pathological gambling and other impulse control disorders

Patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other urges, reported, include: increased sexual urges, compulsive shopping, binge or compulsive eating, and other impulsive and compulsive behaviours. It is important for prescribers to ask patients or their caregivers specifically about the development of new or

increased gambling urges, sexual urges, compulsive shopping, binge or compulsive eating, or other urges while being treated with aripiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder; however, in some cases, urges were reported to have stopped when the dose was reduced or the medication was discontinued. Impulse control disorders may result in harm to the patient and others if not recognised. Consider dose reduction or stopping the medication if a patient develops such urges while taking aripiprazole (see section 4.8).

Lactose

ABILIFY tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Patients with attention deficit hyperactivity disorder (ADHD) comorbidity

Despite the high comorbidity frequency of Bipolar I Disorder and ADHD, very limited safety data are available on concomitant use of aripiprazole and stimulants; therefore, extreme caution should be taken when these medicinal products are co-administered.

Falls

Aripiprazole may cause somnolence, postural hypotension, motor and sensory instability, 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).

4.5 Interaction with other medicinal products and other forms of interaction

Due to its α_1-adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive medicinal products.

Given the primary CNS effects of aripiprazole, caution should be used when aripiprazole is administered in combination with alcohol or other CNS medicinal products with overlapping adverse reactions such as sedation (see section 4.8).

If aripiprazole is administered concomitantly with medicinal products known to cause QT prolongation or electrolyte imbalance, caution should be used.

Potential for other medicinal products to affect aripiprazole

A gastric acid blocker, the H_2 antagonist famotidine, reduces aripiprazole rate of absorption but this effect is deemed not clinically relevant. Aripiprazole is metabolised by multiple pathways involving the CYP2D6 and CYP3A4 enzymes but not CYP1A enzymes. Thus, no dosage adjustment is required for smokers.

Quinidine and other CYP2D6 inhibitors
In a clinical trial in healthy subjects, a strong inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107 %, while C_{max} was unchanged. The AUC and C_{max} of dehydro-aripiprazole, the active metabolite, decreased by 32 % and 47 %, respectively. Aripiprazole dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of aripiprazole with quinidine occurs. Other strong inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be expected to have similar effects and similar dose reductions should therefore be applied.

Ketoconazole and other CYP3A4 inhibitors
In a clinical trial in healthy subjects, a strong inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and C_{max} by 63 % and 37 %, respectively. The AUC and C_{max} of dehydro-aripiprazole increased by 77 % and 43 %, respectively. In CYP2D6 poor metabolisers, concomitant use of strong inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolizers. When considering concomitant administration of

ketoconazole or other strong CYP3A4 inhibitors with aripiprazole, potential benefits should outweigh the potential risks to the patient. When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole dose should be reduced to approximately one-half of its prescribed dose. Other strong inhibitors of CYP3A4, such as itraconazole and HIV protease inhibitors may be expected to have similar effects and similar dose reductions should therefore be applied (see section 4.2). Upon discontinuation of the CYP2D6 or CYP3A4 inhibitor, the dosage of aripiprazole should be increased to the level prior to the initiation of the concomitant therapy. When weak inhibitors of CYP3A4 (e.g. diltiazem) or CYP2D6 (e.g. escitalopram) are used concomitantly with aripiprazole, modest increases in plasma aripiprazole concentrations may be expected.

Carbamazepine and other CYP3A4 inducers
Following concomitant administration of carbamazepine, a strong inducer of CYP3A4, and oral aripiprazole to patients with schizophrenia or schizoaffective disorder, the geometric means of C_{max} and AUC for aripiprazole were 68 % and 73 % lower, respectively, compared to when aripiprazole (30 mg) was administered alone. Similarly, for dehydro-aripiprazole the geometric means of C_{max} and AUC after carbamazepine co-administration were 69 % and 71 % lower, respectively, than those following treatment with aripiprazole alone. Aripiprazole dose should be doubled when concomitant administration of aripiprazole occurs with carbamazepine. Concomitant administration of aripiprazole and other inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) may be expected to have similar effects and similar dose increases should therefore be applied. Upon discontinuation of strong CYP3A4 inducers, the dosage of aripiprazole should be reduced to the recommended dose.

Valproate and lithium
When either valproate or lithium was administered concomitantly with aripiprazole, there was no clinically significant change in aripiprazole concentrations and therefore no dose adjustment is necessary when either valproate or lithium is administered with aripiprazole.

Potential for aripiprazole to affect other medicinal products

In clinical studies, 10 mg/day to 30 mg/day doses of aripiprazole had no significant effect on the metabolism of substrates of CYP2D6 (dextromethorphan/3-methoxymorphinan ratio), CYP2C9 (warfarin), CYP2C19 (omeprazole), and CYP3A4 (dextromethorphan). Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro*. Thus, aripiprazole is unlikely to cause clinically important medicinal product interactions mediated by these enzymes.

When aripiprazole was administered concomitantly with either valproate, lithium or lamotrigine, there was no clinically important change in valproate, lithium or lamotrigine concentrations.

Serotonin syndrome
Cases of serotonin syndrome have been reported in patients taking aripiprazole, and possible signs and symptoms for this condition can occur especially in cases of concomitant use with other serotonergic medicinal products, such as selective serotonin reuptake inhibitor/selective serotonin noradrenaline reuptake inhibitor (SSRI/SNRI), or with medicinal products that are known to increase aripiprazole concentrations (see section 4.8).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled trials of aripiprazole in pregnant women. Congenital anomalies have been reported; however, causal relationship with aripiprazole could not be established. Animal studies could not exclude potential developmental toxicity (see section 5.3). Patients must be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole. Due to insufficient safety information in humans and concerns raised by animal reproductive studies, this medicinal product should not be used in pregnancy unless the

expected benefit clearly justifies the potential risk to the foetus.

Newborn infants exposed to antipsychotics (including aripiprazole) 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, newborn infants should be monitored carefully (see section 4.8).

Breast-feeding

Aripiprazole/metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from aripiprazole therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Aripiprazole did not impair fertility based on data from reproductive toxicity studies.

4.7 Effects on ability to drive and use machines

Aripiprazole has minor to moderate influence on the ability to drive and use machines due to potential nervous system and visual effects, such as sedation, somnolence, syncope, vision blurred, diplopia (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in placebo-controlled trials were akathisia and nausea each occurring in more than 3 % of patients treated with oral aripiprazole.

Tabulated list of adverse reactions

The incidences of the Adverse Drug Reactions (ADRs) associated with aripiprazole therapy are tabulated below. The table is based on adverse events reported during clinical trials and/or post-marketing use.

All ADRs are listed by system organ 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) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports. Consequently, the frequency of these adverse events is qualified as "not known".

	Common	**Uncommon**	**Not known**
Blood and lymphatic system disorders			Leukopenia Neutropenia Thrombocytopenia
Immune system disorders			Allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus allergic, or urticaria)

	Common	Uncommon	Not known
Endocrine disorders		Hyperprolactinaemia Blood prolactin decreased	Diabetic hyperosmolar coma Diabetic ketoacidosis
Metabolism and nutrition disorders	Diabetes mellitus	Hyperglycaemia	Hyponatremia Anorexia
Psychiatric disorders	Insomnia Anxiety Restlessness	Depression Hypersexuality	Suicide attempt, suicidal ideation and completed suicide (see section 4.4) Pathological gambling Impulse-control disorder Binge eating Compulsive shopping Poriomania Aggression Agitation Nervousness
Nervous system disorders	Akathisia Extrapyramidal disorder Tremor Headache Sedation Somnolence Dizziness	Tardive dyskinesia Dystonia Restless legs syndrome	Neuroleptic Malignant Syndrome Grand mal convulsion Serotonin syndrome Speech disorder
Eye disorders	Vision blurred	Diplopia Photophobia	Oculogyric crisis
Cardiac disorders		Tachycardia	Sudden death unexplained Torsades de pointes Ventricular arrhythmia Cardiac arrest Bradycardia
Vascular disorders		Orthostatic hypotension	Venous thromboembolism (including pulmonary embolism and deep vein thrombosis) Hypertension Syncope
Respiratory, thoracic and mediastinal disorders		Hiccups	Aspiration pneumonia Laryngospasm Oropharyngeal spasm
Gastrointestinal disorders	Constipation Dyspepsia Nausea Salivary hypersecretion Vomiting		Pancreatitis Dysphagia Diarrhoea Abdominal discomfort Stomach discomfort
Hepatobiliary disorders			Hepatic failure Hepatitis Jaundice
Skin and subcutaneous tissue disorders			Rash Photosensitivity reaction Alopecia Hyperhidrosis Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

	Common	Uncommon	Not known
Musculoskeletal and connective tissue disorders			Rhabdomyolysis Myalgia Stiffness
Renal and urinary disorders			Urinary incontinence Urinary retention
Pregnancy, puerperium and perinatal conditions			Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders			Priapism
General disorders and administration site conditions	Fatigue		Temperature regulation disorder (e.g. hypothermia, pyrexia) Chest pain Peripheral oedema
Investigations			Weight decreased Weight gain Alanine Aminotransferase increased Aspartate Aminotransferase increased Gamma-glutamyltransferase increased Alkaline phosphatase increased QT prolonged Blood glucose increased Glycosylated haemoglobin increased Blood glucose fluctuation Creatine phosphokinase increased

Description of selected adverse reactions

Adults

Extrapyramidal symptoms (EPS)
Schizophrenia: in a long-term 52-week controlled trial, aripiprazole-treated patients had an overall-lower incidence (25.8 %) of EPS including Parkinsonism, akathisia, dystonia and dyskinesia compared with those treated with haloperidol (57.3 %). In a long-term 26-week placebo-controlled trial, the incidence of EPS was 19 % for aripiprazole-treated patients and 13.1 % for placebo-treated patients. In another long-term 26-week controlled trial, the incidence of EPS was 14.8 % for aripiprazole-treated patients and 15.1 % for olanzapine-treated patients.

Manic episodes in Bipolar I Disorder: in a 12-week controlled trial, the incidence of EPS was 23.5 % for aripiprazole-treated patients and 53.3 % for haloperidol-treated patients. In another 12-week trial, the incidence of EPS was 26.6 % for patients treated with aripiprazole and 17.6 % for those treated with lithium. In the long-term 26-week maintenance phase of a placebo-controlled trial, the incidence of EPS was 18.2 % for aripiprazole-treated patients and 15.7 % for placebo-treated patients.

Akathisia
In placebo-controlled trials, the incidence of akathisia in bipolar patients was 12.1 % with aripiprazole and 3.2 % with placebo. In schizophrenia patients the incidence of akathisia was 6.2 % with aripiprazole and 3.0 % with placebo.

Dystonia
Class effect: 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. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high 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.

Prolactin
In clinical trials for the approved indications and post-marketing, both increase and decrease in serum prolactin as compared to baseline was observed with aripiprazole (section 5.1).

Laboratory parameters
Comparisons between aripiprazole and placebo in the proportions of patients experiencing potentially clinically significant changes in routine laboratory and lipid parameters (see section 5.1) revealed no medically important differences. Elevations of CPK (Creatine Phosphokinase), generally transient and asymptomatic, were observed in 3.5 % of aripiprazole treated patients as compared to 2.0 % of patients who received placebo.

Paediatric population

Schizophrenia in adolescents aged 15 years and older
In a short-term placebo-controlled clinical trial involving 302 adolescents (13 to 17 years) with schizophrenia, the frequency and type of adverse reactions were similar to those in adults except for the following reactions that were reported more frequently in adolescents receiving aripiprazole than in adults receiving aripiprazole (and more frequently than placebo):
Somnolence/sedation and extrapyramidal disorder were reported very commonly (≥ 1/10), and dry mouth, increased appetite, and orthostatic hypotension were reported commonly (≥ 1/100, < 1/10).
The safety profile in a 26-week open-label extension trial was similar to that observed in the short-term, placebo-controlled trial.
The safety profile of a long-term, double-blind, placebo-controlled trial was also similar except for the following reactions that were reported more frequently than paediatric patients taking placebo: weight decreased, blood insulin increased, arrhythmia, and leukopenia were reported commonly (≥ 1/100, < 1/10).

In the pooled adolescent schizophrenia population (13 to 17 years) with exposure up to 2 years, incidence of low serum prolactin levels in females (< 3 ng/mL) and males (< 2 ng/mL) was 29.5 % and 48.3 %, respectively. In the adolescent (13 to 17 years) schizophrenia population with aripiprazole exposure of 5 mg to 30 mg up to 72 months, incidence of low serum prolactin levels in females (< 3 ng/mL) and males (< 2 ng/mL) was 25.6 % and 45.0 %, respectively.
In two long-term trials with adolescent (13 to 17 years) schizophrenia and bipolar patients treated with aripiprazole, incidence of low serum prolactin levels in females (< 3 ng/mL) and males (< 2 ng/mL) was 37.0 % and 59.4 %, respectively.

Manic episodes in Bipolar I Disorder in adolescents aged 13 years and older
The frequency and type of adverse reactions in adolescents with Bipolar I Disorder were similar to those in adults except for the following reactions: very commonly (≥ 1/10) somnolence (23.0 %), extrapyramidal disorder (18.4 %), akathisia (16.0 %), and fatigue (11.8 %); and commonly (≥ 1/100, < 1/10) abdominal pain upper, heart rate increased, weight increased, increased appetite, muscle twitching, and dyskinesia.

The following adverse reactions had a possible dose response relationship; extrapyramidal disorder (incidences were 10 mg, 9.1 %; 30 mg, 28.8 %; placebo, 1.7 %); and akathisia (incidences were 10 mg, 12.1 %; 30 mg, 20.3 %; placebo, 1.7 %).

Mean changes in body weight in adolescents with Bipolar I Disorder at 12 and 30 weeks for aripiprazole were 2.4 kg and 5.8 kg, and for placebo 0.2 kg and 2.3 kg, respectively.

In the paediatric population somnolence and fatigue were observed more frequently in patients with bipolar disorder compared to patients with schizophrenia.

In the paediatric bipolar population (10 to 17 years) with exposure up to 30 weeks, incidence of low serum prolactin levels in females (< 3 ng/mL) and males (< 2 ng/mL) was 28.0 % and 53.3 %, respectively.

Pathological gambling and other impulse control disorders
Pathological gambling, hypersexuality, compulsive shopping and binge or compulsive eating can occur in patients treated with aripiprazole (see section 4.4).

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

In clinical trials and post-marketing experience, accidental or intentional acute overdose of aripiprazole alone was identified in adult patients with reported estimated doses up to 1,260 mg with no fatalities. The potentially medically important signs and symptoms observed included lethargy, increased blood pressure, somnolence, tachycardia, nausea, vomiting and diarrhoea. In addition, reports of accidental overdose with aripiprazole alone (up to 195 mg) in children have been received with no fatalities. The potentially medically serious signs and symptoms reported included somnolence, transient loss of consciousness and extrapyramidal symptoms.

Management of overdose

Management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. The possibility of multiple medicinal product involvement should be considered. Therefore cardiovascular monitoring should be started immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. Following any confirmed or suspected overdose with aripiprazole, close medical supervision and monitoring should continue until the patient recovers.

Activated charcoal (50 g), administered one hour after aripiprazole, decreased aripiprazole C_{max} by about 41 % and AUC by about 51 %, suggesting that charcoal may be effective in the treatment of overdose.

Haemodialysis

Although there is no information on the effect of haemodialysis in treating an overdose with aripiprazole, haemodialysis is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, other antipsychotics, ATC code: N05AX12

Mechanism of action

It has been proposed that aripiprazole's efficacy in schizophrenia and Bipolar I Disorder is mediated through a combination of partial agonism at dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonism of serotonin 5-HT_{2A} receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity. Aripiprazole exhibited high binding affinity *in vitro* for dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors and moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha-1 adrenergic and histamine H_1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

Aripiprazole doses ranging from 0.5 mg to 30 mg administered once a day to healthy subjects for 2 weeks produced a dose-dependent reduction in the binding of ^{11}C-raclopride, a D_2/D_3 receptor ligand, to the caudate and putamen detected by positron emission tomography.

Clinical efficacy and safety

Adults

Schizophrenia
In three short-term (4 to 6 weeks) placebo-controlled trials involving 1,228 schizophrenic adult patients, presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

Aripiprazole is effective in maintaining the clinical improvement during continuation therapy in adult patients who have shown an initial treatment response. In a haloperidol-controlled trial, the proportion of responder patients maintaining response to medicinal product at 52-weeks was similar in both groups (aripiprazole 77 % and haloperidol 73 %). The overall completion rate was significantly higher for patients on aripiprazole (43 %) than for haloperidol (30 %). Actual scores in rating scales used as secondary endpoints, including PANSS and the Montgomery-Åsberg Depression Rating Scale (MADRS) showed a significant improvement over haloperidol.

In a 26-week, placebo-controlled trial in adult stabilised patients with chronic schizophrenia, aripiprazole had significantly greater reduction in relapse rate, 34 % in aripiprazole group and 57 % in placebo.

Weight gain
In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain. In a 26-week, olanzapine-controlled, double-blind, multi-national study of schizophrenia which included 314 adult patients and where the primary endpoint was weight gain, significantly less patients had at least 7 % weight gain over baseline (i.e. a gain of at least 5.6 kg for a mean baseline weight of ~80.5 kg) on aripiprazole (n = 18, or 13 % of evaluable patients), compared to olanzapine (n = 45, or 33 % of evaluable patients).

Lipid parameters
In a pooled analysis on lipid parameters from placebo controlled clinical trials in adults, aripiprazole has not been shown to induce clinically relevant alterations in levels of total cholesterol, triglycerides, High Density Lipoprotein (HDL) and Low Density Lipoprotein (LDL).

Prolactin
Prolactin levels were evaluated in all trials of all doses of aripiprazole (n = 28,242). The incidence of hyperprolactinaemia or increased serum prolactin in patients treated with aripiprazole (0.3 %) was similar to that of placebo (0.2 %). For patients receiving aripiprazole, the median time to onset was 42 days and median duration was 34 days.

The incidence of hypoprolactinaemia or decreased serum prolactin in patients treated with aripiprazole was 0.4 %, compared with 0.02 % for patients treated with placebo. For patients receiving aripiprazole, the median time to onset was 30 days and median duration was 194 days.

Manic episodes in Bipolar I Disorder
In two 3-week, flexible-dose, placebo-controlled monotherapy trials involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole demonstrated superior efficacy to placebo in reduction of manic symptoms over 3 weeks. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

In one 3-week, fixed-dose, placebo-controlled monotherapy trial involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole failed to demonstrate superior efficacy to placebo.

In two 12-week, placebo- and active-controlled monotherapy trials in patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, aripiprazole demonstrated superior efficacy to placebo at week 3 and a maintenance of effect comparable to lithium or haloperidol at week 12. Aripiprazole also demonstrated a comparable proportion of patients in symptomatic remission from mania as lithium or haloperidol at week 12.

In a 6-week, placebo-controlled trial involving patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, who were partially non-responsive to lithium or valproate monotherapy for 2 weeks at therapeutic serum levels, the addition of aripiprazole as adjunctive therapy resulted in superior efficacy in reduction of manic symptoms than lithium or valproate monotherapy.

In a 26-week, placebo-controlled trial, followed by a 74-week extension, in manic patients who achieved remission on aripiprazole during a stabilization phase prior to randomisation, aripiprazole demonstrated superiority over placebo in preventing bipolar recurrence, primarily in preventing recurrence into mania but failed to demonstrate superiority over placebo in preventing recurrence into depression.

In a 52-week, placebo-controlled trial, in patients with a current manic or mixed episode of Bipolar I Disorder who achieved sustained remission (Young Mania Rating Scale [YMRS] and MADRS with total scores ≤ 12) on aripiprazole (10 mg/day to 30 mg/day) adjunctive to lithium or valproate for 12 consecutive weeks, adjunctive aripiprazole demonstrated superiority over placebo with a 46 % decreased risk (hazard ratio of 0.54) in preventing bipolar recurrence and a 65 % decreased risk (hazard ratio of 0.35) in preventing recurrence into mania over adjunctive placebo but failed to demonstrate superiority over placebo in preventing recurrence into depression. Adjunctive aripiprazole demonstrated superiority over placebo on the secondary outcome measure in Clinical Global Impression - Bipolar version (CGI-BP) Severity of Illness (SOI; mania) scores. In this trial, patients were assigned by investigators with either open-label lithium or valproate monotherapy to determine partial non-response. Patients were stabilised for at least 12 consecutive weeks with the combination of aripiprazole and the same mood stabilizer. Stabilized patients were then randomised to continue the same mood stabilizer with double-blind aripiprazole or placebo. Four mood stabilizer subgroups were assessed in the randomised phase: aripiprazole + lithium; aripiprazole + valproate; placebo + lithium; placebo + valproate. The Kaplan-Meier rates for recurrence to any mood episode for the adjunctive treatment arm were 16 % in aripiprazole + lithium and 18 % in aripiprazole + valproate compared to 45 % in placebo + lithium and 19 % in placebo + valproate.

Paediatric population

Schizophrenia in adolescents
In a 6-week placebo-controlled trial involving 302 schizophrenic adolescent patients (13 to 17 years), presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo. In a sub-analysis of the adolescent patients between the ages of 15 to 17 years, representing 74 % of the total enrolled population, maintenance of effect was observed over the 26-week open-label extension trial.

In a 60- to 89-week, randomised, double-blind, placebo-controlled trial in adolescent subjects (n = 146; ages 13 to 17 years) with schizophrenia, there was a statistically significant difference in the rate of relapse of psychotic symptoms between the aripiprazole (19.39 %) and placebo (37.50 %) groups. The point estimate of the hazard ratio (HR) was 0.461 (95 % confidence interval, 0.242 to 0.879) in the full population. In sub-group analyses the point estimate of the HR was 0.495 for subjects 13 to 14 years of age compared to 0.454 for subjects 15 to 17 years of age. However, the estimation of the HR for the younger (13 to 14 years) group was not precise, reflecting the smaller number of subjects in that group (aripiprazole, n = 29; placebo, n = 12), and the confidence interval for this estimation (ranging from 0.151 to 1.628) did not allow conclusions to be drawn on the presence of a treatment effect. In contrast the 95 % confidence interval for the HR in the older subgroup (aripiprazole, n = 69; placebo, n = 36) was 0.242 to 0.879 and hence a treatment effect could be concluded in the older patients.

Manic episodes in Bipolar I Disorder in children and adolescents
Aripiprazole was studied in a 30-week placebo-controlled trial involving 296 children and adolescents (10 to 17 years), who met DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders) for Bipolar I Disorder with manic or mixed episodes with or without psychotic features and had a YMRS score ≥ 20 at baseline. Among the patients included in the primary efficacy analysis, 139 patients had a current co-morbid diagnosis of ADHD.

Aripiprazole was superior to placebo in change from baseline at week 4 and at week 12 on the Y-MRS total score. In a post-hoc analysis, the improvement over placebo was more pronounced in the patients with associated co-morbidity of ADHD compared to the group without ADHD, where there was no difference from placebo. Recurrence prevention was not established.

The most common treatment-emergent adverse events among patients receiving 30 mg were extrapyramidal disorder (28.3 %), somnolence (27.3 %), headache (23.2 %), and nausea (14.1 %). Mean weight gain in the 30 weeks treatment-interval was 2.9 kg as compared to 0.98 kg in patients treated with placebo.

Irritability associated with autistic disorder in paediatric patients (see section 4.2)
Aripiprazole was studied in patients aged 6 to 17 years in two 8-week, placebo-controlled trials [one flexible-dose (2 mg/day to 15 mg/day) and one fixed-dose (5 mg/day, 10 mg/day, or 15 mg/day)] and in one 52-week open-label trial. Dosing in these trials was initiated at 2 mg/day, increased to 5 mg/day after one week, and increased by 5 mg/day in weekly increments to the target dose. Over 75 % of patients were less than 13 years of age. Aripiprazole demonstrated statistically superior efficacy compared to placebo on the Aberrant Behaviour Checklist Irritability subscale. However, the clinical relevance of this finding has not been established. The safety profile included weight gain and changes in prolactin levels. The duration of the long-term safety study was limited to 52 weeks. In the pooled trials, the incidence of low serum prolactin levels in females (< 3 ng/mL) and males (< 2 ng/mL) in aripiprazole-treated patients was 27/46 (58.7 %) and 258/298 (86.6 %), respectively. In the placebo-controlled trials, the mean weight gain was 0.4 kg for placebo and 1.6 kg for aripiprazole.

Aripiprazole was also studied in a placebo-controlled, long-term maintenance trial. After a 13 to 26-week stabilisation on aripiprazole (2 mg/day to 15 mg/day) patients with a stable response were either maintained on aripiprazole or substituted to placebo for further 16 weeks. Kaplan-Meier relapse rates at week 16 were 35 % for aripiprazole and 52 % for placebo; the hazard ratio for relapse within 16 weeks (aripiprazole/placebo) was 0.57 (non-statistically significant difference). The mean weight gain over the stabilisation phase (up to 26 weeks) on aripiprazole was 3.2 kg, and a further mean increase of 2.2 kg for aripiprazole as compared to 0.6 kg for placebo was observed in the second phase (16 weeks) of the trial. Extrapyramidal symptoms were mainly reported during the stabilisation phase in 17 % of patients, with tremor accounting for 6.5 %.

Tics associated with Tourette's disorder in paediatric patients (see section 4.2)
The efficacy of aripiprazole was studied in paediatric subjects with Tourette's disorder (aripiprazole: n = 99, placebo: n = 44) in a randomised, double-blind, placebo-controlled, 8 week study using a fixed

dose weight-based treatment group design over the dose range of 5 mg/day to 20 mg/day and a starting dose of 2 mg. Patients were 7 to 17 years of age and presented an average score of 30 on Total Tic Score on the Yale Global Tic Severity Scale (TTS-YGTSS) at baseline. Aripiprazole showed an improvement on TTS-YGTSS change from baseline to week 8 of 13.35, for the low dose group (5 mg or 10 mg) and 16.94 for the high dose group (10 mg or 20 mg) as compared with an improvement of 7.09 in the placebo group.

The efficacy of aripiprazole in paediatric subjects with Tourette's syndrome (aripiprazole: n = 32, placebo: n = 29) was also evaluated over a flexible dose range of 2 mg/day to 20 mg/day and a starting dose of 2 mg, in a 10 week, randomised, double blind, placebo-controlled study conducted in South-Korea. Patients were 6 to 18 years and presented an average score of 29 on TTS-YGTSS at baseline. Aripiprazole group showed an improvement of 14.97 on TTS-YGTSS change from baseline to week 10 as compared with an improvement of 9.62 in the placebo group.

In both of these short-term trials, the clinical relevance of the efficacy findings has not been established, considering the magnitude of treatment effect compared to the large placebo effect and the unclear effects regarding psycho-social functioning. No long-term data are available with regard to the efficacy and the safety of aripiprazole in this fluctuating disorder.

The European Medicines Agency has deferred the obligation to submit the results of studies with ABILIFY in one or more subsets of the paediatric population in the treatment of schizophrenia and in the treatment of bipolar affective disorder (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3 to 5 hours after dosing. Aripiprazole undergoes minimal pre-systemic metabolism. The absolute oral bioavailability of the tablet formulation is 87 %. There is no effect of a high fat meal on the pharmacokinetics of aripiprazole.

Distribution

Aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4.9 L/kg, indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and dehydro-aripiprazole are greater than 99 % bound to serum proteins, binding primarily to albumin.

Biotransformation

Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicinal product moiety in systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40 % of aripiprazole AUC in plasma.

Elimination

The mean elimination half-lives for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6.

The total body clearance of aripiprazole is 0.7 mL/min/kg, which is primarily hepatic.

Following a single oral dose of [^{14}C]-labelled aripiprazole, approximately 27 % of the administered radioactivity was recovered in the urine and approximately 60 % in the faeces. Less than 1 % of unchanged aripiprazole was excreted in the urine and approximately 18 % was recovered unchanged

in the faeces.

Paediatric population

The pharmacokinetics of aripiprazole and dehydro-aripiprazole in paediatric patients 10 to 17 years of age were similar to those in adults after correcting for the differences in body weights.

Pharmacokinetics in special patient groups

Elderly
There are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects, nor is there any detectable effect of age in a population pharmacokinetic analysis in schizophrenic patients.

Gender
There are no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects nor is there any detectable effect of gender in a population pharmacokinetic analysis in schizophrenic patients.

Smoking
Population pharmacokinetic evaluation has revealed no evidence of clinically significant effects from smoking on the pharmacokinetics of aripiprazole.

Race
Population pharmacokinetic evaluation showed no evidence of race-related differences on the pharmacokinetics of aripiprazole.

Renal impairment
The pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to young healthy subjects.

Hepatic impairment
A single-dose study in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C) did not reveal a significant effect of hepatic impairment on the pharmacokinetics of aripiprazole and dehydro-aripiprazole, but the study included only 3 patients with Class C liver cirrhosis, which is insufficient to draw conclusions on their metabolic capacity.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Toxicologically significant effects were observed only at doses or exposures that were sufficiently in excess of the maximum human dose or exposure, indicating that these effects were limited or of no relevance to clinical use. These included: dose-dependent adrenocortical toxicity (lipofuscin pigment accumulation and/or parenchymal cell loss) in rats after 104 weeks at 20 mg/kg/day to 60 mg/kg/day (3 to 10 times the mean steady-state AUC at the maximum recommended human dose) and increased adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas in female rats at 60 mg/kg/day (10 times the mean steady-state AUC at the maximum recommended human dose). The highest nontumorigenic exposure in female rats was 7 times the human exposure at the recommended dose.

An additional finding was cholelithiasis as a consequence of precipitation of sulphate conjugates of hydroxy metabolites of aripiprazole in the bile of monkeys after repeated oral dosing at 25 mg/kg/day to 125 mg/kg/day (1 to 3 times the mean steady-state AUC at the maximum recommended clinical dose or 16 to 81 times the maximum recommended human dose based on mg/m^2). However, the

concentrations of the sulphate conjugates of hydroxy aripiprazole in human bile at the highest dose proposed, 30 mg per day, were no more than 6 % of the bile concentrations found in the monkeys in the 39-week study and are well below (6 %) their limits of *in vitro* solubility.

In repeat-dose studies in juvenile rats and dogs, the toxicity profile of aripiprazole was comparable to that observed in adult animals, and there was no evidence of neurotoxicity or adverse reactions on development.

Based on results of a full range of standard genotoxicity tests, aripiprazole was considered non-genotoxic. Aripiprazole did not impair fertility in reproductive toxicity studies. Developmental toxicity, including dose-dependent delayed foetal ossification and possible teratogenic effects, were observed in rats at doses resulting in subtherapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures 3 and 11 times the mean steady-state AUC at the maximum recommended clinical dose. Maternal toxicity occurred at doses similar to those eliciting developmental toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Maize starch
Microcrystalline cellulose
Hydroxypropyl cellulose
Magnesium stearate

Tablet coat

ABILIFY 5 mg tablets
Indigo carmine aluminium lake (E 132)

ABILIFY 10 mg tablets
Red iron oxide (E 172)

ABILIFY 15 mg tablets
Yellow iron oxide (E 172)

ABILIFY 30 mg tablets
Red iron oxide (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Aluminium perforated unit dose blisters in cartons of 14 × 1, 28 × 1, 49 × 1, 56 × 1, 98 × 1 tablets.

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

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

ABILIFY 5 mg tablets
EU/1/04/276/001 (5 mg, 14 × 1 tablets)
EU/1/04/276/002 (5 mg, 28 × 1 tablets)
EU/1/04/276/003 (5 mg, 49 × 1 tablets)
EU/1/04/276/004 (5 mg, 56 × 1 tablets)
EU/1/04/276/005 (5 mg, 98 × 1 tablets)

ABILIFY 10 mg tablets
EU/1/04/276/006 (10 mg, 14 × 1 tablets)
EU/1/04/276/007 (10 mg, 28 × 1 tablets)
EU/1/04/276/008 (10 mg, 49 × 1 tablets)
EU/1/04/276/009 (10 mg, 56 × 1 tablets)
EU/1/04/276/010 (10 mg, 98 × 1 tablets)

ABILIFY 15 mg tablets
EU/1/04/276/011 (15 mg, 14 × 1 tablets)
EU/1/04/276/012 (15 mg, 28 × 1 tablets)
EU/1/04/276/013 (15 mg, 49 × 1 tablets)
EU/1/04/276/014 (15 mg, 56 × 1 tablets)
EU/1/04/276/015 (15 mg, 98 × 1 tablets)

ABILIFY 30 mg tablets
EU/1/04/276/016 (30 mg, 14 × 1 tablets)
EU/1/04/276/017 (30 mg, 28 × 1 tablets)
EU/1/04/276/018 (30 mg, 49 × 1 tablets)
EU/1/04/276/019 (30 mg, 56 × 1 tablets)
EU/1/04/276/020 (30 mg, 98 × 1 tablets)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 June 2004
Date of latest renewal: 04 June 2009

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

ABILIFY 10 mg orodispersible tablets
ABILIFY 15 mg orodispersible tablets
ABILIFY 30 mg orodispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ABILIFY 10 mg orodispersible tablets
Each orodispersible tablet contains 10 mg of aripiprazole.
Excipient with known effect
2 mg aspartame (E 951) and 0.075 mg lactose per orodispersible tablet

ABILIFY 15 mg orodispersible tablets
Each orodispersible tablet contains 15 mg of aripiprazole.
Excipient with known effect
3 mg aspartame (E 951) and 0.1125 mg lactose per orodispersible tablet

ABILIFY 30 mg orodispersible tablets
Each orodispersible tablet contains 30 mg of aripiprazole.
Excipient with known effect
6 mg aspartame (E 951) and 0.225 mg lactose per orodispersible tablet

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablet

ABILIFY 10 mg orodispersible tablets
10 mg: Round and pink, marked with "A" over "640" on one side and "10" on the other.

ABILIFY 15 mg orodispersible tablets
15 mg: Round and yellow, marked with "A" over "641" on one side and "15" on the other.

ABILIFY 30 mg orodispersible tablets
30 mg: Round and pink, marked with "A" over "643" on one side and "30" on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ABILIFY is indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older.

ABILIFY is indicated for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment (see section 5.1).

ABILIFY is indicated for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older (see section 5.1).

4.2 Posology and method of administration

Posology

Adults

Schizophrenia: the recommended starting dose for ABILIFY is 10 mg/day or 15 mg/day with a maintenance dose of 15 mg/day administered on a once-a-day schedule without regard to meals. ABILIFY is effective in a dose range of 10 mg/day to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 15 mg has not been demonstrated although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Manic episodes in Bipolar I Disorder: the recommended starting dose for ABILIFY is 15 mg administered on a once-a-day schedule without regard to meals as monotherapy or combination therapy (see section 5.1). Some patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Recurrence prevention of manic episodes in Bipolar I Disorder: for preventing recurrence of manic episodes in patients, who have been receiving aripiprazole as monotherapy or combination therapy, continue therapy at the same dose. Adjustments of daily dosage, including dose reduction should be considered on the basis of clinical status.

Paediatric population

Schizophrenia in adolescents aged 15 years and older: the recommended dose for ABILIFY is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using ABILIFY oral solution 1 mg/mL) for 2 days, titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg. When appropriate, subsequent dose increases should be administered in 5 mg increments without exceeding the maximum daily dose of 30 mg (see section 5.1). ABILIFY is effective in a dose range of 10 mg/day to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated although individual patients may benefit from a higher dose.
ABILIFY is not recommended for use in patients with schizophrenia below 15 years of age due to insufficient data on safety and efficacy (see sections 4.8 and 5.1).

Manic episodes in Bipolar I Disorder in adolescents aged 13 years and older: the recommended dose for ABILIFY is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using ABILIFY oral solution 1 mg/mL) for 2 days, titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg. The treatment duration should be the minimum necessary for symptom control and must not exceed 12 weeks. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated, and a daily dose of 30 mg is associated with a substantially higher incidence of significant adverse reactions including EPS related events, somnolence, fatigue and weight gain (see section 4.8). Doses higher than 10 mg/day should therefore only be used in exceptional cases and with close clinical monitoring (see sections 4.4, 4.8 and 5.1). Younger patients are at increased risk of experiencing adverse events associated with aripiprazole. Therefore, ABILIFY is not recommended for use in patients below 13 years of age (see sections 4.8 and 5.1).

Irritability associated with autistic disorder: the safety and efficacy of ABILIFY in children and adolescents aged below 18 years have not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Tics associated with Tourette's disorder: the safety and efficacy of ABILIFY in children and adolescents 6 to 18 years of age have not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Special populations

Hepatic impairment

No dosage adjustment is required for patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In these patients dosing should be managed cautiously. However, the maximum daily dose of 30 mg should be used with caution in patients with severe hepatic impairment (see section 5.2).

Renal impairment
No dosage adjustment is required in patients with renal impairment.

Elderly
The safety and efficacy of ABILIFY in the treatment of schizophrenia or manic episodes in Bipolar I Disorder in patients aged 65 years and older has not been established. Owing to the greater sensitivity of this population, a lower starting dose should be considered when clinical factors warrant (see section 4.4).

Gender
No dosage adjustment is required for female patients as compared to male patients (see section 5.2).

Smoking status
According to the metabolic pathway of aripiprazole no dosage adjustment is required for smokers (see section 4.5).

Dose adjustments due to interactions
When concomitant administration of strong CYP3A4 or CYP2D6 inhibitors with aripiprazole occurs, the aripiprazole dose should be reduced. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased (see section 4.5).
When concomitant administration of strong CYP3A4 inducers with aripiprazole occurs, the aripiprazole dose should be increased. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced to the recommended dose (see section 4.5).

Method of administration

ABILIFY is for oral use.

The orodispersible tablet should be placed in the mouth on the tongue, where it will rapidly disperse in saliva. It can be taken with or without liquid. Removal of the intact orodispersible tablet from the mouth is difficult. Since the orodispersible tablet is fragile, it should be taken immediately on opening the blister. Alternatively, disperse the tablet in water and drink the resulting suspension.

Orodispersible tablets or oral solution may be used as an alternative to ABILIFY tablets for patients who have difficulty swallowing ABILIFY tablets (see section 5.2).

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

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

Suicidality

The occurrence of suicidal behaviour is inherent in psychotic illnesses and mood disorders and in some cases has been reported early after initiation or switch of antipsychotic treatment, including treatment with aripiprazole (see section 4.8). Close supervision of high-risk patients should accompany antipsychotic treatment.

Cardiovascular disorders

Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medicinal products) or hypertension, including accelerated or malignant. 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 aripiprazole and preventive measures undertaken.

QT prolongation

In clinical trials of aripiprazole, the incidence of QT prolongation was comparable to placebo. Aripiprazole should be used with caution in patients with a family history of QT prolongation (see section 4.8).

Tardive dyskinesia

In clinical trials of one year or less duration, there were uncommon reports of treatment emergent dyskinesia during treatment with aripiprazole. If signs and symptoms of tardive dyskinesia appear in a patient on aripiprazole, dose reduction or discontinuation should be considered (see section 4.8). These symptoms can temporally deteriorate or can even arise after discontinuation of treatment.

Other extrapyramidal symptoms

In paediatric clinical trials of aripiprazole akathisia and Parkinsonism were observed. If signs and symptoms of other EPS appear in a patient taking aripiprazole, dose reduction and close clinical monitoring should be considered.

Neuroleptic Malignant Syndrome (NMS)

NMS is a potentially fatal symptom complex associated with antipsychotics. In clinical trials, rare cases of NMS were reported during treatment with aripiprazole. 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. However, elevated creatine phosphokinase and rhabdomyolysis, not necessarily in association with NMS, have also been reported. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotics, including aripiprazole, must be discontinued.

Seizure

In clinical trials, uncommon cases of seizure were reported during treatment with aripiprazole. Therefore, aripiprazole should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures (see section 4.8).

Elderly patients with dementia-related psychosis

Increased mortality
In three placebo-controlled trials (n = 938; mean age: 82.4 years; range: 56 to 99 years) of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease, patients treated with aripiprazole were at increased risk of death compared to placebo. The rate of death in aripiprazole-treated patients was 3.5 % compared to 1.7 % in the placebo group. Although the causes of deaths were varied, most of the deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia) in nature (see section 4.8).

Cerebrovascular adverse reactions
In the same trials, cerebrovascular adverse reactions (e.g. stroke, transient ischaemic attack), including fatalities, were reported in patients (mean age: 84 years; range: 78 to 88 years). Overall, 1.3 % of aripiprazole-treated patients reported cerebrovascular adverse reactions compared with 0.6 % of placebo-treated patients in these trials. This difference was not statistically significant. However, in one of these trials, a fixed-dose trial, there was a significant dose response relationship for cerebrovascular adverse reactions in patients treated with aripiprazole (see section 4.8).

Aripiprazole is not indicated for the treatment of patients with dementia-related psychosis.

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including aripiprazole. Risk factors that may predispose patients to severe complications include obesity and family history of diabetes. In clinical trials with aripiprazole, there were no significant differences in the incidence rates of hyperglycaemia-related adverse reactions (including diabetes) or in abnormal glycaemia laboratory values compared to placebo. Precise risk estimates for hyperglycaemia-related adverse reactions in patients treated with aripiprazole and with other atypical antipsychotics are not available to allow direct comparisons. Patients treated with any antipsychotics, including aripiprazole, 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 (see section 4.8).

Hypersensitivity

Hypersensitivity reactions, characterised by allergic symptoms, may occur with aripiprazole (see section 4.8).

Weight gain

Weight gain is commonly seen in schizophrenic and bipolar mania patients due to co-morbidities, use of antipsychotics known to cause weight gain, poorly managed life-style, and might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed aripiprazole. When seen, it is usually in those with significant risk factors such as history of diabetes, thyroid disorder or pituitary adenoma. In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain in adults (see section 5.1). In clinical trials of adolescent patients with bipolar mania, aripiprazole has been shown to be associated with weight gain after 4 weeks of treatment. Weight gain should be monitored in adolescent patients with bipolar mania. If weight gain is clinically significant, dose reduction should be considered (see section 4.8).

Dysphagia

Oesophageal dysmotility and aspiration have been associated with the use of antipsychotics, including aripiprazole. Aripiprazole should be used cautiously in patients at risk for aspiration pneumonia.

Pathological gambling and other impulse control disorders

Patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other urges, reported, include: increased sexual urges, compulsive shopping, binge or compulsive eating, and other impulsive and compulsive behaviours. It is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, sexual urges, compulsive shopping, binge or compulsive eating, or other urges while being treated with aripiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder; however, in some cases, urges were reported to have stopped when the dose was reduced or the medication was discontinued. Impulse control disorders may result

in harm to the patient and others if not recognised. Consider dose reduction or stopping the medication if a patient develops such urges while taking aripiprazole (see section 4.8).

Aspartame

ABILIFY orodispersible tablets contain aspartame. Aspartame is a source of phenylalanine. It may be harmful for people with phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

Lactose

ABILIFY orodispersible tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

ABILIFY orodispersible tablets contain sodium. This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

Patients with attention deficit hyperactivity disorder (ADHD) comorbidity

Despite the high comorbidity frequency of Bipolar I Disorder and ADHD, very limited safety data are available on concomitant use of aripiprazole and stimulants; therefore, extreme caution should be taken when these medicinal products are co-administered.

Falls

Aripiprazole may cause somnolence, postural hypotension, motor and sensory instability, 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).

4.5 Interaction with other medicinal products and other forms of interaction

Due to its α_1-adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive medicinal products.

Given the primary CNS effects of aripiprazole, caution should be used when aripiprazole is administered in combination with alcohol or other CNS medicinal products with overlapping adverse reactions such as sedation (see section 4.8).

If aripiprazole is administered concomitantly with medicinal products known to cause QT prolongation or electrolyte imbalance, caution should be used.

Potential for other medicinal products to affect aripiprazole

A gastric acid blocker, the H_2 antagonist famotidine, reduces aripiprazole rate of absorption but this effect is deemed not clinically relevant. Aripiprazole is metabolised by multiple pathways involving the CYP2D6 and CYP3A4 enzymes but not CYP1A enzymes. Thus, no dosage adjustment is required for smokers.

Quinidine and other CYP2D6 inhibitors
In a clinical trial in healthy subjects, a strong inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107 %, while C_{max} was unchanged. The AUC and C_{max} of dehydro-aripiprazole, the active metabolite, decreased by 32 % and 47 %, respectively. Aripiprazole dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of aripiprazole with quinidine occurs. Other strong inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be

expected to have similar effects and similar dose reductions should therefore be applied.

Ketoconazole and other CYP3A4 inhibitors
In a clinical trial in healthy subjects, a strong inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and C_{max} by 63 % and 37 %, respectively. The AUC and C_{max} of dehydro-aripiprazole increased by 77 % and 43 %, respectively. In CYP2D6 poor metabolisers, concomitant use of strong inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolizers. When considering concomitant administration of ketoconazole or other strong CYP3A4 inhibitors with aripiprazole, potential benefits should outweigh the potential risks to the patient. When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole dose should be reduced to approximately one-half of its prescribed dose. Other strong inhibitors of CYP3A4, such as itraconazole and HIV protease inhibitors may be expected to have similar effects and similar dose reductions should therefore be applied (see section 4.2). Upon discontinuation of the CYP2D6 or CYP3A4 inhibitor, the dosage of aripiprazole should be increased to the level prior to the initiation of the concomitant therapy. When weak inhibitors of CYP3A4 (e.g. diltiazem) or CYP2D6 (e.g. escitalopram) are used concomitantly with aripiprazole, modest increases in plasma aripiprazole concentrations may be expected.

Carbamazepine and other CYP3A4 inducers
Following concomitant administration of carbamazepine, a strong inducer of CYP3A4, and oral aripiprazole to patients with schizophrenia or schizoaffective disorder, the geometric means of C_{max} and AUC for aripiprazole were 68 % and 73 % lower, respectively, compared to when aripiprazole (30 mg) was administered alone. Similarly, for dehydro-aripiprazole the geometric means of C_{max} and AUC after carbamazepine co-administration were 69 % and 71 % lower, respectively, than those following treatment with aripiprazole alone. Aripiprazole dose should be doubled when concomitant administration of aripiprazole occurs with carbamazepine. Concomitant administration of aripiprazole and other inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) may be expected to have similar effects and similar dose increases should therefore be applied. Upon discontinuation of strong CYP3A4 inducers, the dosage of aripiprazole should be reduced to the recommended dose.

Valproate and lithium
When either valproate or lithium was administered concomitantly with aripiprazole, there was no clinically significant change in aripiprazole concentrations and therefore no dose adjustment is necessary when either valproate or lithium is administered with aripiprazole.

Potential for aripiprazole to affect other medicinal products

In clinical studies, 10 mg/day to 30 mg/day doses of aripiprazole had no significant effect on the metabolism of substrates of CYP2D6 (dextromethorphan/3-methoxymorphinan ratio), CYP2C9 (warfarin), CYP2C19 (omeprazole), and CYP3A4 (dextromethorphan). Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro*. Thus, aripiprazole is unlikely to cause clinically important medicinal product interactions mediated by these enzymes.

When aripiprazole was administered concomitantly with either valproate, lithium or lamotrigine, there was no clinically important change in valproate, lithium or lamotrigine concentrations.

Serotonin syndrome
Cases of serotonin syndrome have been reported in patients taking aripiprazole, and possible signs and symptoms for this condition can occur especially in cases of concomitant use with other serotonergic medicinal products, such as selective serotonin reuptake inhibitor/selective serotonin noradrenaline reuptake inhibitor (SSRI/SNRI), or with medicinal products that are known to increase aripiprazole concentrations (see section 4.8).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled trials of aripiprazole in pregnant women. Congenital anomalies have been reported; however, causal relationship with aripiprazole could not be established. Animal studies could not exclude potential developmental toxicity (see section 5.3). Patients must be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole. Due to insufficient safety information in humans and concerns raised by animal reproductive studies, this medicinal product should not be used in pregnancy unless the expected benefit clearly justifies the potential risk to the foetus.

Newborn infants exposed to antipsychotics (including aripiprazole) 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, newborn infants should be monitored carefully (see section 4.8).

Breast-feeding

Aripiprazole/metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from aripiprazole therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Aripiprazole did not impair fertility based on data from reproductive toxicity studies.

4.7 Effects on ability to drive and use machines

Aripiprazole has minor to moderate influence on the ability to drive and use machines due to potential nervous system and visual effects, such as sedation, somnolence, syncope, vision blurred, diplopia (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in placebo-controlled trials were akathisia and nausea each occurring in more than 3 % of patients treated with oral aripiprazole.

Tabulated list of adverse reactions

The incidences of the Adverse Drug Reactions (ADRs) associated with aripiprazole therapy are tabulated below. The table is based on adverse events reported during clinical trials and/or post-marketing use.

All ADRs are listed by system organ 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) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports. Consequently, the frequency of these adverse events is qualified as "not known".

	Common	Uncommon	Not known
Blood and lymphatic system disorders			Leukopenia Neutropenia Thrombocytopenia
Immune system disorders			Allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus allergic, or urticaria)
Endocrine disorders		Hyperprolactinaemia Blood prolactin decreased	Diabetic hyperosmolar coma Diabetic ketoacidosis
Metabolism and nutrition disorders	Diabetes mellitus	Hyperglycaemia	Hyponatremia Anorexia
Psychiatric disorders	Insomnia Anxiety Restlessness	Depression Hypersexuality	Suicide attempt, suicidal ideation and completed suicide (see section 4.4) Pathological gambling Impulse-control disorder Binge eating Compulsive shopping Poriomania Aggression Agitation Nervousness
Nervous system disorders	Akathisia Extrapyramidal disorder Tremor Headache Sedation Somnolence Dizziness	Tardive dyskinesia Dystonia Restless legs syndrome	Neuroleptic Malignant Syndrome Grand mal convulsion Serotonin syndrome Speech disorder
Eye disorders	Vision blurred	Diplopia Photophobia	Oculogyric crisis
Cardiac disorders		Tachycardia	Sudden death unexplained Torsades de pointes Ventricular arrhythmia Cardiac arrest Bradycardia
Vascular disorders		Orthostatic hypotension	Venous thromboembolism (including pulmonary embolism and deep vein thrombosis) Hypertension Syncope
Respiratory, thoracic and mediastinal disorders		Hiccups	Aspiration pneumonia Laryngospasm Oropharyngeal spasm
Gastrointestinal disorders	Constipation Dyspepsia Nausea Salivary hypersecretion Vomiting		Pancreatitis Dysphagia Diarrhoea Abdominal discomfort Stomach discomfort

	Common	Uncommon	Not known
Hepatobiliary disorders			Hepatic failure Hepatitis Jaundice
Skin and subcutaneous tissue disorders			Rash Photosensitivity reaction Alopecia Hyperhidrosis Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders			Rhabdomyolysis Myalgia Stiffness
Renal and urinary disorders			Urinary incontinence Urinary retention
Pregnancy, puerperium and perinatal conditions			Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders			Priapism
General disorders and administration site conditions	Fatigue		Temperature regulation disorder (e.g. hypothermia, pyrexia) Chest pain Peripheral oedema
Investigations			Weight decreased Weight gain Alanine Aminotransferase increased Aspartate Aminotransferase increased Gamma-glutamyltransferase increased Alkaline phosphatase increased QT prolonged Blood glucose increased Glycosylated haemoglobin increased Blood glucose fluctuation Creatine phosphokinase increased

Description of selected adverse reactions

Adults

Extrapyramidal symptoms (EPS)
Schizophrenia: in a long-term 52-week controlled trial, aripiprazole-treated patients had an overall-lower incidence (25.8 %) of EPS including Parkinsonism, akathisia, dystonia and dyskinesia compared with those treated with haloperidol (57.3 %). In a long-term 26-week placebo-controlled trial, the incidence of EPS was 19 % for aripiprazole-treated patients and 13.1 % for placebo-treated patients. In another long-term 26-week controlled trial, the incidence of EPS was 14.8 % for aripiprazole-treated patients and 15.1 % for olanzapine-treated patients.

Manic episodes in Bipolar I Disorder: in a 12-week controlled trial, the incidence of EPS was 23.5 % for aripiprazole-treated patients and 53.3 % for haloperidol-treated patients. In another 12-week trial,

the incidence of EPS was 26.6 % for patients treated with aripiprazole and 17.6 % for those treated with lithium. In the long-term 26-week maintenance phase of a placebo-controlled trial, the incidence of EPS was 18.2 % for aripiprazole-treated patients and 15.7 % for placebo-treated patients.

Akathisia
In placebo-controlled trials, the incidence of akathisia in bipolar patients was 12.1 % with aripiprazole and 3.2 % with placebo. In schizophrenia patients the incidence of akathisia was 6.2 % with aripiprazole and 3.0 % with placebo.

Dystonia
Class effect: 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. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high 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.

Prolactin
In clinical trials for the approved indications and post-marketing, both increase and decrease in serum prolactin as compared to baseline was observed with aripiprazole (section 5.1).

Laboratory parameters
Comparisons between aripiprazole and placebo in the proportions of patients experiencing potentially clinically significant changes in routine laboratory and lipid parameters (see section 5.1) revealed no medically important differences. Elevations of CPK (Creatine Phosphokinase), generally transient and asymptomatic, were observed in 3.5 % of aripiprazole treated patients as compared to 2.0 % of patients who received placebo.

Paediatric population

Schizophrenia in adolescents aged 15 years and older
In a short-term placebo-controlled clinical trial involving 302 adolescents (13 to 17 years) with schizophrenia, the frequency and type of adverse reactions were similar to those in adults except for the following reactions that were reported more frequently in adolescents receiving aripiprazole than in adults receiving aripiprazole (and more frequently than placebo):
Somnolence/sedation and extrapyramidal disorder were reported very commonly (≥ 1/10), and dry mouth, increased appetite, and orthostatic hypotension were reported commonly (≥ 1/100, < 1/10).
The safety profile in a 26-week open-label extension trial was similar to that observed in the short-term, placebo-controlled trial.
The safety profile of a long-term, double-blind, placebo-controlled trial was also similar except for the following reactions that were reported more frequently than paediatric patients taking placebo: weight decreased, blood insulin increased, arrhythmia, and leukopenia were reported commonly (≥ 1/100, < 1/10).

In the pooled adolescent schizophrenia population (13 to 17 years) with exposure up to 2 years, incidence of low serum prolactin levels in females (< 3 ng/mL) and males (< 2 ng/mL) was 29.5 % and 48.3 %, respectively. In the adolescent (13 to 17 years) schizophrenia population with aripiprazole exposure of 5 mg to 30 mg up to 72 months, incidence of low serum prolactin levels in females (< 3 ng/mL) and males (< 2 ng/mL) was 25.6 % and 45.0 %, respectively.
In two long-term trials with adolescent (13 to 17 years) schizophrenia and bipolar patients treated with aripiprazole, incidence of low serum prolactin levels in females (< 3 ng/mL) and males (< 2 ng/mL) was 37.0 % and 59.4 %, respectively.

Manic episodes in Bipolar I Disorder in adolescents aged 13 years and older
The frequency and type of adverse reactions in adolescents with Bipolar I Disorder were similar to those in adults except for the following reactions: very commonly (≥ 1/10) somnolence (23.0 %),

extrapyramidal disorder (18.4 %), akathisia (16.0 %), and fatigue (11.8 %); and commonly (≥ 1/100, < 1/10) abdominal pain upper, heart rate increased, weight increased, increased appetite, muscle twitching, and dyskinesia.

The following adverse reactions had a possible dose response relationship; extrapyramidal disorder (incidences were 10 mg, 9.1 %; 30 mg, 28.8 %; placebo, 1.7 %); and akathisia (incidences were 10 mg, 12.1 %; 30 mg, 20.3 %; placebo, 1.7 %).

Mean changes in body weight in adolescents with Bipolar I Disorder at 12 and 30 weeks for aripiprazole were 2.4 kg and 5.8 kg, and for placebo 0.2 kg and 2.3 kg, respectively.

In the paediatric population somnolence and fatigue were observed more frequently in patients with bipolar disorder compared to patients with schizophrenia.

In the paediatric bipolar population (10 to 17 years) with exposure up to 30 weeks, incidence of low serum prolactin levels in females (< 3 ng/mL) and males (< 2 ng/mL) was 28.0 % and 53.3 %, respectively.

Pathological gambling and other impulse control disorders
Pathological gambling, hypersexuality, compulsive shopping and binge or compulsive eating can occur in patients treated with aripiprazole (see section 4.4).

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

In clinical trials and post-marketing experience, accidental or intentional acute overdose of aripiprazole alone was identified in adult patients with reported estimated doses up to 1,260 mg with no fatalities. The potentially medically important signs and symptoms observed included lethargy, increased blood pressure, somnolence, tachycardia, nausea, vomiting and diarrhoea. In addition, reports of accidental overdose with aripiprazole alone (up to 195 mg) in children have been received with no fatalities. The potentially medically serious signs and symptoms reported included somnolence, transient loss of consciousness and extrapyramidal symptoms.

Management of overdose

Management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. The possibility of multiple medicinal product involvement should be considered. Therefore cardiovascular monitoring should be started immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. Following any confirmed or suspected overdose with aripiprazole, close medical supervision and monitoring should continue until the patient recovers.

Activated charcoal (50 g), administered one hour after aripiprazole, decreased aripiprazole C_{max} by about 41 % and AUC by about 51 %, suggesting that charcoal may be effective in the treatment of overdose.

Haemodialysis

Although there is no information on the effect of haemodialysis in treating an overdose with aripiprazole, haemodialysis is unlikely to be useful in overdose management since aripiprazole is

highly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, other antipsychotics, ATC code: N05AX12

Mechanism of action

It has been proposed that aripiprazole's efficacy in schizophrenia and Bipolar I Disorder is mediated through a combination of partial agonism at dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonism of serotonin 5-HT_{2A} receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity. Aripiprazole exhibited high binding affinity *in vitro* for dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors and moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha-1 adrenergic and histamine H_1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

Aripiprazole doses ranging from 0.5 mg to 30 mg administered once a day to healthy subjects for 2 weeks produced a dose-dependent reduction in the binding of ^{11}C-raclopride, a D_2/D_3 receptor ligand, to the caudate and putamen detected by positron emission tomography.

Clinical efficacy and safety

Adults

Schizophrenia
In three short-term (4 to 6 weeks) placebo-controlled trials involving 1,228 schizophrenic adult patients, presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

Aripiprazole is effective in maintaining the clinical improvement during continuation therapy in adult patients who have shown an initial treatment response. In a haloperidol-controlled trial, the proportion of responder patients maintaining response to medicinal product at 52-weeks was similar in both groups (aripiprazole 77 % and haloperidol 73 %). The overall completion rate was significantly higher for patients on aripiprazole (43 %) than for haloperidol (30 %). Actual scores in rating scales used as secondary endpoints, including PANSS and the Montgomery-Åsberg Depression Rating Scale (MADRS) showed a significant improvement over haloperidol.

In a 26-week, placebo-controlled trial in adult stabilised patients with chronic schizophrenia, aripiprazole had significantly greater reduction in relapse rate, 34 % in aripiprazole group and 57 % in placebo.

Weight gain
In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain. In a 26-week, olanzapine-controlled, double-blind, multi-national study of schizophrenia which included 314 adult patients and where the primary endpoint was weight gain, significantly less patients had at least 7 % weight gain over baseline (i.e. a gain of at least 5.6 kg for a mean baseline weight of ~80.5 kg) on aripiprazole (n = 18, or 13 % of evaluable patients), compared to olanzapine (n = 45, or 33 % of evaluable patients).

Lipid parameters
In a pooled analysis on lipid parameters from placebo controlled clinical trials in adults, aripiprazole

has not been shown to induce clinically relevant alterations in levels of total cholesterol, triglycerides, High Density Lipoprotein (HDL) and Low Density Lipoprotein (LDL).

Prolactin
Prolactin levels were evaluated in all trials of all doses of aripiprazole (n = 28,242). The incidence of hyperprolactinaemia or increased serum prolactin in patients treated with aripiprazole (0.3 %) was similar to that of placebo (0.2 %). For patients receiving aripiprazole, the median time to onset was 42 days and median duration was 34 days.

The incidence of hypoprolactinaemia or decreased serum prolactin in patients treated with aripiprazole was 0.4 %, compared with 0.02 % for patients treated with placebo. For patients receiving aripiprazole, the median time to onset was 30 days and median duration was 194 days.

Manic episodes in Bipolar I Disorder
In two 3-week, flexible-dose, placebo-controlled monotherapy trials involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole demonstrated superior efficacy to placebo in reduction of manic symptoms over 3 weeks. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

In one 3-week, fixed-dose, placebo-controlled monotherapy trial involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole failed to demonstrate superior efficacy to placebo.

In two 12-week, placebo- and active-controlled monotherapy trials in patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, aripiprazole demonstrated superior efficacy to placebo at week 3 and a maintenance of effect comparable to lithium or haloperidol at week 12. Aripiprazole also demonstrated a comparable proportion of patients in symptomatic remission from mania as lithium or haloperidol at week 12.

In a 6-week, placebo-controlled trial involving patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, who were partially non-responsive to lithium or valproate monotherapy for 2 weeks at therapeutic serum levels, the addition of aripiprazole as adjunctive therapy resulted in superior efficacy in reduction of manic symptoms than lithium or valproate monotherapy.

In a 26-week, placebo-controlled trial, followed by a 74-week extension, in manic patients who achieved remission on aripiprazole during a stabilization phase prior to randomisation, aripiprazole demonstrated superiority over placebo in preventing bipolar recurrence, primarily in preventing recurrence into mania but failed to demonstrate superiority over placebo in preventing recurrence into depression.

In a 52-week, placebo-controlled trial, in patients with a current manic or mixed episode of Bipolar I Disorder who achieved sustained remission (Young Mania Rating Scale [YMRS] and MADRS with total scores ≤ 12) on aripiprazole (10 mg/day to 30 mg/day) adjunctive to lithium or valproate for 12 consecutive weeks, adjunctive aripiprazole demonstrated superiority over placebo with a 46 % decreased risk (hazard ratio of 0.54) in preventing bipolar recurrence and a 65 % decreased risk (hazard ratio of 0.35) in preventing recurrence into mania over adjunctive placebo but failed to demonstrate superiority over placebo in preventing recurrence into depression. Adjunctive aripiprazole demonstrated superiority over placebo on the secondary outcome measure in Clinical Global Impression - Bipolar version (CGI-BP) Severity of Illness (SOI; mania) scores. In this trial, patients were assigned by investigators with either open-label lithium or valproate monotherapy to determine partial non-response. Patients were stabilised for at least 12 consecutive weeks with the combination of aripiprazole and the same mood stabilizer. Stabilized patients were then randomised to continue the same mood stabilizer with double-blind aripiprazole or placebo. Four mood stabilizer subgroups were assessed in the randomised phase: aripiprazole + lithium; aripiprazole + valproate; placebo + lithium; placebo + valproate. The Kaplan-Meier rates for recurrence to any mood episode for the adjunctive treatment arm were 16 % in aripiprazole + lithium and 18 % in aripiprazole + valproate compared to 45 % in placebo + lithium and 19 % in placebo + valproate.

Paediatric population

Schizophrenia in adolescents
In a 6-week placebo-controlled trial involving 302 schizophrenic adolescent patients (13 to 17 years), presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo. In a sub-analysis of the adolescent patients between the ages of 15 to 17 years, representing 74 % of the total enrolled population, maintenance of effect was observed over the 26-week open-label extension trial.

In a 60- to 89-week, randomised, double-blind, placebo-controlled trial in adolescent subjects (n = 146; ages 13 to 17 years) with schizophrenia, there was a statistically significant difference in the rate of relapse of psychotic symptoms between the aripiprazole (19.39 %) and placebo (37.50 %) groups. The point estimate of the hazard ratio (HR) was 0.461 (95 % confidence interval, 0.242 to 0.879) in the full population. In subgroup analyses the point estimate of the HR was 0.495 for subjects 13 to 14 years of age compared to 0.454 for subjects 15 to 17 years of age. However, the estimation of the HR for the younger (13 to 14 years) group was not precise, reflecting the smaller number of subjects in that group (aripiprazole, n = 29; placebo, n = 12), and the confidence interval for this estimation (ranging from 0.151 to 1.628) did not allow conclusions to be drawn on the presence of a treatment effect. In contrast the 95 % confidence interval for the HR in the older subgroup (aripiprazole, n = 69; placebo, n = 36) was 0.242 to 0.879 and hence a treatment effect could be concluded in the older patients.

Manic episodes in Bipolar I Disorder in children and adolescents
Aripiprazole was studied in a 30-week placebo-controlled trial involving 296 children and adolescents (10 to 17 years), who met DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders) for Bipolar I Disorder with manic or mixed episodes with or without psychotic features and had a YMRS score ≥ 20 at baseline. Among the patients included in the primary efficacy analysis, 139 patients had a current co-morbid diagnosis of ADHD.

Aripiprazole was superior to placebo in change from baseline at week 4 and at week 12 on the Y-MRS total score. In a post-hoc analysis, the improvement over placebo was more pronounced in the patients with associated co-morbidity of ADHD compared to the group without ADHD, where there was no difference from placebo. Recurrence prevention was not established.

The most common treatment-emergent adverse events among patients receiving 30 mg were extrapyramidal disorder (28.3 %), somnolence (27.3 %), headache (23.2 %), and nausea (14.1 %). Mean weight gain in the 30 weeks treatment-interval was 2.9 kg as compared to 0.98 kg in patients treated with placebo.

Irritability associated with autistic disorder in paediatric patients (see section 4.2)
Aripiprazole was studied in patients aged 6 to 17 years in two 8-week, placebo-controlled trials [one flexible-dose (2 mg/day to 15 mg/day) and one fixed-dose (5 mg/day, 10 mg/day, or 15 mg/day)] and in one 52-week open-label trial. Dosing in these trials was initiated at 2 mg/day, increased to 5 mg/day after one week, and increased by 5 mg/day in weekly increments to the target dose. Over 75 % of patients were less than 13 years of age. Aripiprazole demonstrated statistically superior efficacy compared to placebo on the Aberrant Behaviour Checklist Irritability subscale. However, the clinical relevance of this finding has not been established. The safety profile included weight gain and changes in prolactin levels. The duration of the long-term safety study was limited to 52 weeks. In the pooled trials, the incidence of low serum prolactin levels in females (< 3 ng/mL) and males (< 2 ng/mL) in aripiprazole-treated patients was 27/46 (58.7 %) and 258/298 (86.6 %), respectively. In the placebo-controlled trials, the mean weight gain was 0.4 kg for placebo and 1.6 kg for aripiprazole.

Aripiprazole was also studied in a placebo-controlled, long-term maintenance trial. After a 13 to 26-week stabilisation on aripiprazole (2 mg/day to 15 mg/day) patients with a stable response were either maintained on aripiprazole or substituted to placebo for further 16 weeks. Kaplan-Meier relapse rates at week 16 were 35 % for aripiprazole and 52 % for placebo; the hazard ratio for relapse within

16 weeks (aripiprazole/placebo) was 0.57 (non-statistically significant difference). The mean weight gain over the stabilisation phase (up to 26 weeks) on aripiprazole was 3.2 kg, and a further mean increase of 2.2 kg for aripiprazole as compared to 0.6 kg for placebo was observed in the second phase (16 weeks) of the trial. Extrapyramidal symptoms were mainly reported during the stabilisation phase in 17 % of patients, with tremor accounting for 6.5 %.

Tics associated with Tourette's disorder in paediatric patients (see section 4.2)
The efficacy of aripiprazole was studied in paediatric subjects with Tourette's disorder (aripiprazole: n = 99, placebo: n = 44) in a randomised, double-blind, placebo controlled, 8 week study using a fixed dose weight-based treatment group design over the dose range of 5 mg/day to 20 mg/day and a starting dose of 2 mg. Patients were 7 to 17 years of age and presented an average score of 30 on Total Tic Score on the Yale Global Tic Severity Scale (TTS-YGTSS) at baseline. Aripiprazole showed an improvement on TTS-YGTSS change from baseline to week 8 of 13.35, for the low dose group (5 mg or 10 mg) and 16.94 for the high dose group (10 mg or 20 mg) as compared with an improvement of 7.09 in the placebo group.

The efficacy of aripiprazole in paediatric subjects with Tourette's syndrome (aripiprazole: n = 32, placebo: n = 29) was also evaluated over a flexible dose range of 2 mg/day to 20 mg/day and a starting dose of 2 mg, in a 10 week, randomised, double blind, placebo-controlled study conducted in South-Korea. Patients were 6 to 18 years and presented an average score of 29 on TTS-YGTSS at baseline. Aripiprazole group showed an improvement of 14.97 on TTS-YGTSS change from baseline to week 10 as compared with an improvement of 9.62 in the placebo group.

In both of these short-term trials, the clinical relevance of the efficacy findings has not been established, considering the magnitude of treatment effect compared to the large placebo effect and the unclear effects regarding psycho-social functioning. No long-term data are available with regard to the efficacy and the safety of aripiprazole in this fluctuating disorder.

The European Medicines Agency has deferred the obligation to submit the results of studies with ABILIFY in one or more subsets of the paediatric population in the treatment of schizophrenia and in the treatment of bipolar affective disorder (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3 to 5 hours after dosing. Aripiprazole undergoes minimal pre-systemic metabolism. The absolute oral bioavailability of the tablet formulation is 87 %. There is no effect of a high fat meal on the pharmacokinetics of aripiprazole.

Distribution

Aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4.9 L/kg, indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and dehydro-aripiprazole are greater than 99 % bound to serum proteins, binding primarily to albumin.

Biotransformation

Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicinal product moiety in systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40 % of aripiprazole AUC in plasma.

Elimination

The mean elimination half-lives for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6.

The total body clearance of aripiprazole is 0.7 mL/min/kg, which is primarily hepatic.

Following a single oral dose of [^{14}C]-labelled aripiprazole, approximately 27 % of the administered radioactivity was recovered in the urine and approximately 60 % in the faeces. Less than 1 % of unchanged aripiprazole was excreted in the urine and approximately 18 % was recovered unchanged in the faeces.

Paediatric population

The pharmacokinetics of aripiprazole and dehydro-aripiprazole in paediatric patients 10 to 17 years of age were similar to those in adults after correcting for the differences in body weights.

Pharmacokinetics in special patient groups

Elderly
There are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects, nor is there any detectable effect of age in a population pharmacokinetic analysis in schizophrenic patients.

Gender
There are no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects nor is there any detectable effect of gender in a population pharmacokinetic analysis in schizophrenic patients.

Smoking
Population pharmacokinetic evaluation has revealed no evidence of clinically significant effects from smoking on the pharmacokinetics of aripiprazole.

Race
Population pharmacokinetic evaluation showed no evidence of race-related differences on the pharmacokinetics of aripiprazole.

Renal impairment
The pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to young healthy subjects.

Hepatic impairment
A single-dose study in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C) did not reveal a significant effect of hepatic impairment on the pharmacokinetics of aripiprazole and dehydro-aripiprazole, but the study included only 3 patients with Class C liver cirrhosis, which is insufficient to draw conclusions on their metabolic capacity.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Toxicologically significant effects were observed only at doses or exposures that were sufficiently in excess of the maximum human dose or exposure, indicating that these effects were limited or of no relevance to clinical use. These included: dose-dependent adrenocortical toxicity (lipofuscin pigment accumulation and/or parenchymal cell loss) in rats after 104 weeks at 20 mg/kg/day to 60 mg/kg/day (3 to 10 times the mean steady-state AUC at the maximum recommended human dose) and increased

adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas in female rats at 60 mg/kg/day (10 times the mean steady-state AUC at the maximum recommended human dose). The highest nontumorigenic exposure in female rats was 7 times the human exposure at the recommended dose.

An additional finding was cholelithiasis as a consequence of precipitation of sulphate conjugates of hydroxy metabolites of aripiprazole in the bile of monkeys after repeated oral dosing at 25 mg/kg/day to 125 mg/kg/day (1 to 3 times the mean steady-state AUC at the maximum recommended clinical dose or 16 to 81 times the maximum recommended human dose based on mg/m^2). However, the concentrations of the sulphate conjugates of hydroxy aripiprazole in human bile at the highest dose proposed, 30 mg per day, were no more than 6 % of the bile concentrations found in the monkeys in the 39-week study and are well below (6 %) their limits of *in vitro* solubility.

In repeat-dose studies in juvenile rats and dogs, the toxicity profile of aripiprazole was comparable to that observed in adult animals, and there was no evidence of neurotoxicity or adverse reactions on development.

Based on results of a full range of standard genotoxicity tests, aripiprazole was considered non-genotoxic. Aripiprazole did not impair fertility in reproductive toxicity studies. Developmental toxicity, including dose-dependent delayed foetal ossification and possible teratogenic effects, were observed in rats at doses resulting in subtherapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures 3 and 11 times the mean steady-state AUC at the maximum recommended clinical dose. Maternal toxicity occurred at doses similar to those eliciting developmental toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Calcium silicate
Croscarmellose sodium
Crospovidone
Silicon dioxide
Xylitol
Microcrystalline cellulose
Aspartame (E 951)
Acesulfame potassium
Vanilla flavour (including vanillin, ethyl vanillin and lactose)
Tartaric acid
Magnesium stearate

Tablet coat

ABILIFY 10 mg orodispersible tablets
Red iron oxide (E 172)

ABILIFY 15 mg orodispersible tablets
Yellow iron oxide (E 172)

ABILIFY 30 mg orodispersible tablets
Red iron oxide (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Aluminium perforated unit dose blisters in cartons of 14 × 1, 28 × 1, 49 × 1 tablets.

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

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

ABILIFY 10 mg orodispersible tablets
EU/1/04/276/024 (10 mg, 14 × 1 orodispersible tablets)
EU/1/04/276/025 (10 mg, 28 × 1 orodispersible tablets)
EU/1/04/276/026 (10 mg, 49 × 1 orodispersible tablets)

ABILIFY 15 mg orodispersible tablets
EU/1/04/276/027 (15 mg, 14 × 1 orodispersible tablets)
EU/1/04/276/028 (15 mg, 28 × 1 orodispersible tablets)
EU/1/04/276/029 (15 mg, 49 × 1 orodispersible tablets)

ABILIFY 30 mg orodispersible tablets
EU/1/04/276/030 (30 mg, 14 × 1 orodispersible tablets)
EU/1/04/276/031 (30 mg, 28 × 1 orodispersible tablets)
EU/1/04/276/032 (30 mg, 49 × 1 orodispersible tablets)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 June 2004
Date of latest renewal: 04 June 2009

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

ABILIFY 1 mg/mL oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL oral solution contains 1 mg of aripiprazole.

Excipients with known effect (per mL)
200 mg fructose, 400 mg sucrose, 1.8 mg methyl parahydroxybenzoate (E218), 0.2 mg propyl parahydroxybenzoate (E 216)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution

Clear, colourless to light yellow liquid solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ABILIFY is indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older.

ABILIFY is indicated for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment (see section 5.1).

ABILIFY is indicated for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older (see section 5.1).

4.2 Posology and method of administration

Posology

Adults

Schizophrenia: the recommended starting dose for ABILIFY is 10 mg/day or 15 mg/day (i.e. 10 mL or 15 mL solution/day) with a maintenance dose of 15 mg/day administered on a once-a-day schedule without regard to meals. ABILIFY is effective in a dose range of 10 mg/day to 30 mg/day (i.e. 10 mL to 30 mL solution/day). Enhanced efficacy at doses higher than a daily dose of 15 mg has not been demonstrated although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Manic episodes in Bipolar I Disorder: the recommended starting dose for ABILIFY is 15 mg (i.e. 15 mL solution/day) administered on a once-a-day schedule without regard to meals as monotherapy or combination therapy (see section 5.1). Some patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Recurrence prevention of manic episodes in Bipolar I Disorder: for preventing recurrence of manic episodes in patients, who have been receiving aripiprazole as monotherapy or combination therapy,

continue therapy at the same dose. Adjustments of daily dosage, including dose reduction should be considered on the basis of clinical status.

Paediatric population

Schizophrenia in adolescents aged 15 years and older: the recommended dose for ABILIFY is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using ABILIFY oral solution 1 mg/mL) for 2 days, titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg. When appropriate, subsequent dose increases should be administered in 5 mg increments without exceeding the maximum daily dose of 30 mg (see section 5.1). ABILIFY is effective in a dose range of 10 mg/day to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated although individual patients may benefit from a higher dose.
ABILIFY is not recommended for use in patients with schizophrenia below 15 years of age due to insufficient data on safety and efficacy (see sections 4.8 and 5.1).

Manic episodes in Bipolar I Disorder in adolescents aged 13 years and older: the recommended dose for ABILIFY is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using ABILIFY oral solution 1 mg/mL) for 2 days, titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg. The treatment duration should be the minimum necessary for symptom control and must not exceed 12 weeks. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated, and a daily dose of 30 mg is associated with a substantially higher incidence of significant adverse reactions including EPS related events, somnolence, fatigue and weight gain (see section 4.8). Doses higher than 10 mg/day should therefore only be used in exceptional cases and with close clinical monitoring (see sections 4.4, 4.8 and 5.1). Younger patients are at increased risk of experiencing adverse events associated with aripiprazole. Therefore, ABILIFY is not recommended for use in patients below 13 years of age (see sections 4.8 and 5.1).

Irritability associated with autistic disorder: the safety and efficacy of ABILIFY in children and adolescents aged below 18 years have not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Tics associated with Tourette's disorder: the safety and efficacy of ABILIFY in children and adolescents 6 to 18 years of age have not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Special populations

Hepatic impairment
No dosage adjustment is required for patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In these patients dosing should be managed cautiously. However, the maximum daily dose of 30 mg should be used with caution in patients with severe hepatic impairment (see section 5.2).

Renal impairment
No dosage adjustment is required in patients with renal impairment.

Elderly
The safety and efficacy of ABILIFY in the treatment of schizophrenia or manic episodes in Bipolar I Disorder in patients aged 65 years and older has not been established. Owing to the greater sensitivity of this population, a lower starting dose should be considered when clinical factors warrant (see section 4.4).

Gender
No dosage adjustment is required for female patients as compared to male patients (see section 5.2).

Smoking status
According to the metabolic pathway of aripiprazole no dosage adjustment is required for smokers (see section 4.5).

Dose adjustments due to interactions
When concomitant administration of strong CYP3A4 or CYP2D6 inhibitors with aripiprazole occurs, the aripiprazole dose should be reduced. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased (see section 4.5).
When concomitant administration of strong CYP3A4 inducers with aripiprazole occurs, the aripiprazole dose should be increased. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced to the recommended dose (see section 4.5).

Method of administration

ABILIFY is for oral use.

Orodispersible tablets or oral solution may be used as an alternative to ABILIFY tablets for patients who have difficulty swallowing ABILIFY tablets (see section 5.2).

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

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

Suicidality

The occurrence of suicidal behaviour is inherent in psychotic illnesses and mood disorders and in some cases has been reported early after initiation or switch of antipsychotic treatment, including treatment with aripiprazole (see section 4.8). Close supervision of high-risk patients should accompany antipsychotic treatment.

Cardiovascular disorders

Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medicinal products) or hypertension, including accelerated or malignant. 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 aripiprazole and preventive measures undertaken.

QT prolongation

In clinical trials of aripiprazole, the incidence of QT prolongation was comparable to placebo. Aripiprazole should be used with caution in patients with a family history of QT prolongation (see section 4.8).

Tardive dyskinesia

In clinical trials of one year or less duration, there were uncommon reports of treatment emergent dyskinesia during treatment with aripiprazole. If signs and symptoms of tardive dyskinesia appear in a patient on aripiprazole, dose reduction or discontinuation should be considered (see section 4.8). These

symptoms can temporally deteriorate or can even arise after discontinuation of treatment.

Other extrapyramidal symptoms

In paediatric clinical trials of aripiprazole akathisia and Parkinsonism were observed. If signs and symptoms of other EPS appear in a patient taking aripiprazole, dose reduction and close clinical monitoring should be considered.

Neuroleptic Malignant Syndrome (NMS)

NMS is a potentially fatal symptom complex associated with antipsychotics. In clinical trials, rare cases of NMS were reported during treatment with aripiprazole. 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. However, elevated creatine phosphokinase and rhabdomyolysis, not necessarily in association with NMS, have also been reported. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotics, including aripiprazole, must be discontinued.

Seizure

In clinical trials, uncommon cases of seizure were reported during treatment with aripiprazole. Therefore, aripiprazole should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures (see section 4.8).

Elderly patients with dementia-related psychosis

Increased mortality
In three placebo-controlled trials (n = 938; mean age: 82.4 years; range: 56 to 99 years) of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease, patients treated with aripiprazole were at increased risk of death compared to placebo. The rate of death in aripiprazole-treated patients was 3.5 % compared to 1.7 % in the placebo group. Although the causes of deaths were varied, most of the deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia) in nature (see section 4.8).

Cerebrovascular adverse reactions
In the same trials, cerebrovascular adverse reactions (e.g. stroke, transient ischaemic attack), including fatalities, were reported in patients (mean age: 84 years; range: 78 to 88 years). Overall, 1.3 % of aripiprazole-treated patients reported cerebrovascular adverse reactions compared with 0.6 % of placebo-treated patients in these trials. This difference was not statistically significant. However, in one of these trials, a fixed-dose trial, there was a significant dose response relationship for cerebrovascular adverse reactions in patients treated with aripiprazole (see section 4.8).

Aripiprazole is not indicated for the treatment of patients with dementia-related psychosis.

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including aripiprazole. Risk factors that may predispose patients to severe complications include obesity and family history of diabetes. In clinical trials with aripiprazole, there were no significant differences in the incidence rates of hyperglycaemia-related adverse reactions (including diabetes) or in abnormal glycaemia laboratory values compared to placebo. Precise risk estimates for hyperglycaemia-related adverse reactions in patients treated with aripiprazole and with other atypical antipsychotics are not available to allow direct comparisons. Patients treated with any antipsychotics, including aripiprazole, 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 (see section 4.8).

Hypersensitivity

Hypersensitivity reactions, characterised by allergic symptoms, may occur with aripiprazole (see section 4.8).

Weight gain

Weight gain is commonly seen in schizophrenic and bipolar mania patients due to co-morbidities, use of antipsychotics known to cause weight gain, poorly managed life-style, and might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed aripiprazole. When seen, it is usually in those with significant risk factors such as history of diabetes, thyroid disorder or pituitary adenoma. In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain in adults (see section 5.1). In clinical trials of adolescent patients with bipolar mania, aripiprazole has been shown to be associated with weight gain after 4 weeks of treatment. Weight gain should be monitored in adolescent patients with bipolar mania. If weight gain is clinically significant, dose reduction should be considered (see section 4.8).

Dysphagia

Oesophageal dysmotility and aspiration have been associated with the use of antipsychotics, including aripiprazole. Aripiprazole should be used cautiously in patients at risk for aspiration pneumonia.

Pathological gambling and other impulse control disorders

Patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other urges, reported, include: increased sexual urges, compulsive shopping, binge or compulsive eating, and other impulsive and compulsive behaviours. It is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, sexual urges, compulsive shopping, binge or compulsive eating, or other urges while being treated with aripiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder; however, in some cases, urges were reported to have stopped when the dose was reduced or the medication was discontinued. Impulse control disorders may result in harm to the patient and others if not recognised. Consider dose reduction or stopping the medication if a patient develops such urges while taking aripiprazole (see section 4.8).

Fructose

The oral solution contains fructose. Fructose may damage teeth. Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

Sucrose

The oral solution contains sucrose. Sucrose may be harmful to the teeth. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicinal product.

Parahydroxybenzoate

The oral solution contains methyl parahydroxybenzoate and propyl parahydroxybenzoate. May cause allergic reactions (possibly delayed).

Sodium

The oral solution contains sodium. This medicinal product contains less than 1 mmol sodium (23 mg)

per dosage unit, that is to say essentially ‘sodium-free’.

Patients with attention deficit hyperactivity disorder (ADHD) comorbidity

Despite the high comorbidity frequency of Bipolar I Disorder and ADHD, very limited safety data are available on concomitant use of aripiprazole and stimulants; therefore, extreme caution should be taken when these medicinal products are co-administered.

Falls

Aripiprazole may cause somnolence, postural hypotension, motor and sensory instability, 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).

4.5 Interaction with other medicinal products and other forms of interaction

Due to its α_1-adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive medicinal products.

Given the primary CNS effects of aripiprazole, caution should be used when aripiprazole is administered in combination with alcohol or other CNS medicinal products with overlapping adverse reactions such as sedation (see section 4.8).

If aripiprazole is administered concomitantly with medicinal products known to cause QT prolongation or electrolyte imbalance, caution should be used.

Potential for other medicinal products to affect aripiprazole

A gastric acid blocker, the H_2 antagonist famotidine, reduces aripiprazole rate of absorption but this effect is deemed not clinically relevant. Aripiprazole is metabolised by multiple pathways involving the CYP2D6 and CYP3A4 enzymes but not CYP1A enzymes. Thus, no dosage adjustment is required for smokers.

Quinidine and other CYP2D6 inhibitors
In a clinical trial in healthy subjects, a strong inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107 %, while C_{max} was unchanged. The AUC and C_{max} of dehydro-aripiprazole, the active metabolite, decreased by 32 % and 47 %, respectively. Aripiprazole dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of aripiprazole with quinidine occurs. Other strong inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be expected to have similar effects and similar dose reductions should therefore be applied.

Ketoconazole and other CYP3A4 inhibitors
In a clinical trial in healthy subjects, a strong inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and C_{max} by 63 % and 37 %, respectively. The AUC and C_{max} of dehydro-aripiprazole increased by 77 % and 43 %, respectively. In CYP2D6 poor metabolisers, concomitant use of strong inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolizers. When considering concomitant administration of ketoconazole or other strong CYP3A4 inhibitors with aripiprazole, potential benefits should outweigh the potential risks to the patient. When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole dose should be reduced to approximately one-half of its prescribed dose. Other strong inhibitors of CYP3A4, such as itraconazole and HIV protease inhibitors may be expected to have similar effects and similar dose reductions should therefore be applied (see section 4.2). Upon discontinuation of the CYP2D6 or CYP3A4 inhibitor, the dosage of aripiprazole should be increased to the level prior to the initiation of the concomitant therapy. When weak inhibitors of CYP3A4 (e.g. diltiazem) or CYP2D6 (e.g. escitalopram) are used concomitantly with aripiprazole, modest increases in plasma aripiprazole concentrations may be expected.

Carbamazepine and other CYP3A4 inducers
Following concomitant administration of carbamazepine, a strong inducer of CYP3A4, and oral aripiprazole to patients with schizophrenia or schizoaffective disorder, the geometric means of C_{max} and AUC for aripiprazole were 68 % and 73 % lower, respectively, compared to when aripiprazole (30 mg) was administered alone. Similarly, for dehydro-aripiprazole the geometric means of C_{max} and AUC after carbamazepine co-administration were 69 % and 71 % lower, respectively, than those following treatment with aripiprazole alone. Aripiprazole dose should be doubled when concomitant administration of aripiprazole occurs with carbamazepine. Concomitant administration of aripiprazole and other inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) may be expected to have similar effects and similar dose increases should therefore be applied. Upon discontinuation of strong CYP3A4 inducers, the dosage of aripiprazole should be reduced to the recommended dose.

Valproate and lithium
When either valproate or lithium was administered concomitantly with aripiprazole, there was no clinically significant change in aripiprazole concentrations and therefore no dose adjustment is necessary when either valproate or lithium is administered with aripiprazole.

Potential for aripiprazole to affect other medicinal products

In clinical studies, 10 mg/day to 30 mg/day doses of aripiprazole had no significant effect on the metabolism of substrates of CYP2D6 (dextromethorphan/3-methoxymorphinan ratio), CYP2C9 (warfarin), CYP2C19 (omeprazole), and CYP3A4 (dextromethorphan). Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro*. Thus, aripiprazole is unlikely to cause clinically important medicinal product interactions mediated by these enzymes.

When aripiprazole was administered concomitantly with either valproate, lithium or lamotrigine, there was no clinically important change in valproate, lithium or lamotrigine concentrations.

Serotonin syndrome
Cases of serotonin syndrome have been reported in patients taking aripiprazole, and possible signs and symptoms for this condition can occur especially in cases of concomitant use with other serotonergic medicinal products, such as selective serotonin reuptake inhibitor/selective serotonin noradrenaline reuptake inhibitor (SSRI/SNRI), or with medicinal products that are known to increase aripiprazole concentrations (see section 4.8).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled trials of aripiprazole in pregnant women. Congenital anomalies have been reported; however, causal relationship with aripiprazole could not be established. Animal studies could not exclude potential developmental toxicity (see section 5.3). Patients must be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole. Due to insufficient safety information in humans and concerns raised by animal reproductive studies, this medicinal product should not be used in pregnancy unless the expected benefit clearly justifies the potential risk to the foetus.

Newborn infants exposed to antipsychotics (including aripiprazole) 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, newborn infants should be monitored carefully (see section 4.8).

Breast-feeding

Aripiprazole/metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from aripiprazole therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Aripiprazole did not impair fertility based on data from reproductive toxicity studies.

4.7 Effects on ability to drive and use machines

Aripiprazole has minor to moderate influence on the ability to drive and use machines due to potential nervous system and visual effects, such as sedation, somnolence, syncope, vision blurred, diplopia (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in placebo-controlled trials were akathisia and nausea each occurring in more than 3 % of patients treated with oral aripiprazole.

Tabulated list of adverse reactions

The incidences of the Adverse Drug Reactions (ADRs) associated with aripiprazole therapy are tabulated below. The table is based on adverse events reported during clinical trials and/or post-marketing use.

All ADRs are listed by system organ 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) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports. Consequently, the frequency of these adverse events is qualified as "not known".

	Common	**Uncommon**	**Not known**
Blood and lymphatic system disorders			Leukopenia Neutropenia Thrombocytopenia
Immune system disorders			Allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus allergic, or urticaria)
Endocrine disorders		Hyperprolactinaemia Blood prolactin decreased	Diabetic hyperosmolar coma Diabetic ketoacidosis
Metabolism and nutrition disorders	Diabetes mellitus	Hyperglycaemia	Hyponatremia Anorexia
Psychiatric disorders	Insomnia Anxiety Restlessness	Depression Hypersexuality	Suicide attempt, suicidal ideation and completed suicide (see section 4.4) Pathological gambling Impulse-control disorder

	Common	Uncommon	Not known
			Binge eating Compulsive shopping Poriomania Aggression Agitation Nervousness
Nervous system disorders	Akathisia Extrapyramidal disorder Tremor Headache Sedation Somnolence Dizziness	Tardive dyskinesia Dystonia Restless legs syndrome	Neuroleptic Malignant Syndrome Grand mal convulsion Serotonin syndrome Speech disorder
Eye disorders	Vision blurred	Diplopia Photophobia	Oculogyric crisis
Cardiac disorders		Tachycardia	Sudden death unexplained Torsades de pointes Ventricular arrhythmia Cardiac arrest Bradycardia
Vascular disorders		Orthostatic hypotension	Venous thromboembolism (including pulmonary embolism and deep vein thrombosis) Hypertension Syncope
Respiratory, thoracic and mediastinal disorders		Hiccups	Aspiration pneumonia Laryngospasm Oropharyngeal spasm
Gastrointestinal disorders	Constipation Dyspepsia Nausea Salivary hypersecretion Vomiting		Pancreatitis Dysphagia Diarrhoea Abdominal discomfort Stomach discomfort
Hepatobiliary disorders			Hepatic failure Hepatitis Jaundice
Skin and subcutaneous tissue disorders			Rash Photosensitivity reaction Alopecia Hyperhidrosis Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders			Rhabdomyolysis Myalgia Stiffness
Renal and urinary disorders			Urinary incontinence Urinary retention
Pregnancy, puerperium and perinatal conditions			Drug withdrawal syndrome neonatal (see section 4.6)

	Common	Uncommon	Not known
Reproductive system and breast disorders			Priapism
General disorders and administration site conditions	Fatigue		Temperature regulation disorder (e.g. hypothermia, pyrexia) Chest pain Peripheral oedema
Investigations			Weight decreased Weight gain Alanine Aminotransferase increased Aspartate Aminotransferase increased Gamma-glutamyltransferase increased Alkaline phosphatase increased QT prolonged Blood glucose increased Glycosylated haemoglobin increased Blood glucose fluctuation Creatine phosphokinase increased

Description of selected adverse reactions

Adults

Extrapyramidal symptoms (EPS)
Schizophrenia: in a long-term 52-week controlled trial, aripiprazole-treated patients had an overall-lower incidence (25.8 %) of EPS including Parkinsonism, akathisia, dystonia and dyskinesia compared with those treated with haloperidol (57.3 %). In a long-term 26-week placebo-controlled trial, the incidence of EPS was 19 % for aripiprazole-treated patients and 13.1 % for placebo-treated patients. In another long-term 26-week controlled trial, the incidence of EPS was 14.8 % for aripiprazole-treated patients and 15.1 % for olanzapine-treated patients.

Manic episodes in Bipolar I Disorder: in a 12-week controlled trial, the incidence of EPS was 23.5 % for aripiprazole-treated patients and 53.3 % for haloperidol-treated patients. In another 12-week trial, the incidence of EPS was 26.6 % for patients treated with aripiprazole and 17.6 % for those treated with lithium. In the long-term 26-week maintenance phase of a placebo-controlled trial, the incidence of EPS was 18.2 % for aripiprazole-treated patients and 15.7 % for placebo-treated patients.

Akathisia
In placebo-controlled trials, the incidence of akathisia in bipolar patients was 12.1 % with aripiprazole and 3.2 % with placebo. In schizophrenia patients the incidence of akathisia was 6.2 % with aripiprazole and 3.0 % with placebo.

Dystonia
Class effect: 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. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high 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.

Prolactin
In clinical trials for the approved indications and post-marketing, both increase and decrease in serum prolactin as compared to baseline was observed with aripiprazole (section 5.1).

Laboratory parameters
Comparisons between aripiprazole and placebo in the proportions of patients experiencing potentially clinically significant changes in routine laboratory and lipid parameters (see section 5.1) revealed no medically important differences. Elevations of CPK (Creatine Phosphokinase), generally transient and asymptomatic, were observed in 3.5 % of aripiprazole treated patients as compared to 2.0 % of patients who received placebo.

Paediatric population

Schizophrenia in adolescents aged 15 years and older
In a short-term placebo-controlled clinical trial involving 302 adolescents (13 to 17 years) with schizophrenia, the frequency and type of adverse reactions were similar to those in adults except for the following reactions that were reported more frequently in adolescents receiving aripiprazole than in adults receiving aripiprazole (and more frequently than placebo):
Somnolence/sedation and extrapyramidal disorder were reported very commonly (≥ 1/10), and dry mouth, increased appetite, and orthostatic hypotension were reported commonly (≥ 1/100, < 1/10).
The safety profile in a 26-week open-label extension trial was similar to that observed in the short-term, placebo-controlled trial.
The safety profile of a long-term, double-blind, placebo-controlled trial was also similar except for the following reactions that were reported more frequently than paediatric patients taking placebo: weight decreased, blood insulin increased, arrhythmia, and leukopenia were reported commonly (≥ 1/100, < 1/10).

In the pooled adolescent schizophrenia population (13 to 17 years) with exposure up to 2 years, incidence of low serum prolactin levels in females (< 3 ng/mL) and males (< 2 ng/mL) was 29.5 % and 48.3 %, respectively. In the adolescent (13 to 17 years) schizophrenia population with aripiprazole exposure of 5 mg to 30 mg up to 72 months, incidence of low serum prolactin levels in females (< 3 ng/mL) and males (< 2 ng/mL) was 25.6 % and 45.0 %, respectively.
In two long-term trials with adolescent (13 to 17 years) schizophrenia and bipolar patients treated with aripiprazole, incidence of low serum prolactin levels in females (< 3 ng/mL) and males (< 2 ng/mL) was 37.0 % and 59.4 %, respectively.

Manic episodes in Bipolar I Disorder in adolescents aged 13 years and older
The frequency and type of adverse reactions in adolescents with Bipolar I Disorder were similar to those in adults except for the following reactions: very commonly (≥ 1/10) somnolence (23.0 %), extrapyramidal disorder (18.4 %), akathisia (16.0 %), and fatigue (11.8 %); and commonly (≥ 1/100, < 1/10) abdominal pain upper, heart rate increased, weight increased, increased appetite, muscle twitching, and dyskinesia.

The following adverse reactions had a possible dose response relationship; extrapyramidal disorder (incidences were 10 mg, 9.1 %; 30 mg, 28.8 %; placebo, 1.7 %); and akathisia (incidences were 10 mg, 12.1 %; 30 mg, 20.3 %; placebo, 1.7 %).

Mean changes in body weight in adolescents with Bipolar I Disorder at 12 and 30 weeks for aripiprazole were 2.4 kg and 5.8 kg, and for placebo 0.2 kg and 2.3 kg, respectively.

In the paediatric population somnolence and fatigue were observed more frequently in patients with bipolar disorder compared to patients with schizophrenia.

In the paediatric bipolar population (10 to 17 years) with exposure up to 30 weeks, incidence of low serum prolactin levels in females (< 3 ng/mL) and males (< 2 ng/mL) was 28.0 % and 53.3 %, respectively.

Pathological gambling and other impulse control disorders
Pathological gambling, hypersexuality, compulsive shopping and binge or compulsive eating can occur in patients treated with aripiprazole (see section 4.4).

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

In clinical trials and post-marketing experience, accidental or intentional acute overdose of aripiprazole alone was identified in adult patients with reported estimated doses up to 1,260 mg with no fatalities. The potentially medically important signs and symptoms observed included lethargy, increased blood pressure, somnolence, tachycardia, nausea, vomiting and diarrhoea. In addition, reports of accidental overdose with aripiprazole alone (up to 195 mg) in children have been received with no fatalities. The potentially medically serious signs and symptoms reported included somnolence, transient loss of consciousness and extrapyramidal symptoms.

Management of overdose

Management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. The possibility of multiple medicinal product involvement should be considered. Therefore cardiovascular monitoring should be started immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. Following any confirmed or suspected overdose with aripiprazole, close medical supervision and monitoring should continue until the patient recovers.

Activated charcoal (50 g), administered one hour after aripiprazole, decreased aripiprazole C_{max} by about 41 % and AUC by about 51 %, suggesting that charcoal may be effective in the treatment of overdose.

Haemodialysis

Although there is no information on the effect of haemodialysis in treating an overdose with aripiprazole, haemodialysis is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, other antipsychotics, ATC code: N05AX12

Mechanism of action

It has been proposed that aripiprazole's efficacy in schizophrenia and Bipolar I Disorder is mediated through a combination of partial agonism at dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonism of serotonin 5-HT_{2A} receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity. Aripiprazole exhibited high binding affinity *in vitro* for dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors and moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha-1 adrenergic and histamine H_1 receptors. Aripiprazole also exhibited moderate binding affinity

for the serotonin reuptake site and no appreciable affinity for muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

Aripiprazole doses ranging from 0.5 mg to 30 mg administered once a day to healthy subjects for 2 weeks produced a dose-dependent reduction in the binding of ^{11}C-raclopride, a D_2/D_3 receptor ligand, to the caudate and putamen detected by positron emission tomography.

Clinical efficacy and safety

Adults

Schizophrenia
In three short-term (4 to 6 weeks) placebo-controlled trials involving 1,228 schizophrenic adult patients, presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

Aripiprazole is effective in maintaining the clinical improvement during continuation therapy in adult patients who have shown an initial treatment response. In a haloperidol-controlled trial, the proportion of responder patients maintaining response to medicinal product at 52-weeks was similar in both groups (aripiprazole 77 % and haloperidol 73 %). The overall completion rate was significantly higher for patients on aripiprazole (43 %) than for haloperidol (30 %). Actual scores in rating scales used as secondary endpoints, including PANSS and the Montgomery-Åsberg Depression Rating Scale (MADRS) showed a significant improvement over haloperidol.

In a 26-week, placebo-controlled trial in adult stabilised patients with chronic schizophrenia, aripiprazole had significantly greater reduction in relapse rate, 34 % in aripiprazole group and 57 % in placebo.

Weight gain
In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain. In a 26-week, olanzapine-controlled, double-blind, multi-national study of schizophrenia which included 314 adult patients and where the primary endpoint was weight gain, significantly less patients had at least 7 % weight gain over baseline (i.e. a gain of at least 5.6 kg for a mean baseline weight of ~80.5 kg) on aripiprazole (n = 18, or 13 % of evaluable patients), compared to olanzapine (n = 45, or 33 % of evaluable patients).

Lipid parameters
In a pooled analysis on lipid parameters from placebo controlled clinical trials in adults, aripiprazole has not been shown to induce clinically relevant alterations in levels of total cholesterol, triglycerides, High Density Lipoprotein (HDL) and Low Density Lipoprotein (LDL).

Prolactin
Prolactin levels were evaluated in all trials of all doses of aripiprazole (n = 28,242). The incidence of hyperprolactinaemia or increased serum prolactin in patients treated with aripiprazole (0.3 %) was similar to that of placebo (0.2 %). For patients receiving aripiprazole, the median time to onset was 42 days and median duration was 34 days.

The incidence of hypoprolactinaemia or decreased serum prolactin in patients treated with aripiprazole was 0.4 %, compared with 0.02 % for patients treated with placebo. For patients receiving aripiprazole, the median time to onset was 30 days and median duration was 194 days.

Manic episodes in Bipolar I Disorder
In two 3-week, flexible-dose, placebo-controlled monotherapy trials involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole demonstrated superior efficacy to placebo in reduction of manic symptoms over 3 weeks. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

In one 3-week, fixed-dose, placebo-controlled monotherapy trial involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole failed to demonstrate superior efficacy to placebo.

In two 12-week, placebo- and active-controlled monotherapy trials in patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, aripiprazole demonstrated superior efficacy to placebo at week 3 and a maintenance of effect comparable to lithium or haloperidol at week 12. Aripiprazole also demonstrated a comparable proportion of patients in symptomatic remission from mania as lithium or haloperidol at week 12.

In a 6-week, placebo-controlled trial involving patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, who were partially non-responsive to lithium or valproate monotherapy for 2 weeks at therapeutic serum levels, the addition of aripiprazole as adjunctive therapy resulted in superior efficacy in reduction of manic symptoms than lithium or valproate monotherapy.

In a 26-week, placebo-controlled trial, followed by a 74-week extension, in manic patients who achieved remission on aripiprazole during a stabilization phase prior to randomisation, aripiprazole demonstrated superiority over placebo in preventing bipolar recurrence, primarily in preventing recurrence into mania but failed to demonstrate superiority over placebo in preventing recurrence into depression.

In a 52-week, placebo-controlled trial, in patients with a current manic or mixed episode of Bipolar I Disorder who achieved sustained remission (Young Mania Rating Scale [YMRS] and MADRS with total scores ≤ 12) on aripiprazole (10 mg/day to 30 mg/day) adjunctive to lithium or valproate for 12 consecutive weeks, adjunctive aripiprazole demonstrated superiority over placebo with a 46 % decreased risk (hazard ratio of 0.54) in preventing bipolar recurrence and a 65 % decreased risk (hazard ratio of 0.35) in preventing recurrence into mania over adjunctive placebo but failed to demonstrate superiority over placebo in preventing recurrence into depression. Adjunctive aripiprazole demonstrated superiority over placebo on the secondary outcome measure in Clinical Global Impression – Bipolar version (CGI-BP) Severity of Illness (SOI; mania) scores. In this trial, patients were assigned by investigators with either open-label lithium or valproate monotherapy to determine partial non-response. Patients were stabilised for at least 12 consecutive weeks with the combination of aripiprazole and the same mood stabilizer. Stabilized patients were then randomised to continue the same mood stabilizer with double-blind aripiprazole or placebo. Four mood stabilizer subgroups were assessed in the randomised phase: aripiprazole + lithium; aripiprazole + valproate; placebo + lithium; placebo + valproate. The Kaplan-Meier rates for recurrence to any mood episode for the adjunctive treatment arm were 16 % in aripiprazole + lithium and 18 % in aripiprazole + valproate compared to 45 % in placebo + lithium and 19 % in placebo + valproate.

Paediatric population

Schizophrenia in adolescents
In a 6-week placebo-controlled trial involving 302 schizophrenic adolescent patients (13 to 17 years), presenting with positive or negative symptoms, aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo. In a sub-analysis of the adolescent patients between the ages of 15 to 17 years, representing 74 % of the total enrolled population, maintenance of effect was observed over the 26-week open-label extension trial.

In a 60- to 89-week, randomised, double-blind, placebo-controlled trial in adolescent subjects (n = 146; ages 13 to 17 years) with schizophrenia, there was a statistically significant difference in the rate of relapse of psychotic symptoms between the aripiprazole (19.39 %) and placebo (37.50 %) groups. The point estimate of the hazard ratio (HR) was 0.461 (95 % confidence interval, 0.242 to 0.879) in the full population. In subgroup analyses the point estimate of the HR was 0.495 for subjects 13 to 14 years of age compared to 0.454 for subjects 15 to 17 years of age. However, the estimation of the HR for the younger (13 to 14 years) group was not precise, reflecting the smaller number of subjects in that group (aripiprazole, n = 29; placebo, n = 12), and the confidence interval for this

estimation (ranging from 0.151 to 1.628) did not allow conclusions to be drawn on the presence of a treatment effect. In contrast the 95 % confidence interval for the HR in the older subgroup (aripiprazole, n = 69; placebo, n = 36) was 0.242 to 0.879 and hence a treatment effect could be concluded in the older patients.

Manic episodes in Bipolar I Disorder in children and adolescents
Aripiprazole was studied in a 30-week placebo-controlled trial involving 296 children and adolescents (10 to 17 years), who met DSM-IV criteria (Diagnostic and Statistical Manual of Mental Disorders) for Bipolar I Disorder with manic or mixed episodes with or without psychotic features and had a YMRS score ≥ 20 at baseline. Among the patients included in the primary efficacy analysis, 139 patients had a current co-morbid diagnosis of ADHD.

Aripiprazole was superior to placebo in change from baseline at week 4 and at week 12 on the Y-MRS total score. In a post-hoc analysis, the improvement over placebo was more pronounced in the patients with associated co-morbidity of ADHD compared to the group without ADHD, where there was no difference from placebo. Recurrence prevention was not established.
The most common treatment-emergent adverse events among patients receiving 30 mg were extrapyramidal disorder (28.3 %), somnolence (27.3 %), headache (23.2 %), and nausea (14.1 %). Mean weight gain in the 30 weeks treatment-interval was 2.9 kg as compared to 0.98 kg in patients treated with placebo.

Irritability associated with autistic disorder in paediatric patients (see section 4.2)
Aripiprazole was studied in patients aged 6 to 17 years in two 8-week, placebo-controlled trials [one flexible-dose (2 mg/day to 15 mg/day) and one fixed-dose (5 mg/day, 10 mg/day, or 15 mg/day)] and in one 52-week open-label trial. Dosing in these trials was initiated at 2 mg/day, increased to 5 mg/day after one week, and increased by 5 mg/day in weekly increments to the target dose. Over 75 % of patients were less than 13 years of age. Aripiprazole demonstrated statistically superior efficacy compared to placebo on the Aberrant Behaviour Checklist Irritability subscale. However, the clinical relevance of this finding has not been established. The safety profile included weight gain and changes in prolactin levels. The duration of the long-term safety study was limited to 52 weeks. In the pooled trials, the incidence of low serum prolactin levels in females (< 3 ng/mL) and males (< 2 ng/mL) in aripiprazole-treated patients was 27/46 (58.7 %) and 258/298 (86.6 %), respectively. In the placebo-controlled trials, the mean weight gain was 0.4 kg for placebo and 1.6 kg for aripiprazole.

Aripiprazole was also studied in a placebo-controlled, long-term maintenance trial. After a 13 to 26-week stabilisation on aripiprazole (2 mg/day to 15 mg/day) patients with a stable response were either maintained on aripiprazole or substituted to placebo for further 16 weeks. Kaplan-Meier relapse rates at week 16 were 35 % for aripiprazole and 52 % for placebo; the hazard ratio for relapse within 16 weeks (aripiprazole/placebo) was 0.57 (non-statistically significant difference). The mean weight gain over the stabilisation phase (up to 26 weeks) on aripiprazole was 3.2 kg, and a further mean increase of 2.2 kg for aripiprazole as compared to 0.6 kg for placebo was observed in the second phase (16 weeks) of the trial. Extrapyramidal symptoms were mainly reported during the stabilisation phase in 17 % of patients, with tremor accounting for 6.5 %.

Tics associated with Tourette's disorder in paediatric patients (see section 4.2)
The efficacy of aripiprazole was studied in paediatric subjects with Tourette's disorder (aripiprazole: n = 99, placebo: n = 44) in a randomised, double-blind, placebo controlled, 8 week study using a fixed dose weight-based treatment group design over the dose range of 5 mg/day to 20 mg/day and a starting dose of 2 mg. Patients were 7 to 17 years of age and presented an average score of 30 on Total Tic Score on the Yale Global Tic Severity Scale (TTS-YGTSS) at baseline. Aripiprazole showed an improvement on TTS-YGTSS change from baseline to week 8 of 13.35, for the low dose group (5 mg or 10 mg) and 16.94 for the high dose group (10 mg or 20 mg) as compared with an improvement of 7.09 in the placebo group.

The efficacy of aripiprazole in paediatric subjects with Tourette's syndrome (aripiprazole: n = 32, placebo: n = 29) was also evaluated over a flexible dose range of 2 mg/day to 20 mg/day and a starting dose of 2 mg, in a 10 week, randomised, double blind, placebo-controlled study conducted in South-

Korea. Patients were 6 to 18 years and presented an average score of 29 on TTS-YGTSS at baseline. Aripiprazole group showed an improvement of 14.97 on TTS-YGTSS change from baseline to week 10 as compared with an improvement of 9.62 in the placebo group.

In both of these short-term trials, the clinical relevance of the efficacy findings has not been established, considering the magnitude of treatment effect compared to the large placebo effect and the unclear effects regarding psycho-social functioning. No long-term data are available with regard to the efficacy and the safety of aripiprazole in this fluctuating disorder.

The European Medicines Agency has deferred the obligation to submit the results of studies with ABILIFY in one or more subsets of the paediatric population in the treatment of schizophrenia and in the treatment of bipolar affective disorder (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3 to 5 hours after dosing. Aripiprazole undergoes minimal pre-systemic metabolism. The absolute oral bioavailability of the tablet formulation is 87 %. There is no effect of a high fat meal on the pharmacokinetics of aripiprazole.

Distribution

Aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4.9 L/kg, indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and dehydro-aripiprazole are greater than 99 % bound to serum proteins, binding primarily to albumin.

Biotransformation

Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicinal product moiety in systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40 % of aripiprazole AUC in plasma.

Elimination

The mean elimination half-lives for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6.

The total body clearance of aripiprazole is 0.7 mL/min/kg, which is primarily hepatic.

Following a single oral dose of [^{14}C]-labelled aripiprazole, approximately 27 % of the administered radioactivity was recovered in the urine and approximately 60 % in the faeces. Less than 1 % of unchanged aripiprazole was excreted in the urine and approximately 18 % was recovered unchanged in the faeces.

Oral Solution
Aripiprazole is well absorbed when administered orally as the solution. At equivalent doses, the peak plasma concentrations of aripiprazole (C_{max}) from the solution were somewhat higher but the systemic exposure (AUC) was equivalent to tablets. In a relative bioavailability study comparing the pharmacokinetics of 30 mg aripiprazole as the oral solution to 30 mg aripiprazole tablets in healthy subjects, the solution to the tablet ratio of geometric mean C_{max} values was 122 % (n = 30). The single-dose pharmacokinetics of aripiprazole was linear and dose-proportional.

Paediatric population

The pharmacokinetics of aripiprazole and dehydro-aripiprazole in paediatric patients 10 to 17 years of age were similar to those in adults after correcting for the differences in body weights.

Pharmacokinetics in special patient groups

Elderly
There are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects, nor is there any detectable effect of age in a population pharmacokinetic analysis in schizophrenic patients.

Gender
There are no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects nor is there any detectable effect of gender in a population pharmacokinetic analysis in schizophrenic patients.

Smoking
Population pharmacokinetic evaluation has revealed no evidence of clinically significant effects from smoking on the pharmacokinetics of aripiprazole.

Race
Population pharmacokinetic evaluation showed no evidence of race-related differences on the pharmacokinetics of aripiprazole.

Renal impairment
The pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to young healthy subjects.

Hepatic impairment
A single-dose study in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C) did not reveal a significant effect of hepatic impairment on the pharmacokinetics of aripiprazole and dehydro-aripiprazole, but the study included only 3 patients with Class C liver cirrhosis, which is insufficient to draw conclusions on their metabolic capacity.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Toxicologically significant effects were observed only at doses or exposures that were sufficiently in excess of the maximum human dose or exposure, indicating that these effects were limited or of no relevance to clinical use. These included: dose-dependent adrenocortical toxicity (lipofuscin pigment accumulation and/or parenchymal cell loss) in rats after 104 weeks at 20 mg/kg/day to 60 mg/kg/day (3 to 10 times the mean steady-state AUC at the maximum recommended human dose) and increased adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas in female rats at 60 mg/kg/day (10 times the mean steady-state AUC at the maximum recommended human dose). The highest nontumorigenic exposure in female rats was 7 times the human exposure at the recommended dose.

An additional finding was cholelithiasis as a consequence of precipitation of sulphate conjugates of hydroxy metabolites of aripiprazole in the bile of monkeys after repeated oral dosing at 25 mg/kg/day to 125 mg/kg/day (1 to 3 times the mean steady-state AUC at the maximum recommended clinical dose or 16 to 81 times the maximum recommended human dose based on mg/m^2). However, the concentrations of the sulphate conjugates of hydroxy aripiprazole in human bile at the highest dose proposed, 30 mg per day, were no more than 6 % of the bile concentrations found in the monkeys in

the 39-week study and are well below (6 %) their limits of *in vitro* solubility.

In repeat-dose studies in juvenile rats and dogs, the toxicity profile of aripiprazole was comparable to that observed in adult animals, and there was no evidence of neurotoxicity or adverse reactions on development.

Based on results of a full range of standard genotoxicity tests, aripiprazole was considered non-genotoxic. Aripiprazole did not impair fertility in reproductive toxicity studies. Developmental toxicity, including dose-dependent delayed foetal ossification and possible teratogenic effects, were observed in rats at doses resulting in subtherapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures 3 and 11 times the mean steady-state AUC at the maximum recommended clinical dose. Maternal toxicity occurred at doses similar to those eliciting developmental toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Fructose
Glycerin
Lactic acid
Methyl parahydroxybenzoate (E 218)
Propylene glycol
Propyl parahydroxybenzoate (E 216)
Sodium hydroxide
Sucrose
Purified water
Orange flavour

6.2 Incompatibilities

The oral solution should not be diluted with other liquids or mixed with any food prior to administration.

6.3 Shelf life

3 years
After first opening: 6 months.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

PET-bottles with polypropylene child-resistant closure containing 50 mL, 150 mL or 480 mL per bottle.
Each carton contains 1 bottle and both a calibrated polypropylene measuring cup with a graduation interval of 2.5 mL and a calibrated polypropylene low-density polyethylene dropping pipette with a graduation interval of 0.5 mL.

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

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/033 (1 mg/mL, 50 mL per bottle)
EU/1/04/276/034 (1 mg/mL, 150 mL per bottle)
EU/1/04/276/035 (1 mg/mL, 480 mL per bottle)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 June 2004
Date of latest renewal: 04 June 2009

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

ABILIFY 7.5 mg/mL solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 7.5 mg of aripiprazole. Each vial contains 9.75 mg aripiprazole.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Clear, colourless, aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ABILIFY solution for injection is indicated for the rapid control of agitation and disturbed behaviours in adult patients with schizophrenia or with manic episodes in Bipolar I Disorder, when oral therapy is not appropriate.

Treatment with ABILIFY solution for injection should be discontinued as soon as clinically appropriate and the use of oral aripiprazole should be initiated.

4.2 Posology and method of administration

Posology

The recommended initial dose for ABILIFY solution for injection is 9.75 mg (1.3 mL), administered as a single intramuscular injection. The effective dose range of ABILIFY solution for injection is 5.25 mg to 15 mg as a single injection. A lower dose of 5.25 mg (0.7 mL) 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 4.5).

A second injection may be administered 2 hours after the first injection, on the basis of individual clinical status and no more than three injections should be given in any 24-hour period.

The maximum daily dose of aripiprazole is 30 mg (including all formulations of ABILIFY).

If continued treatment is indicated with oral aripiprazole, see the Summary of Product Characteristics for ABILIFY tablets, ABILIFY orodispersible tablets, or ABILIFY oral solution.

Special populations

Paediatric population
The safety and efficacy of ABILIFY solution for injection in children and adolescents aged 0 to 17 years have not been established. No data are available.

Hepatic impairment
No dosage adjustment is required for patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In

these patients dosing should be managed cautiously. However, the maximum daily dose of 30 mg should be used with caution in patients with severe hepatic impairment (see section 5.2).

R*enal impairment*
No dosage adjustment is required in patients with renal impairment.

Elderly
The safety and efficacy of ABILIFY in the treatment of schizophrenia or manic episodes in Bipolar I Disorder in patients aged 65 years and older has not been established. Owing to the greater sensitivity of this population, a lower starting dose should be considered when clinical factors warrant (see section 4.4).

Gender
No dosage adjustment is required for female patients as compared to male patients (see section 5.2).

Smoking status
According to the metabolic pathway of aripiprazole no dosage adjustment is required for smokers (see section 4.5).

Dose adjustments due to interactions
When concomitant administration of strong CYP3A4 or CYP2D6 inhibitors with aripiprazole occurs, the aripiprazole dose should be reduced. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased (see section 4.5).
When concomitant administration of strong CYP3A4 inducers with aripiprazole occurs, the aripiprazole dose should be increased. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced to the recommended dose (see section 4.5).

Method of administration

ABILIFY solution for injection is for intramuscular use.

To enhance absorption and minimise variability, injection into the deltoid or deep within the gluteus maximus muscle, avoiding adipose regions, is recommended.

ABILIFY solution for injection should not be administered intravenously or subcutaneously.

It is ready to use and intended for short-term use only (see section 5.1).

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

The efficacy of ABILIFY solution for injection in patients with agitation and disturbed behaviours has not been established related to conditions other than schizophrenia and manic episodes in Bipolar I Disorder.

Simultaneous administration of injectable antipsychotics and parenteral benzodiazepine may be associated with excessive sedation and cardiorespiratory depression. If parenteral benzodiazepine therapy is deemed necessary in addition to aripiprazole solution for injection, patients should be monitored for excessive sedation and for orthostatic hypotension (see section 4.5).

Patients receiving ABILIFY solution for injection should be observed for orthostatic hypotension. Blood pressure, pulse, respiratory rate and level of consciousness should be monitored regularly.

The safety and efficacy of ABILIFY solution for injection has not been evaluated in patients with

alcohol or medicinal product intoxication (either with prescribed or illicit medicinal products).

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

Suicidality

The occurrence of suicidal behaviour is inherent in psychotic illnesses and mood disorders and in some cases has been reported early after initiation or switch of antipsychotic treatment, including treatment with aripiprazole (see section 4.8). Close supervision of high-risk patients should accompany antipsychotic treatment.

Cardiovascular disorders

Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medicinal products) or hypertension, including accelerated or malignant. 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 aripiprazole and preventive measures undertaken (see section 4.8).

QT prolongation

In clinical trials of treatment with oral aripiprazole, the incidence of QT prolongation was comparable to placebo. Aripiprazole should be used with caution in patients with a family history of QT prolongation (see section 4.8).

Tardive dyskinesia

In clinical trials of one year or less duration, there were uncommon reports of treatment emergent dyskinesia during treatment with aripiprazole. If signs and symptoms of tardive dyskinesia appear in a patient on aripiprazole, dose reduction or discontinuation should be considered (see section 4.8). These symptoms can temporally deteriorate or can even arise after discontinuation of treatment.

Other extrapyramidal symptoms

In paediatric clinical trials of aripiprazole akathisia and Parkinsonism were observed. If signs and symptoms of other EPS appear in a patient taking aripiprazole, dose reduction and close clinical monitoring should be considered.

Neuroleptic Malignant Syndrome (NMS)

NMS is a potentially fatal symptom complex associated with antipsychotics. In clinical trials, rare cases of NMS were reported during treatment with aripiprazole. 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. However, elevated creatine phosphokinase and rhabdomyolysis, not necessarily in association with NMS, have also been reported. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotics, including aripiprazole, must be discontinued.

Seizure

In clinical trials, uncommon cases of seizure were reported during treatment with aripiprazole.

Therefore, aripiprazole should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures (see section 4.8).

Elderly patients with dementia-related psychosis

Increased mortality
In three placebo-controlled trials (n = 938; mean age: 82.4 years; range: 56 to 99 years) of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease, patients treated with aripiprazole were at increased risk of death compared to placebo. The rate of death in aripiprazole-treated patients was 3.5 % compared to 1.7 % in the placebo group. Although the causes of deaths were varied, most of the deaths appeared to be either cardiovascular (e.g. heart failure, sudden death) or infectious (e.g. pneumonia) in nature (see section 4.8).

Cerebrovascular adverse reactions
In the same trials, cerebrovascular adverse reactions (e.g. stroke, transient ischaemic attack), including fatalities, were reported in patients (mean age: 84 years; range: 78 to 88 years). Overall, 1.3 % of aripiprazole-treated patients reported cerebrovascular adverse reactions compared with 0.6 % of placebo-treated patients in these trials. This difference was not statistically significant. However, in one of these trials, a fixed-dose trial, there was a significant dose response relationship for cerebrovascular adverse reactions in patients treated with aripiprazole (see section 4.8).

Aripiprazole is not indicated for the treatment of patients with dementia-related psychosis.

Hyperglycaemia and diabetes mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including aripiprazole. Risk factors that may predispose patients to severe complications include obesity and family history of diabetes. In clinical trials with aripiprazole, there were no significant differences in the incidence rates of hyperglycaemia-related adverse reactions (including diabetes) or in abnormal glycaemia laboratory values compared to placebo. Precise risk estimates for hyperglycaemia-related adverse reactions in patients treated with aripiprazole and with other atypical antipsychotics are not available to allow direct comparisons. Patients treated with any antipsychotics, including aripiprazole, 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 (see section 4.8).

Hypersensitivity

Hypersensitivity reactions, characterised by allergic symptoms, may occur with aripiprazole (see section 4.8).

Weight gain

Weight gain is commonly seen in schizophrenic and bipolar mania patients due to co-morbidities, use of antipsychotics known to cause weight gain, poorly managed life-style, and might lead to severe complications. Weight gain has been reported post-marketing among patients prescribed oral aripiprazole. When seen, it is usually in those with significant risk factors such as history of diabetes, thyroid disorder or pituitary adenoma. In clinical trials aripiprazole has not been shown to induce clinically relevant weight gain in adults (see section 5.1). In clinical trials of adolescent patients with bipolar mania, aripiprazole has been shown to be associated with weight gain after 4 weeks of treatment. Weight gain should be monitored in adolescent patients with bipolar mania. If weight gain is clinically significant, dose reduction should be considered (see section 4.8).

Dysphagia

Oesophageal dysmotility and aspiration have been associated with the use of antipsychotics, including

aripiprazole. Aripiprazole should be used cautiously in patients at risk for aspiration pneumonia.

Pathological gambling and other impulse control disorders

Patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other urges, reported, include: increased sexual urges, compulsive shopping, binge or compulsive eating, and other impulsive and compulsive behaviours. It is important for prescribers to ask patients or their caregivers specifically about the development of new or increased gambling urges, sexual urges, compulsive shopping, binge or compulsive eating, or other urges while being treated with aripiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder; however, in some cases, urges were reported to have stopped when the dose was reduced or the medication was discontinued. Impulse control disorders may result in harm to the patient and others if not recognised. Consider dose reduction or stopping the medication if a patient develops such urges while taking aripiprazole (see section 4.8).

Sodium

ABILIFY solution for injection contains sodium. This medicinal product contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially ‘sodium-free’.

Patients with attention deficit hyperactivity disorder (ADHD) comorbidity

Despite the high comorbidity frequency of Bipolar I Disorder and ADHD, very limited safety data are available on concomitant use of aripiprazole and stimulants; therefore, extreme caution should be taken when these medicinal products are co-administered.

Falls

Aripiprazole may cause somnolence, postural hypotension, motor and sensory instability, 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).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with ABILIFY solution for injection. The information below is obtained from studies with oral aripiprazole.

Due to its α_1-adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive medicinal products.

Given the primary CNS effects of aripiprazole, caution should be used when aripiprazole is administered in combination with alcohol or other CNS medicinal products with overlapping adverse reactions such as sedation (see section 4.8).

If aripiprazole is administered concomitantly with medicinal products known to cause QT prolongation or electrolyte imbalance, caution should be used.

Potential for other medicinal products to affect ABILIFY solution for injection

The administration of lorazepam solution for injection had no effect on the pharmacokinetics of ABILIFY solution for injection when administered concomitantly. However, in a single-dose, intramuscular study of aripiprazole (dose 15 mg) in healthy subjects, administered simultaneously with intramuscular lorazepam (dose 2 mg), the intensity of sedation was greater with the combination as compared to that observed with aripiprazole alone.

A gastric acid blocker, the H_2 antagonist famotidine, reduces aripiprazole rate of absorption but this effect is deemed not clinically relevant. Aripiprazole is metabolised by multiple pathways involving

the CYP2D6 and CYP3A4 enzymes but not CYP1A enzymes. Thus, no dosage adjustment is required for smokers.

Quinidine and other CYP2D6 inhibitors
In a clinical trial of oral aripiprazole in healthy subjects, a strong inhibitor of CYP2D6 (quinidine) increased aripiprazole AUC by 107 %, while C_{max} was unchanged. The AUC and C_{max} of dehydro-aripiprazole, the active metabolite, decreased by 32 % and 47 %, respectively. Aripiprazole dose should be reduced to approximately one-half of its prescribed dose when concomitant administration of aripiprazole with quinidine occurs. Other strong inhibitors of CYP2D6, such as fluoxetine and paroxetine, may be expected to have similar effects and similar dose reductions should therefore be applied.

Ketoconazole and other CYP3A4 inhibitors
In a clinical trial of oral aripiprazole in healthy subjects, a strong inhibitor of CYP3A4 (ketoconazole) increased aripiprazole AUC and C_{max} by 63 % and 37 %, respectively. The AUC and C_{max} of dehydro-aripiprazole increased by 77 % and 43 %, respectively. In CYP2D6 poor metabolisers, concomitant use of strong inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 extensive metabolizers. When considering concomitant administration of ketoconazole or other strong CYP3A4 inhibitors with aripiprazole, potential benefits should outweigh the potential risks to the patient. When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole dose should be reduced to approximately one-half of its prescribed dose. Other strong inhibitors of CYP3A4, such as itraconazole and HIV protease inhibitors may be expected to have similar effects and similar dose reductions should therefore be applied (see section 4.2). Upon discontinuation of the CYP2D6 or CYP3A4 inhibitor, the dosage of aripiprazole should be increased to the level prior to the initiation of the concomitant therapy. When weak inhibitors of CYP3A4 (e.g. diltiazem) or CYP2D6 (e.g. escitalopram) are used concomitantly with aripiprazole, modest increases in plasma aripiprazole concentrations may be expected.

Carbamazepine and other CYP3A4 inducers
Following concomitant administration of carbamazepine, a strong inducer of CYP3A4, and oral aripiprazole to patients with schizophrenia or schizoaffective disorder, the geometric means of C_{max} and AUC for aripiprazole were 68 % and 73 % lower, respectively, compared to when aripiprazole (30 mg) was administered alone. Similarly, for dehydro-aripiprazole the geometric means of C_{max} and AUC after carbamazepine co-administration were 69 % and 71 % lower, respectively, than those following treatment with aripiprazole alone. Aripiprazole dose should be doubled when concomitant administration of aripiprazole occurs with carbamazepine. Concomitant administration of aripiprazole and other inducers of CYP3A4 (such as rifampicin, rifabutin, phenytoin, phenobarbital, primidone, efavirenz, nevirapine and St. John's Wort) may be expected to have similar effects and similar dose increases should therefore be applied. Upon discontinuation of strong CYP3A4 inducers, the dosage of aripiprazole should be reduced to the recommended dose.

Valproate and lithium
When either valproate or lithium was administered concomitantly with aripiprazole, there was no clinically significant change in aripiprazole concentrations and therefore no dose adjustment is necessary when either valproate or lithium is administered with aripiprazole.

<u>Potential for aripiprazole to affect other medicinal products</u>

The administration of ABILIFY solution for injection had no effect on the pharmacokinetics of lorazepam solution for injection when administered concomitantly. However, in a single-dose, intramuscular study of aripiprazole (dose 15 mg) in healthy subjects, administered simultaneously with intramuscular lorazepam (dose 2 mg), the orthostatic hypotension observed was greater with the combination as compared to that observed with lorazepam alone.

In clinical studies, oral doses of 10 mg/day to 30 mg/day of aripiprazole had no significant effect on the metabolism of substrates of CYP2D6 (dextromethorphan/3-methoxymorphinan ratio), CYP2C9 (warfarin), CYP2C19 (omeprazole), and CYP3A4 (dextromethorphan). Additionally,

aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro*. Thus, aripiprazole is unlikely to cause clinically important medicinal product interactions mediated by these enzymes.

When aripiprazole was administered concomitantly with either valproate, lithium or lamotrigine, there was no clinically important change in valproate, lithium or lamotrigine concentrations.

Serotonin syndrome
Cases of serotonin syndrome have been reported in patients taking aripiprazole, and possible signs and symptoms for this condition can occur especially in cases of concomitant use with other serotonergic medicinal products, such as selective serotonin reuptake inhibitor/selective serotonin noradrenaline reuptake inhibitor (SSRI/SNRI), or with medicinal products that are known to increase aripiprazole concentrations (see section 4.8).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate and well-controlled trials of aripiprazole in pregnant women. Congenital anomalies have been reported; however, causal relationship with aripiprazole could not be established. Animal studies could not exclude potential developmental toxicity (see section 5.3). Patients must be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole. Due to insufficient safety information in humans and concerns raised by animal reproductive studies, this medicinal product should not be used in pregnancy unless the expected benefit clearly justifies the potential risk to the foetus.

Newborn infants exposed to antipsychotics (including aripiprazole) 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, newborn infants should be monitored carefully (see section 4.8).

Breast-feeding

Aripiprazole/metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from aripiprazole therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Aripiprazole did not impair fertility based on data from reproductive toxicity studies.

4.7 Effects on ability to drive and use machines

Aripiprazole has minor to moderate influence on the ability to drive and use machines due to potential nervous system and visual effects, such as sedation, somnolence, syncope, vision blurred, diplopia (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions in placebo-controlled trials were nausea, dizziness and somnolence each occurring in more than 3 % of patients treated with aripiprazole solution for injection.

Tabulated list of adverse reactions

The incidences of the Adverse Drug Reactions (ADRs) associated with aripiprazole therapy are tabulated below. The table is based on adverse events reported during clinical trials and/or post-marketing use.

All ADRs are listed by system organ 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) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

The frequency of adverse reactions reported during post-marketing use cannot be determined as they are derived from spontaneous reports. Consequently, the frequency of these adverse events is qualified as "not known".

	Common	**Uncommon**	**Not known**
Blood and lymphatic system disorders			Leukopenia Neutropenia Thrombocytopenia
Immune system disorders			Allergic reaction (e.g. anaphylactic reaction, angioedema including swollen tongue, tongue oedema, face oedema, pruritus allergic, or urticaria)
Endocrine disorders		Hyperprolactinaemia Blood prolactin decreased	Diabetic hyperosmolar coma Diabetic ketoacidosis
Metabolism and nutrition disorders	Diabetes mellitus	Hyperglycaemia	Hyponatremia Anorexia
Psychiatric disorders	Insomnia Anxiety Restlessness	Depression Hypersexuality	Suicide attempt, suicidal ideation and completed suicide (see section 4.4) Pathological gambling Impulse-control disorder Binge eating Compulsive shopping Poriomania Aggression Agitation Nervousness
Nervous system disorders	Akathisia Extrapyramidal disorder Tremor Headache Sedation Somnolence Dizziness	Tardive dyskinesia Dystonia Restless legs syndrome	Neuroleptic Malignant Syndrome Grand mal convulsion Serotonin syndrome Speech disorder
Eye disorders	Vision blurred	Diplopia Photophobia	Oculogyric crisis
Cardiac disorders		Tachycardia	Sudden death unexplained Torsades de pointes Ventricular arrhythmia Cardiac arrest Bradycardia

	Common	Uncommon	Not known
Vascular disorders		Orthostatic hypotension	Venous thromboembolism (including pulmonary embolism and deep vein thrombosis) Hypertension Syncope
Respiratory, thoracic and mediastinal disorders		Hiccups	Aspiration pneumonia Laryngospasm Oropharyngeal spasm
Gastrointestinal disorders	Constipation Dyspepsia Nausea Salivary hypersecretion Vomiting	Mouth dry	Pancreatitis Dysphagia Diarrhoea Abdominal discomfort Stomach discomfort
Hepatobiliary disorders			Hepatic failure Hepatitis Jaundice
Skin and subcutaneous tissue disorders			Rash Photosensitivity reaction Alopecia Hyperhidrosis Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders			Rhabdomyolysis Myalgia Stiffness
Renal and urinary disorders			Urinary incontinence Urinary retention
Pregnancy, puerperium and perinatal conditions			Drug withdrawal syndrome neonatal (see section 4.6)
Reproductive system and breast disorders			Priapism
General disorders and administration site conditions	Fatigue		Temperature regulation disorder (e.g. hypothermia, pyrexia) Chest pain Peripheral oedema
Investigations		Diastolic blood pressure increased	Weight decreased Weight gain Alanine Aminotransferase increased Aspartate Aminotransferase increased Gamma-glutamyltransferase increased Alkaline phosphatase increased QT prolonged Blood glucose increased Glycosylated haemoglobin increased Blood glucose fluctuation Creatine phosphokinase increased

Description of selected adverse reactions

Extrapyramidal symptoms (EPS)
Schizophrenia: in a long-term 52-week controlled trial, aripiprazole-treated patients had an overall-lower incidence (25.8 %) of EPS including Parkinsonism, akathisia, dystonia and dyskinesia compared with those treated with haloperidol (57.3 %). In a long-term 26-week placebo-controlled trial, the incidence of EPS was 19 % for aripiprazole-treated patients and 13.1 % for placebo-treated patients. In another long-term 26-week controlled trial, the incidence of EPS was 14.8 % for aripiprazole-treated patients and 15.1 % for olanzapine-treated patients.

Manic episodes in Bipolar I Disorder: in a 12-week controlled trial, the incidence of EPS was 23.5 % for aripiprazole-treated patients and 53.3 % for haloperidol-treated patients. In another 12-week trial, the incidence of EPS was 26.6 % for patients treated with aripiprazole and 17.6 % for those treated with lithium. In the long-term 26-week maintenance phase of a placebo-controlled trial, the incidence of EPS was 18.2 % for aripiprazole-treated patients and 15.7 % for placebo-treated patients.

Akathisia
In placebo-controlled trials, the incidence of akathisia in bipolar patients was 12.1 % with aripiprazole and 3.2 % with placebo. In schizophrenia patients the incidence of akathisia was 6.2 % with aripiprazole and 3.0 % with placebo.

Dystonia
Class effect: 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. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high 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.

Prolactin
In clinical trials for the approved indications and post-marketing, both increase and decrease in serum prolactin as compared to baseline was observed with aripiprazole (section 5.1).

Laboratory parameters
Comparisons between aripiprazole and placebo in the proportions of patients experiencing potentially clinically significant changes in routine laboratory and lipid parameters (see section 5.1) revealed no medically important differences. Elevations of CPK (Creatine Phosphokinase), generally transient and asymptomatic, were observed in 3.5 % of aripiprazole treated patients as compared to 2.0 % of patients who received placebo.

Pathological gambling and other impulse control disorders
Pathological gambling, hypersexuality, compulsive shopping and binge or compulsive eating can occur in patients treated with aripiprazole (see section 4.4).

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

No cases of overdose associated with adverse reactions were reported in clinical studies with ABILIFY solution for injection. Care must be taken to avoid inadvertent injection of this medicinal product into a blood vessel. Following any confirmed or suspected accidental overdose/inadvertent

intravenous administration, close observation of the patient is needed and if any potentially medically serious sign or symptom develops, monitoring, which should include continuous electrocardiographic monitoring, is required. The medical supervision and monitoring should continue until the patient recovers.

Signs and symptoms

In clinical trials and post-marketing experience, accidental or intentional acute overdose of aripiprazole alone was identified in adult patients with reported estimated doses up to 1,260 mg with no fatalities. The potentially medically important signs and symptoms observed included lethargy, increased blood pressure, somnolence, tachycardia, nausea, vomiting and diarrhoea. In addition, reports of accidental overdose with aripiprazole alone (up to 195 mg) in children have been received with no fatalities. The potentially medically serious signs and symptoms reported included somnolence, transient loss of consciousness and extrapyramidal symptoms.

Management of overdose

Management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. The possibility of multiple medicinal product involvement should be considered. Therefore cardiovascular monitoring should be started immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. Following any confirmed or suspected overdose with aripiprazole, close medical supervision and monitoring should continue until the patient recovers.

Activated charcoal (50 g), administered one hour after aripiprazole, decreased aripiprazole C_{max} by about 41 % and AUC by about 51 %, suggesting that charcoal may be effective in the treatment of overdose.

Haemodialysis

Although there is no information on the effect of haemodialysis in treating an overdose with aripiprazole, haemodialysis is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, other antipsychotics, ATC code: N05AX12

Mechanism of action

It has been proposed that aripiprazole's efficacy in schizophrenia and Bipolar I Disorder is mediated through a combination of partial agonism at dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonism of serotonin 5-HT_{2A} receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity. Aripiprazole exhibited high binding affinity *in vitro* for dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors and moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha-1 adrenergic and histamine H_1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

Aripiprazole doses ranging from 0.5 mg to 30 mg administered once a day to healthy subjects for 2 weeks produced a dose-dependent reduction in the binding of ^{11}C-raclopride, a D_2/D_3 receptor ligand, to the caudate and putamen detected by positron emission tomography.

Clinical efficacy and safety

Agitation in schizophrenia and Bipolar I Disorder with ABILIFY solution for injection
In two short-term (24-hour) placebo-controlled trials involving 554 schizophrenic adult patients presenting with agitation and disturbed behaviours, ABILIFYsolution for injection was associated with statistically significant greater improvements in agitation/behavioural symptoms compared to placebo and was similar to haloperidol.

In one short-term (24-hour) placebo-controlled trial involving 291 patients with bipolar disorder presenting with agitation and disturbed behaviours, ABILIFY solution for injection was associated with statistically significant greater improvements in agitation/behavioural symptoms compared to placebo and was similar to the reference arm lorazepam. The observed mean improvement from baseline on the PANSS Excitement Component score at the primary 2-hour endpoint was 5.8 for placebo, 9.6 for lorazepam, and 8.7 for ABILIFY solution for injection. In subpopulation analyses on patients with mixed episodes or on patients with severe agitation, a similar pattern of efficacy to the overall population was observed but statistical significance could not be established due to a reduced sample size.

Schizophrenia with oral aripiprazole
In three short-term (4 to 6 weeks) placebo-controlled trials involving 1,228 schizophrenic adult patients, presenting with positive or negative symptoms, oral aripiprazole was associated with statistically significantly greater improvements in psychotic symptoms compared to placebo.

Aripiprazole is effective in maintaining the clinical improvement during continuation therapy in adult patients who have shown an initial treatment response. In a haloperidol-controlled trial, the proportion of responder patients maintaining response to medicinal product at 52-weeks was similar in both groups (oral aripiprazole 77 % and haloperidol 73 %). The overall completion rate was significantly higher for patients on oral aripiprazole (43 %) than for oral haloperidol (30 %). Actual scores in rating scales used as secondary endpoints, including PANSS and the Montgomery-Åsberg Depression Rating Scale (MADRS) showed a significant improvement over haloperidol.

In a 26-week, placebo-controlled trial in adult stabilised patients with chronic schizophrenia, oral aripiprazole had significantly greater reduction in relapse rate, 34 % in oral aripiprazole group and 57 % in placebo.

Weight gain
In clinical trials oral aripiprazole has not been shown to induce clinically relevant weight gain. In a 26-week, olanzapine-controlled, double-blind, multi-national study of schizophrenia which included 314 adult patients and where the primary endpoint was weight gain, significantly less patients had at least 7 % weight gain over baseline (i.e. a gain of at least 5.6 kg for a mean baseline weight of ~80.5 kg) on oral aripiprazole (n = 18, or 13 % of evaluable patients), compared to oral olanzapine (n = 45, or 33 % of evaluable patients).

Lipid parameters
In a pooled analysis on lipid parameters from placebo controlled clinical trials in adults, aripiprazole has not been shown to induce clinically relevant alterations in levels of total cholesterol, triglycerides, High Density Lipoprotein (HDL) and Low Density Lipoprotein (LDL).

Prolactin
Prolactin levels were evaluated in all trials of all doses of aripiprazole (n = 28,242). The incidence of hyperprolactinaemia or increased serum prolactin in patients treated with aripiprazole (0.3 %) was similar to that of placebo (0.2 %). For patients receiving aripiprazole, the median time to onset was 42 days and median duration was 34 days.

The incidence of hypoprolactinaemia or decreased serum prolactin in patients treated with aripiprazole was 0.4 %, compared with 0.02 % for patients treated with placebo. For patients receiving aripiprazole, the median time to onset was 30 days and median duration was 194 days.

Manic episodes in Bipolar I Disorder with oral aripiprazole
In two 3-week, flexible-dose, placebo-controlled monotherapy trials involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole demonstrated superior efficacy to placebo in reduction of manic symptoms over 3 weeks. These trials included patients with or without psychotic features and with or without a rapid-cycling course.

In one 3-week, fixed-dose, placebo-controlled monotherapy trial involving patients with a manic or mixed episode of Bipolar I Disorder, aripiprazole failed to demonstrate superior efficacy to placebo.

In two 12-week, placebo- and active-controlled monotherapy trials in patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, aripiprazole demonstrated superior efficacy to placebo at week 3 and a maintenance of effect comparable to lithium or haloperidol at week 12. Aripiprazole also demonstrated a comparable proportion of patients in symptomatic remission from mania as lithium or haloperidol at week 12.

In a 6-week, placebo-controlled trial involving patients with a manic or mixed episode of Bipolar I Disorder, with or without psychotic features, who were partially non-responsive to lithium or valproate monotherapy for 2 weeks at therapeutic serum levels, the addition of aripiprazole as adjunctive therapy resulted in superior efficacy in reduction of manic symptoms than lithium or valproate monotherapy.

In a 26-week, placebo-controlled trial, followed by a 74-week extension, in manic patients who achieved remission on aripiprazole during a stabilization phase prior to randomisation, aripiprazole demonstrated superiority over placebo in preventing bipolar recurrence, primarily in preventing recurrence into mania but failed to demonstrate superiority over placebo in preventing recurrence into depression.

In a 52-week, placebo-controlled trial, in patients with a current manic or mixed episode of Bipolar I Disorder who achieved sustained remission (Young Mania Rating Scale [YMRS] and MADRS with total scores ≤ 12) on aripiprazole (10 mg/day to 30 mg/day) adjunctive to lithium or valproate for 12 consecutive weeks, adjunctive aripiprazole demonstrated superiority over placebo with a 46 % decreased risk (hazard ratio of 0.54) in preventing bipolar recurrence and a 65 % decreased risk (hazard ratio of 0.35) in preventing recurrence into mania over adjunctive placebo but failed to demonstrate superiority over placebo in preventing recurrence into depression. Adjunctive aripiprazole demonstrated superiority over placebo on the secondary outcome measure in Clinical Global Impression - Bipolar version (CGI-BP) Severity of Illness (SOI; mania) scores. In this trial, patients were assigned by investigators with either open-label lithium or valproate monotherapy to determine partial non-response. Patients were stabilised for at least 12 consecutive weeks with the combination of aripiprazole and the same mood stabilizer. Stabilized patients were then randomised to continue the same mood stabilizer with double-blind aripiprazole or placebo. Four mood stabilizer subgroups were assessed in the randomised phase: aripiprazole + lithium; aripiprazole + valproate; placebo + lithium; placebo + valproate. The Kaplan-Meier rates for recurrence to any mood episode for the adjunctive treatment arm were 16 % in aripiprazole + lithium and 18 % in aripiprazole + valproate compared to 45 % in placebo + lithium and 19 % in placebo + valproate.

The European Medicines Agency has deferred the obligation to submit the results of studies with ABILIFY in one or more subsets of the paediatric population in the treatment of schizophrenia and in the treatment of bipolar affective disorder (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Aripiprazole administered intramuscularly as a single-dose to healthy subjects is well absorbed and has an absolute bioavailability of 100 %. The aripiprazole AUC in the first 2 hours after an intramuscular injection was 90 % greater than the AUC after the same dose as a tablet; systemic exposure was generally similar between the 2 formulations. In 2 studies in healthy subjects the median times to the peak plasma concentrations were 1 and 3 hours after dosing.

Distribution

Based on results from trials with oral administration of aripiprazole, aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4.9 L/kg, indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and dehydro-aripiprazole are greater than 99 % bound to serum proteins, binding primarily to albumin.

Biotransformation

Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicinal product moiety in systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40 % of aripiprazole AUC in plasma.

Elimination

The mean elimination half-lives for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6.

The total body clearance of aripiprazole is 0.7 mL/min/kg, which is primarily hepatic.

Following a single oral dose of [^{14}C]-labelled aripiprazole, approximately 27 % of the administered radioactivity was recovered in the urine and approximately 60 % in the faeces. Less than 1 % of unchanged aripiprazole was excreted in the urine and approximately 18 % was recovered unchanged in the faeces.

Pharmacokinetics in special patient groups

Elderly
There are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects, nor is there any detectable effect of age in a population pharmacokinetic analysis in schizophrenic patients.

Gender
There are no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects nor is there any detectable effect of gender in a population pharmacokinetic analysis in schizophrenic patients.

Smoking
Population pharmacokinetic evaluation of oral aripiprazole has revealed no evidence of clinically relevant effects from smoking on the pharmacokinetics of aripiprazole.

Race
Population pharmacokinetic evaluation showed no evidence of race-related differences on the pharmacokinetics of aripiprazole.

Renal impairment
The pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to young healthy subjects.

Hepatic impairment
A single-dose study in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C) did not reveal a significant effect of hepatic impairment on the pharmacokinetics of aripiprazole and dehydro-aripiprazole, but the study included only 3 patients with Class C liver cirrhosis, which is insufficient to draw conclusions on their metabolic capacity.

5.3 Preclinical safety data

Administration of ABILIFY solution for injection was well tolerated and produced no direct target organ toxicity in rats or monkeys after repeated dosing at systemic exposures (AUC) that were 15 and 5 times, respectively, human exposure at the maximum recommended human dose of 30 mg intramuscular. In intravenous reproductive toxicity studies, no new safety concerns were observed at maternal exposures up to 15 (rat) and 29 (rabbit) times human exposure at 30 mg.

Non-clinical data reveal no special hazard for humans based on conventional oral aripiprazole studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

Toxicologically significant effects were observed only at doses or exposures that were sufficiently in excess of the maximum human dose or exposure, indicating that these effects were limited or of no relevance to clinical use. These included: dose-dependent adrenocortical toxicity (lipofuscin pigment accumulation and/or parenchymal cell loss) in rats after 104 weeks at 20 mg/kg/day to 60 mg/kg/day (3 to 10 times the mean steady-state AUC at the maximum recommended human dose) and increased adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas in female rats at 60 mg/kg/day (10 times the mean steady-state AUC at the maximum recommended human dose). The highest nontumorigenic exposure in female rats was 7 times the human exposure at the recommended dose.

An additional finding was cholelithiasis as a consequence of precipitation of sulphate conjugates of hydroxy metabolites of aripiprazole in the bile of monkeys after repeated oral dosing at 25 mg/kg/day to 125 mg/kg/day (1 to 3 times the mean steady-state AUC at the maximum recommended clinical dose or 16 to 81 times the maximum recommended human dose based on mg/m^2). However, the concentrations of the sulphate conjugates of hydroxy aripiprazole in human bile at the highest dose proposed, 30 mg per day, were no more than 6 % of the bile concentrations found in the monkeys in the 39-week study and are well below (6 %) their limits of *in vitro* solubility.

In repeat-dose studies in juvenile rats and dogs, the toxicity profile of aripiprazole was comparable to that observed in adult animals, and there was no evidence of neurotoxicity or adverse reactions on development.

Based on results of a full range of standard genotoxicity tests, aripiprazole was considered non-genotoxic. Aripiprazole did not impair fertility in reproductive toxicity studies. Developmental toxicity, including dose-dependent delayed foetal ossification and possible teratogenic effects, were observed in rats at doses resulting in subtherapeutic exposures (based on AUC) and in rabbits at doses resulting in exposures 3 and 11 times the mean steady-state AUC at the maximum recommended clinical dose. Maternal toxicity occurred at doses similar to those eliciting developmental toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sulfobutylether β-cyclodextrin (SBECD)
Tartaric acid
Sodium hydroxide
Water for injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months
After opening: use product immediately.

6.4 Special precautions for storage

Keep the vial in the outer carton in order to protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Each carton contains one single-use type I glass vial with a rubber butyl stopper and a "tear-off" aluminium seal.

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

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/036

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 June 2004
Date of latest renewal: 04 June 2009

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 manufacturers responsible for batch release

Elaiapharm
2881 Route des Crêtes, Z.I. Les Bouilides-Sophia Antipolis,
06560 Valbonne
France

Zambon S.p.A.
Via della Chimica, 9
I-36100 Vicenza(VI)
Italy

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 5 mg tablets
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 5 mg of aripiprazole.

3. LIST OF EXCIPIENTS

Also contains: lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

14 × 1 tablets
28 × 1 tablets
49 × 1 tablets
56 × 1 tablets
98 × 1 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 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

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/001 (5 mg, 14 × 1 tablets)
EU/1/04/276/002 (5 mg, 28 × 1 tablets)
EU/1/04/276/003 (5 mg, 49 × 1 tablets)
EU/1/04/276/004 (5 mg, 56 × 1 tablets)
EU/1/04/276/005 (5 mg, 98 × 1 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

abilify 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

ABILIFY 5 mg tablets
aripiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Otsuka

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 10 mg tablets
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg of aripiprazole.

3. LIST OF EXCIPIENTS

Also contains: lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

14 × 1 tablets
28 × 1 tablets
49 × 1 tablets
56 × 1 tablets
98 × 1 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 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

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/006 (10 mg, 14 × 1 tablets)
EU/1/04/276/007 (10 mg, 28 × 1 tablets)
EU/1/04/276/008 (10 mg, 49 × 1 tablets)
EU/1/04/276/009 (10 mg, 56 × 1 tablets)
EU/1/04/276/010 (10 mg, 98 × 1 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

abilify 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

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 10 mg tablets
aripiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Otsuka

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 15 mg tablets
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 15 mg of aripiprazole.

3. LIST OF EXCIPIENTS

Also contains: lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

14 × 1 tablets
28 × 1 tablets
49 × 1 tablets
56 × 1 tablets
98 × 1 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 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

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/011 (15 mg, 14 × 1 tablets)
EU/1/04/276/012 (15 mg, 28 × 1 tablets)
EU/1/04/276/013 (15 mg, 49 × 1 tablets)
EU/1/04/276/014 (15 mg, 56 × 1 tablets)
EU/1/04/276/015 (15 mg, 98 × 1 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

abilify 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

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 15 mg tablets
aripiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Otsuka

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 30 mg tablets
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 30 mg of aripiprazole.

3. LIST OF EXCIPIENTS

Also contains: lactose monohydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

Tablets

14 × 1 tablets
28 × 1 tablets
49 × 1 tablets
56 × 1 tablets
98 × 1 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 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

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/016 (30 mg, 14 × 1 tablets)
EU/1/04/276/017 (30 mg, 28 × 1 tablets)
EU/1/04/276/018 (30 mg, 49 × 1 tablets)
EU/1/04/276/019 (30 mg, 56 × 1 tablets)
EU/1/04/276/020 (30 mg, 98 × 1 tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

abilify 30 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

ABILIFY 30 mg tablets
aripiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Otsuka

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 10 mg orodispersible tablets
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg of aripiprazole.

3. LIST OF EXCIPIENTS

Contains aspartame and lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Orodispersible tablets

14 × 1 orodispersible tablets
28 × 1 orodispersible tablets
49 × 1 orodispersible 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 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

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/024 (10 mg, 14 × 1 orodispersible tablets)
EU/1/04/276/025 (10 mg, 28 × 1 orodispersible tablets)
EU/1/04/276/026 (10 mg, 49 × 1 orodispersible tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

abilify 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

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 10 mg orodispersible tablets
aripiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Otsuka

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 15 mg orodispersible tablets
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 15 mg of aripiprazole.

3. LIST OF EXCIPIENTS

Contains aspartame and lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Orodispersible tablets

14 × 1 orodispersible tablets
28 × 1 orodispersible tablets
49 × 1 orodispersible 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 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

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/027 (15 mg, 14 × 1 orodispersible tablets)
EU/1/04/276/028 (15 mg, 28 × 1 orodispersible tablets)
EU/1/04/276/029 (15 mg, 49 × 1 orodispersible tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

abilify 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

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 15 mg orodispersible tablets
aripiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Otsuka

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 30 mg orodispersible tablets
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 30 mg of aripiprazole.

3. LIST OF EXCIPIENTS

Contains aspartame and lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Orodispersible tablets

14 × 1 orodispersible tablets
28 × 1 orodispersible tablets
49 × 1 orodispersible 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 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

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/030 (30 mg, 14 × 1 orodispersible tablets)
EU/1/04/276/031 (30 mg, 28 × 1 orodispersible tablets)
EU/1/04/276/032 (30 mg, 49 × 1 orodispersible tablets)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

abilify 30 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

ABILIFY 30 mg orodispersible tablets
aripiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Otsuka

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

OUTER CARTON AND BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 1 mg/mL oral solution
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL contains 1 mg of aripiprazole.

3. LIST OF EXCIPIENTS

Contains fructose, sucrose, E218, and E216.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral solution

50 mL oral solution
150 mL oral solution
480 mL oral solution

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
Use within 6 months after first opening.

9. SPECIAL STORAGE CONDITIONS

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

Outer carton:
Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/033 - 50 mL bottle
EU/1/04/276/034 - 150 mL bottle
EU/1/04/276/035 - 480 mL bottle

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Outer carton: abilify 1 mg/mL

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 OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ABILIFY 7.5 mg/mL solution for injection
aripiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL contains 7.5 mg of aripiprazole. A vial provides 9.75 mg in 1.3 mL.

3. LIST OF EXCIPIENTS

Also contains sulfobutylether b-cyclodextrin, tartaric acid, sodium hydroxide, and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 vial
9.75 mg / 1.3 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intramuscular 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

Keep the vial in the outer carton 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

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/04/276/036

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

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

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ABILIFY 7.5 mg/mL solution for injection
aripiprazole

IM use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

9.75 mg / 1.3 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

ABILIFY 5 mg tablets
ABILIFY 10 mg tablets
ABILIFY 15 mg tablets
ABILIFY 30 mg tablets

aripiprazole

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 ABILIFY is and what it is used for

ABILIFY contains the active substance aripiprazole and belongs to a group of medicines called antipsychotics. It is used to treat adults and adolescents aged 15 years and older who suffer from a disease characterised by symptoms such as hearing, seeing or sensing things which are not there, suspiciousness, mistaken beliefs, incoherent speech and behaviour and emotional flatness. People with this condition may also feel depressed, guilty, anxious or tense.

ABILIFY is used to treat adults and adolescents aged 13 years and older who suffer from a condition with symptoms such as feeling "high", having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas and sometimes severe irritability. In adults it also prevents this condition from returning in patients who have responded to the treatment with ABILIFY.

2. What you need to know before you take ABILIFY

Do not take ABILIFY
- if you are allergic to aripiprazole or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor before taking ABILIFY.

Suicidal thoughts and behaviours have been reported during aripiprazole treatment. Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself.

Before treatment with ABILIFY, tell your doctor if you suffer from
- high blood sugar (characterised by symptoms such as excessive thirst, passing of large amounts of urine, increase in appetite and feeling weak) or family history of diabetes
- fits (seizures) since your doctor may want to monitor you more closely

- involuntary, irregular muscle movements, especially in the face
- cardiovascular diseases (diseases of the heart and circulation), family history of cardiovascular disease, stroke or "mini" stroke, abnormal blood pressure
- blood clots, or family history of blood clots, as antipsychotics have been associated with formation of blood clots
- past experience with excessive gambling

If you notice you are gaining weight, develop unusual movements, experience somnolence that interferes with normal daily activities, any difficulty in swallowing or allergic symptoms, please tell your doctor.

If you are an elderly patient suffering from dementia (loss of memory and other mental abilities), you or your carer/relative should tell your doctor if you have ever had a stroke or "mini" stroke.

Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself. Suicidal thoughts and behaviours have been reported during aripiprazole treatment.

Tell your doctor immediately if you suffer from muscle stiffness or inflexibility with high fever, sweating, altered mental status, or very rapid or irregular heartbeat.

Tell your doctor if you or your family/carer notices that you are developing urges or cravings to behave in ways that are unusual for you and you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These are called impulse control disorders and can include behaviours such as addictive gambling, excessive eating or spending, an abnormally high sex drive or preoccupation with an increase in sexual thoughts or feelings.
Your doctor may need to adjust or stop your dose.

Aripiprazole may cause sleepiness, fall in blood pressure when standing up, dizziness and changes in your ability to move and balance, which may lead to falls. Caution should be taken, particularly if you are an elderly patient or have some debility.

Children and adolescents
Do not use this medicine in children and adolescents under 13 years of age. It is not known if it is safe and effective in these patients.

Other medicines and ABILIFY
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Blood pressure-lowering medicines: ABILIFY may increase the effect of medicines used to lower the blood pressure. Be sure to tell your doctor if you take a medicine to keep your blood pressure under control.

Taking ABILIFY with some medicines may mean the doctor will need to change your dose of ABILIFY or the other medicines. It is especially important to mention the following to your doctor:

- medicines to correct heart rhythm (such as quinidine, amiodarone, flecainide)
- antidepressants or herbal remedy used to treat depression and anxiety (such as fluoxetine, paroxetine, venlafaxine, St. John's Wort)
- antifungal medicines (such as ketoconazole, itraconazole)
- certain medicines to treat HIV infection (such as efavirenz, nevirapine, an protease inhibitors e.g. indinavir, ritonavir)
- anticonvulsants used to treat epilepsy (such as carbamazepine, phenytoin, phenobarbital)
- certain antibiotics used to treat tuberculosis (rifabutin, rifampicin)

These medicines may increase the risk of side effects or reduce the effect of ABILIFY; if you get any unusual symptom taking any of these medicines together with ABILIFY you should see your doctor.

Medicines that increase the level of serotonin are typically used in conditions including depression, generalised anxiety disorder, obsessive-compulsive disorder (OCD) and social phobia as well as migraine and pain:

- triptans, tramadol and tryptophan used for conditions including depression, generalised anxiety disorder, obsessive compulsive disorder (OCD) and social phobia as well as migraine and pain
- selective-serotonin-reuptake-inhibitors (SSRIs) (such as paroxetine and fluoxetine) used for depression, OCD, panic and anxiety
- other anti-depressants (such as venlafaxine and tryptophan) used in major depression
- tricyclic's (such as clomipramine and amitriptyline) used for depressive illness
- St John's Wort (*Hypericum perforatum*) used as a herbal remedy for mild depression
- pain killers (such as tramadol and pethidine) used for pain relief
- triptans (such as sumatriptan and zolmitripitan) used for treating migraine

These medicines may increase the risk of side effects; if you get any unusual symptom taking any of these medicines together with ABILIFY, you should see your doctor.

ABILIFY with food, drink and alcohol
This medicine can be taken regardless of meals.
Alcohol should be avoided.

Pregnancy, breast-feeding and fertility
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.

The following symptoms may occur in newborn babies, of mothers that have used ABILIFY 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.

If you are taking ABILIFY, your doctor will discuss with you whether you should breast-feed considering the benefit to you of your therapy and the benefit to your baby of breast-feeding. You should not do both. Talk to your doctor about the best way to feed your baby if you are taking this medicine.

Driving and using machines
Dizziness and vision problems may occur during treatment with this medicine (see section 4).
This should be considered in cases where full alertness is required, e.g. when driving a car or handling machines.

ABILIFY contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take ABILIFY

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose for adults is 15 mg once a day. However your doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

Use in children and adolescents
This medicine may be started at a low dose with the oral solution (liquid) form.
The dose may be gradually increased to **the recommended dose for adolescents of 10 mg once a**

day. However your doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

If you have the impression that the effect of ABILIFY is too strong or too weak, talk to your doctor or pharmacist.

Try to take ABILIFY at the same time each day. It does not matter whether you take it with or without food. Always take the tablet with water and swallow it whole.

Even if you feel better, do not alter or discontinue the daily dose of ABILIFY without first consulting your doctor.

If you take more ABILIFY than you should
If you realise you have taken more ABILIFY than your doctor has recommended (or if someone else has taken some of your ABILIFY), contact your doctor right away. If you cannot reach your doctor, go to the nearest hospital and take the pack with you.

Patients who have taken too much aripiprazole have experienced the following symptoms:
- rapid heartbeat, 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, slower breathing, choking, high or low blood pressure, abnormal rhythms of the heart.

Contact your doctor or hospital immediately if you experience any of the above.

If you forget to take ABILIFY
If you miss a dose, take the missed dose as soon as you remember but do not take two doses in one day.

If you stop taking ABILIFY
Do not stop your treatment just because you feel better. It is important that you carry on taking ABILIFY for as long as your doctor has told you to.

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.

Common side effects (may affect up to 1 in 10 people):

- diabetes mellitus,
- difficulty sleeping,
- feeling anxious,
- feeling restless and unable to keep still, difficulty sitting still,
- akathisia (an uncomfortable feeling of inner restlessness and a compelling need to move constantly),
- uncontrollable twitching, jerking or writhing movements,
- trembling,
- headache,
- tiredness,
- sleepiness,
- light-headedness,
- shaking and blurred vision,

- decreased number of or difficulty making bowel movements,
- indigestion,
- feeling sick,
- more saliva in mouth than normal,
- vomiting,
- feeling tired.

Uncommon side effects (may affect up to 1 in 100 people):

- increased or decreased blood levels of the hormone prolactin,
- too much sugar in the blood,
- depression,
- altered or increased sexual interest,
- uncontrollable movements of mouth, tongue and limbs (tardive dyskinesia),
- muscle disorder causing twisting movements (dystonia),
- restless legs,
- double vision,
- eye sensitivity to light,
- fast heartbeat,
- a fall in blood pressure on standing up which causes dizziness, light-headedness or fainting,
- hiccups.

The following side effects have been reported since the marketing of oral aripiprazole but the frequency for them to occur is not known:

- low levels of white blood cells,
- low levels of blood platelets,
- allergic reaction (e.g. swelling in the mouth, tongue, face and throat, itching, hives),
- onset or worsening of diabetes, ketoacidosis (ketones in the blood and urine) or coma,
- high blood sugar,
- not enough sodium in the blood,
- loss of appetite (anorexia),
- weight loss,
- weight gain,
- thoughts of suicide, suicide attempt and suicide,
- feeling aggressive,
- agitation,
- nervousness,
- combination of fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and heart rate, fainting (neuroleptic malignant syndrome),
- seizure,
- serotonin syndrome (a reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles),
- speech disorder,
- fixation of the eyeballs in one position,
- sudden unexplained death,
- life-threatening irregular heartbeat,
- heart attack,
- slower heartbeat,
- 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),
- high blood pressure,
- fainting,
- accidental inhalation of food with risk of pneumonia (lung infection),
- spasm of the muscles around the voice box,
- inflammation of the pancreas,

- difficulty swallowing,
- diarrhoea,
- abdominal discomfort,
- stomach discomfort,
- liver failure,
- inflammation of the liver,
- yellowing of the skin and white part of eyes,
- reports of abnormal liver tests values,
- skin rash,
- skin sensitivity to light,
- baldness,
- excessive sweating,
- 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 in blood tests and an increase in a type of white blood cell (eosinophilia),
- abnormal muscle breakdown which can lead to kidney problems,
- muscle pain,
- stiffness,
- involuntary loss of urine (incontinence),
- difficulty in passing urine,
- withdrawal symptoms in newborn babies in case of exposure during pregnancy,
- prolonged and/or painful erection,
- difficulty controlling core body temperature or overheating,
- chest pain,
- swelling of hands, ankles or feet,
- in blood tests: increased or fluctuating blood sugar, increased glycosylated haemoglobin.
- Inability to resist the impulse, drive or temptation to perform an action that could be harmful to you or others, which may include:
  - strong impulse to gamble excessively despite serious personal or family consequences
  - altered or increased sexual interest and behaviour of significant concern to you or to others, for example, an increased sexual drive
  - uncontrollable excessive shopping
  - binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger)
  - a tendency to wander away.

  Tell your doctor if you experience any of these behaviours; he/she will discuss ways of managing or reducing the symptoms.

In elderly patients with dementia, more fatal cases have been reported while taking aripiprazole. In addition, cases of stroke or "mini" stroke have been reported.

Additional side effects in children and adolescents
Adolescents aged 13 years and older experienced side effects that were similar in frequency and type to those in adults except that sleepiness, uncontrollable twitching or jerking movements, restlessness, and tiredness were very common (greater than 1 in 10 patients) and upper abdominal pain, dry mouth, increased heart rate, weight gain, increased appetite, muscle twitching, uncontrolled movements of the limbs, and feeling dizzy, especially when getting up from a lying or sitting position, were common (greater than 1 in 100 patients).

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 ABILIFY

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 and on the carton after EXP. The expiry date refers to the last day of that month.

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 protect the environment.

6. Contents of the pack and other information

What ABILIFY contains

- The active substance is aripiprazole.
  Each tablet contains 5 mg of aripiprazole.
  Each tablet contains 10 mg of aripiprazole.
  Each tablet contains 15 mg of aripiprazole.
  Each tablet contains 30 mg of aripiprazole.

- The other ingredients are lactose monohydrate, maize starch, microcrystalline cellulose, hydroxypropylcellulose and magnesium stearate.
  Tablet coat

ABILIFY 5 mg tablets:	Indigo carmine aluminium lake (E 132)
ABILIFY 10 mg tablets:	Red iron oxide (E 172)
ABILIFY 15 mg tablets:	Yellow iron oxide (E 172)
ABILIFY 30 mg tablets:	Red iron oxide (E 172)

What ABILIFY looks like and contents of the pack
ABILIFY 5 mg tablets are rectangular and blue, marked with ‘A-007’ and ‘5’ on one side.
ABILIFY 10 mg tablets are rectangular and pink, marked with ‘A-008’ and ‘10’ on one side.
ABILIFY 15 mg tablets are round and yellow, marked with ‘A-009’ and ‘15’ on one side.
ABILIFY 30 mg tablets are round and pink, marked with ‘A-011’ and ‘30’ on one side.

ABILIFY tablets are supplied in perforated unit dose blisters packed in cartons containing 14 × 1, 28 × 1, 49 × 1, 56 × 1, or 98 × 1 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

Manufacturer
Elaiapharm
2881 Route des Crêtes, Z.I. Les Bouilides-Sophia Antipolis,
06560 Valbonne
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

България
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Česká republika
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Danmark
Otsuka Pharma Scandinavia AB
Tlf: +46 (0) 8 545 286 60

Deutschland
Otsuka Pharma GmbH
Tel: +49 (0) 69 1700 860

Eesti
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Ελλάδα
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

España
Otsuka Pharmaceutical, S.A.
Tel: +34 93 550 01 00

France
Otsuka Pharmaceutical France SAS
Tél: +33 (0)1 47 08 00 00

Hrvatska
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Ireland
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Ísland
Vistor hf.
Sími: +354 (0) 535 7000

Italia
Otsuka Pharmaceutical Italy S.r.l.
Tel: +39 (0) 2 0063 2710

Κύπρος
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Lietuva
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Luxembourg/Luxemburg
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Magyarország
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Malta
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Nederland
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Norge
Otsuka Pharma Scandinavia AB
Tlf: +46 (0) 8 545 286 60

Österreich
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Polska
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Portugal
Lundbeck Portugal Lda
Tel: +351 (0) 21 00 45 900

România
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Slovenija
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Slovenská republika
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Suomi/Finland
Otsuka Pharma Scandinavia AB
Puh/Tel: +46 (0) 8 545 286 60

Sverige
Otsuka Pharma Scandinavia AB
Tel: +46 (0) 8 545 286 60

Latvija
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

United Kingdom (Northern Ireland)
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

This leaflet was last revised in {MM/YYYY}

Other sources of information

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

ABILIFY 10 mg orodispersible tablets
ABILIFY 15 mg orodispersible tablets
ABILIFY 30 mg orodispersible tablets

aripiprazole

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 ABILIFY is and what it is used for

ABILIFY contains the active substance aripiprazole and belongs to a group of medicines called antipsychotics. It is used to treat adults and adolescents aged 15 years and older who suffer from a disease characterised by symptoms such as hearing, seeing or sensing things which are not there, suspiciousness, mistaken beliefs, incoherent speech and behaviour and emotional flatness. People with this condition may also feel depressed, guilty, anxious or tense.

ABILIFY is used to treat adults and adolescents aged 13 years and older who suffer from a condition with symptoms such as feeling "high", having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas and sometimes severe irritability. In adults it also prevents this condition from returning in patients who have responded to the treatment with ABILIFY.

2. What you need to know before you take ABILIFY

Do not take ABILIFY
- if you are allergic to aripiprazole or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor before taking ABILIFY.

Suicidal thoughts and behaviours have been reported during aripiprazole treatment. Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself.

Before treatment with ABILIFY, tell your doctor if you suffer from
- high blood sugar (characterised by symptoms such as excessive thirst, passing of large amounts of urine, increase in appetite and feeling weak) or family history of diabetes
- fits (seizures) since your doctor may want to monitor you more closely
- involuntary, irregular muscle movements, especially in the face

- cardiovascular diseases (diseases of the heart and circulation), family history of cardiovascular disease, stroke or "mini" stroke, abnormal blood pressure
- blood clots, or family history of blood clots, as antipsychotics have been associated with formation of blood clots
- past experience with excessive gambling

If you notice you are gaining weight, develop unusual movements, experience somnolence that interferes with normal daily activities, any difficulty in swallowing or allergic symptoms, please tell your doctor.

If you are an elderly patient suffering from dementia (loss of memory and other mental abilities), you or your carer/relative should tell your doctor if you have ever had a stroke or "mini" stroke.

Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself. Suicidal thoughts and behaviours have been reported during aripiprazole treatment.

Tell your doctor immediately if you suffer from muscle stiffness or inflexibility with high fever, sweating, altered mental status, or very rapid or irregular heartbeat.

Tell your doctor if you or your family/carer notices that you are developing urges or cravings to behave in ways that are unusual for you and you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These are called impulse control disorders and can include behaviours such as addictive gambling, excessive eating or spending, an abnormally high sex drive or preoccupation with an increase in sexual thoughts or feelings.
Your doctor may need to adjust or stop your dose.

Aripiprazole may cause sleepiness, fall in blood pressure when standing up, dizziness and changes in your ability to move and balance, which may lead to falls. Caution should be taken, particularly if you are an elderly patient or have some debility.

Children and adolescents
Do not use this medicine in children and adolescents under 13 years of age. It is not known if it is safe and effective in these patients.

Other medicines and ABILIFY
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Blood pressure-lowering medicines: ABILIFY may increase the effect of medicines used to lower the blood pressure. Be sure to tell your doctor if you take a medicine to keep your blood pressure under control.

Taking ABILIFY with some medicines may mean the doctor will need to change your dose of ABILIFY or the other medicines. It is especially important to mention the following to your doctor:

- medicines to correct heart rhythm (such as quinidine, amiodarone, flecainide)
- antidepressants or herbal remedy used to treat depression and anxiety (such as fluoxetine, paroxetine, venlafaxine, St. John's Wort)
- antifungal medicines (such as ketoconazole, itraconazole)
- certain medicines to treat HIV infection (such as efavirenz, nevirapine, an protease inhibitors e.g. indinavir, ritonavir)
- anticonvulsants used to treat epilepsy (such as carbamazepine, phenytoin, phenobarbital)
- certain antibiotics used to treat tuberculosis (rifabutin, rifampicin)

These medicines may increase the risk of side effects or reduce the effect of ABILIFY; if you get any unusual symptom taking any of these medicines together with ABILIFY you should see your doctor.

Medicines that increase the level of serotonin are typically used in conditions including depression, generalised anxiety disorder, obsessive-compulsive disorder (OCD) and social phobia as well as migraine and pain:

- triptans, tramadol and tryptophan used for conditions including depression, generalised anxiety disorder, obsessive compulsive disorder (OCD) and social phobia as well as migraine and pain
- selective-serotonin-reuptake-inhibitors (SSRIs) (such as paroxetine and fluoxetine) used for depression, OCD, panic and anxiety
- other anti-depressants (such as venlafaxine and tryptophan) used in major depression
- tricyclic's (such as clomipramine and amitriptyline) used for depressive illness
- St John's Wort (*Hypericum perforatum*) used as a herbal remedy for mild depression
- pain killers (such as tramadol and pethidine) used for pain relief
- triptans (such as sumatriptan and zolmitripitan) used for treating migraine

These medicines may increase the risk of side effects; if you get any unusual symptom taking any of these medicines together with ABILIFY, you should see your doctor.

ABILIFY with food, drink and alcohol
This medicine can be taken regardless of meals.
Alcohol should be avoided.

Pregnancy, breast-feeding and fertility
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.

The following symptoms may occur in newborn babies, of mothers that have used ABILIFY 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.

If you are taking ABILIFY, your doctor will discuss with you whether you should breast-feed considering the benefit to you of your therapy and the benefit to your baby of breast-feeding. You should not do both. Talk to your doctor about the best way to feed your baby if you are taking this medicine.

Driving and using machines
Dizziness and vision problems may occur during treatment with this medicine (see section 4).
This should be considered in cases where full alertness is required, e.g. when driving a car or handling machines.

ABILIFY contains aspartame
ABILIFY 10 mg orodispersible tablets: This medicine contains 2 mg aspartame in each tablet.
ABILIFY 15 mg orodispersible tablets: This medicine contains 3 mg aspartame in each tablet.
ABILIFY 30 mg orodispersible tablets: This medicine contains 6 mg aspartame in each tablet.
Aspartame is a source of phenylalanine. **It may be harmful if you have phenylketonuria (PKU)**, a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

ABILIFY contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

ABILIFY 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 ABILIFY

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose for adults is 15 mg once a day. However your doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

Use in children and adolescents
This medicine may be started at a low dose with the oral solution (liquid) form.
The dose may be gradually increased to **the recommended dose for adolescents of 10 mg once a day**. However your doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

If you have the impression that the effect of ABILIFY is too strong or too weak, talk to your doctor or pharmacist.

Try to take ABILIFY at the same time each day. It does not matter whether you take it with or without food.

Do not open the blister until ready to administer. For single tablet removal, open the package and peel back the foil on the blister to expose the tablet. Do not push the tablet through the foil because this could damage the tablet. Immediately upon opening the blister, using dry hands, remove the tablet and place the entire orodispersible tablet on the tongue. Tablet disintegration occurs rapidly in saliva. The orodispersible tablet can be taken with or without liquid.
Alternatively, disperse the tablet in water and drink the resulting suspension.

Even if you feel better, do not alter or discontinue the daily dose of ABILIFY without first consulting your doctor.

If you take more ABILIFY than you should
If you realise you have taken more ABILIFY than your doctor has recommended (or if someone else has taken some of your ABILIFY), contact your doctor right away. If you cannot reach your doctor, go to the nearest hospital and take the pack with you.

Patients who have taken too much aripiprazole have experienced the following symptoms:
- rapid heartbeat, 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, slower breathing, choking, high or low blood pressure, abnormal rhythms of the heart.

Contact your doctor or hospital immediately if you experience any of the above.

If you forget to take ABILIFY
If you miss a dose, take the missed dose as soon as you remember but do not take two doses in one day.

If you stop taking ABILIFY
Do not stop your treatment just because you feel better. It is important that you carry on taking ABILIFY for as long as your doctor has told you to.

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.

Common side effects (may affect up to 1 in 10 people):

- diabetes mellitus,
- difficulty sleeping,
- feeling anxious,
- feeling restless and unable to keep still, difficulty sitting still,
- akathisia (an uncomfortable feeling of inner restlessness and a compelling need to move constantly),
- uncontrollable twitching, jerking or writhing movements,
- trembling,
- headache,
- tiredness,
- sleepiness,
- light-headedness,
- shaking and blurred vision,
- decreased number of or difficulty making bowel movements,
- indigestion,
- feeling sick,
- more saliva in mouth than normal,
- vomiting,
- feeling tired.

Uncommon side effects (may affect up to 1 in 100 people):

- increased or decreased blood levels of the hormone prolactin,
- too much sugar in the blood,
- depression,
- altered or increased sexual interest,
- uncontrollable movements of mouth, tongue and limbs (tardive dyskinesia),
- muscle disorder causing twisting movements (dystonia),
- restless legs,
- double vision,
- eye sensitivity to light,
- fast heartbeat,
- a fall in blood pressure on standing up which causes dizziness, light-headedness or fainting,
- hiccups.

The following side effects have been reported since the marketing of oral aripiprazole but the frequency for them to occur is not known:

- low levels of white blood cells,
- low levels of blood platelets,
- allergic reaction (e.g. swelling in the mouth, tongue, face and throat, itching, hives),
- onset or worsening of diabetes, ketoacidosis (ketones in the blood and urine) or coma,
- high blood sugar,
- not enough sodium in the blood,
- loss of appetite (anorexia),
- weight loss,
- weight gain,
- thoughts of suicide, suicide attempt and suicide,
- feeling aggressive,
- agitation,
- nervousness,
- combination of fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and heart rate, fainting (neuroleptic malignant syndrome),

- seizure,
- serotonin syndrome (a reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles),
- speech disorder,
- fixation of the eyeballs in one position,
- sudden unexplained death,
- life-threatening irregular heartbeat,
- heart attack,
- slower heartbeat,
- 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),
- high blood pressure,
- fainting,
- accidental inhalation of food with risk of pneumonia (lung infection),
- spasm of the muscles around the voice box,
- inflammation of the pancreas,
- difficulty swallowing,
- diarrhoea,
- abdominal discomfort,
- stomach discomfort,
- liver failure,
- inflammation of the liver,
- yellowing of the skin and white part of eyes,
- reports of abnormal liver tests values,
- skin rash,
- skin sensitivity to light,
- baldness,
- excessive sweating,
- 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 in blood tests and an increase in a type of white blood cell (eosinophilia),
- abnormal muscle breakdown which can lead to kidney problems,
- muscle pain,
- stiffness,
- involuntary loss of urine (incontinence),
- difficulty in passing urine,
- withdrawal symptoms in newborn babies in case of exposure during pregnancy,
- prolonged and/or painful erection,
- difficulty controlling core body temperature or overheating,
- chest pain,
- swelling of hands, ankles or feet,
- in blood tests: increased or fluctuating blood sugar, increased glycosylated haemoglobin.
- Inability to resist the impulse, drive or temptation to perform an action that could be harmful to you or others, which may include:
  - strong impulse to gamble excessively despite serious personal or family consequences
  - altered or increased sexual interest and behaviour of significant concern to you or to others, for example, an increased sexual drive
  - uncontrollable excessive shopping
  - binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger)
  - a tendency to wander away.

  Tell your doctor if you experience any of these behaviours; he/she will discuss ways of managing or reducing the symptoms.

In elderly patients with dementia, more fatal cases have been reported while taking aripiprazole. In

addition, cases of stroke or "mini" stroke have been reported.

Additional side effects in children and adolescents
Adolescents aged 13 years and older experienced side effects that were similar in frequency and type to those in adults except that sleepiness, uncontrollable twitching or jerking movements, restlessness, and tiredness were very common (greater than 1 in 10 patients) and upper abdominal pain, dry mouth, increased heart rate, weight gain, increased appetite, muscle twitching, uncontrolled movements of the limbs, and feeling dizzy, especially when getting up from a lying or sitting position, were common (greater than 1 in 100 patients).

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 ABILIFY

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 and on the carton after EXP. The expiry date refers to the last day of that month.

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 protect the environment.

6. Contents of the pack and other information

What ABILIFY contains
- The active substance is aripiprazole.
  Each orodispersible tablet contains 10 mg of aripiprazole.
  Each orodispersible tablet contains 15 mg of aripiprazole.
  Each orodispersible tablet contains 30 mg of aripiprazole.

- The other ingredients are calcium silicate, croscarmellose sodium, crospovidone, silicon dioxide, xylitol, microcrystalline cellulose, aspartame, acesulfame potassium, vanilla flavour (contains lactose), tartaric acid and magnesium stearate.
  Tablet coat
  ABILIFY 10 mg orodispersible tablets: Red iron oxide (E 172)
  ABILIFY 15 mg orodispersible tablets: Yellow iron oxide (E 172)
  ABILIFY 30 mg orodispersible tablets: Red iron oxide (E 172)

What ABILIFY looks like and contents of the pack
ABILIFY 10 mg orodispersible tablets are round and pink, marked with ‘"A" over "640"’ on one side and ‘10’ on the other.
ABILIFY 15 mg orodispersible tablets are round and yellow, marked with ‘"A" over "641"’ on one side and ‘15’ on the other.
ABILIFY 30 mg orodispersible tablets are round and pink, marked with ‘"A" over "643"’ on one side and ‘30’ on the other.

ABILIFY orodispersible tablets are supplied in perforated unit dose blisters packed in cartons containing 14 × 1, 28 × 1, or 49 × 1 orodispersible tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

Manufacturer
Elaiapharm
2881 Route des Crêtes, Z.I. Les Bouilides-Sophia Antipolis,
06560 Valbonne
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

България
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Česká republika
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Danmark
Otsuka Pharma Scandinavia AB
Tlf: +46 (0) 8 545 286 60

Deutschland
Otsuka Pharma GmbH
Tel: +49 (0) 69 1700 860

Eesti
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Ελλάδα
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

España
Otsuka Pharmaceutical, S.A.
Tel: +34 93 550 01 00

France
Otsuka Pharmaceutical France SAS
Tél: +33 (0)1 47 08 00 00

Hrvatska
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Lietuva
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Luxembourg/Luxemburg
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Magyarország
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Malta
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Nederland
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Norge
Otsuka Pharma Scandinavia AB
Tlf: +46 (0) 8 545 286 60

Österreich
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Polska
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Portugal
Lundbeck Portugal Lda
Tel: +351 (0) 21 00 45 900

România
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Ireland
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Ísland
Vistor hf.
Sími: +354 (0) 535 7000

Italia
Otsuka Pharmaceutical Italy S.r.l.
Tel: +39 (0) 2 0063 2710

Κύπρος
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Latvija
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Slovenija
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Slovenská republika
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Suomi/Finland
Otsuka Pharma Scandinavia AB
Puh/Tel: +46 (0) 8 545 286 60

Sverige
Otsuka Pharma Scandinavia AB
Tel: +46 (0) 8 545 286 60

United Kingdom (Northern Ireland)
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

This leaflet was last revised in {MM/YYYY}

Other sources of information

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

ABILIFY 1 mg/mL oral solution
aripiprazole

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 ABILIFY is and what it is used for

ABILIFY contains the active substance aripiprazole and belongs to a group of medicines called antipsychotics. It is used to treat adults and adolescents aged 15 years and older who suffer from a disease characterised by symptoms such as hearing, seeing or sensing things which are not there, suspiciousness, mistaken beliefs, incoherent speech and behaviour and emotional flatness. People with this condition may also feel depressed, guilty, anxious or tense.

ABILIFY is used to treat adults and adolescents aged 13 years and older who suffer from a condition with symptoms such as feeling "high", having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas and sometimes severe irritability. In adults it also prevents this condition from returning in patients who have responded to the treatment with ABILIFY.

2. What you need to know before you take ABILIFY

Do not take ABILIFY
- if you are allergic to aripiprazole or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor before taking ABILIFY.

Suicidal thoughts and behaviours have been reported during aripiprazole treatment. Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself.

Before treatment with ABILIFY, tell your doctor if you suffer from
- high blood sugar (characterised by symptoms such as excessive thirst, passing of large amounts of urine, increase in appetite and feeling weak) or family history of diabetes
- fits (seizures) since your doctor may want to monitor you more closely
- involuntary, irregular muscle movements, especially in the face
- cardiovascular diseases (diseases of the heart and circulation), family history of cardiovascular disease, stroke or "mini" stroke, abnormal blood pressure

- blood clots, or family history of blood clots, as antipsychotics have been associated with formation of blood clots
- past experience with excessive gambling

If you notice you are gaining weight, develop unusual movements, experience somnolence that interferes with normal daily activities, any difficulty in swallowing or allergic symptoms, please tell your doctor.

If you are an elderly patient suffering from dementia (loss of memory and other mental abilities), you or your carer/relative should tell your doctor if you have ever had a stroke or "mini" stroke.

Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself. Suicidal thoughts and behaviours have been reported during aripiprazole treatment.

Tell your doctor immediately if you suffer from muscle stiffness or inflexibility with high fever, sweating, altered mental status, or very rapid or irregular heartbeat.

Tell your doctor if you or your family/carer notices that you are developing urges or cravings to behave in ways that are unusual for you and you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These are called impulse control disorders and can include behaviours such as addictive gambling, excessive eating or spending, an abnormally high sex drive or preoccupation with an increase in sexual thoughts or feelings.
Your doctor may need to adjust or stop your dose.

Aripiprazole may cause sleepiness, fall in blood pressure when standing up, dizziness and changes in your ability to move and balance, which may lead to falls. Caution should be taken, particularly if you are an elderly patient or have some debility.

Children and adolescents
Do not use this medicine in children and adolescents under 13 years of age. It is not known if it is safe and effective in these patients.

Other medicines and ABILIFY
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Blood pressure-lowering medicines: ABILIFY may increase the effect of medicines used to lower the blood pressure. Be sure to tell your doctor if you take a medicine to keep your blood pressure under control.

Taking ABILIFY with some medicines may mean the doctor will need to change your dose of ABILIFY or the other medicines. It is especially important to mention the following to your doctor:

- medicines to correct heart rhythm (such as quinidine, amiodarone, flecainide)
- antidepressants or herbal remedy used to treat depression and anxiety *(*such as fluoxetine, paroxetine, venlafaxine, St. John's Wort)
- antifungal medicines (such as ketoconazole, itraconazole)
- certain medicines to treat HIV infection (such as efavirenz, nevirapine, an protease inhibitors e.g. indinavir, ritonavir)
- anticonvulsants used to treat epilepsy (such as carbamazepine, phenytoin, phenobarbital)
- certain antibiotics used to treat tuberculosis (rifabutin, rifampicin)

These medicines may increase the risk of side effects or reduce the effect of ABILIFY; if you get any unusual symptom taking any of these medicines together with ABILIFY you should see your doctor.

Medicines that increase the level of serotonin are typically used in conditions including depression, generalised anxiety disorder, obsessive-compulsive disorder (OCD) and social phobia as well as migraine and pain:

- triptans, tramadol and tryptophan used for conditions including depression, generalised anxiety disorder, obsessive compulsive disorder (OCD) and social phobia as well as migraine and pain
- selective-serotonin-reuptake-inhibitors (SSRIs) (such as paroxetine and fluoxetine) used for depression, OCD, panic and anxiety
- other anti-depressants (such as venlafaxine and tryptophan) used in major depression
- tricyclic's (such as clomipramine and amitriptyline) used for depressive illness
- St John's Wort (*Hypericum perforatum*) used as a herbal remedy for mild depression
- pain killers (such as tramadol and pethidine) used for pain relief
- triptans (such as sumatriptan and zolmitripitan) used for treating migraine

These medicines may increase the risk of side effects; if you get any unusual symptom taking any of these medicines together with ABILIFY, you should see your doctor.

ABILIFY with food, drink and alcohol
This medicine can be taken regardless of meals. However, the oral solution should not be diluted with other liquids or mixed with any food prior to administration.
Alcohol should be avoided.

Pregnancy, breast-feeding and fertility
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.

The following symptoms may occur in newborn babies, of mothers that have used ABILIFY 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.

If you are taking ABILIFY, your doctor will discuss with you whether you should breast-feed considering the benefit to you of your therapy and the benefit to your baby of breast-feeding. You should not do both. Talk to your doctor about the best way to feed your baby if you are taking this medicine.

Driving and using machines
Dizziness and vision problems may occur during treatment with this medicine (see section 4).
This should be considered in cases where full alertness is required, e.g. when driving a car or handling machines.

ABILIFY contains fructose
This medicine contains 200 mg of fructose in each mL. If your doctor has told you that you (or your child) have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you (or your child) take or receive this medicine. Fructose may damage teeth.

ABILIFY contains sucrose
This medicine contains 400 mg of sucrose in each mL. This should be taken into account in patients with diabetes mellitus. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine. Sucrose may be harmful to the teeth.

ABILIFY contains parahydroxybenzoates
May cause allergic reactions (possibly delayed).

ABILIFY contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially

‘sodium-free’.

3. How to take ABILIFY

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose for adults is 15 mL solution (corresponding to 15 mg aripiprazole) once a day. However your doctor may prescribe a lower or higher dose to a maximum of 30 mL (i.e. 30 mg) once a day.

Use in children and adolescents
The recommended dose for adolescents is 10 mL solution (corresponding to 10 mg aripiprazole) once a day. However your doctor may prescribe a lower or higher dose to a maximum of 30 mL (i.e. 30 mg) once a day.

The dose of ABILIFY must be measured using the calibrated cup or the 2 mL calibrated dropping pipette supplied in the carton.

If you have the impression that the effect of ABILIFY is too strong or too weak, talk to your doctor or pharmacist.

Try to take ABILIFY at the same time each day. It does not matter whether you take it with or without food. However, you should not dilute with other liquids or mix with other food prior to taking ABILIFY oral solution.

Even if you feel better, do not alter or discontinue the daily dose of ABILIFY without first consulting your doctor.

If you take more ABILIFY than you should
If you realise you have taken more ABILIFY than your doctor has recommended (or if someone else has taken some of your ABILIFY), contact your doctor right away. If you cannot reach your doctor, go to the nearest hospital and take the pack with you.

Patients who have taken too much aripiprazole have experienced the following symptoms:
- rapid heartbeat, 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, slower breathing, choking, high or low blood pressure, abnormal rhythms of the heart.

Contact your doctor or hospital immediately if you experience any of the above.

If you forget to take ABILIFY
If you miss a dose, take the missed dose as soon as you remember but do not take two doses in one day.

If you stop taking ABILIFY
Do not stop your treatment just because you feel better. It is important that you carry on taking ABILIFY for as long as your doctor has told you to.

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.

Common side effects (may affect up to 1 in 10 people):

- diabetes mellitus,
- difficulty sleeping,
- feeling anxious,
- feeling restless and unable to keep still, difficulty sitting still,
- akathisia (an uncomfortable feeling of inner restlessness and a compelling need to move constantly),
- uncontrollable twitching, jerking or writhing movements,
- trembling,
- headache,
- tiredness,
- sleepiness,
- light-headedness,
- shaking and blurred vision,
- decreased number of or difficulty making bowel movements,
- indigestion,
- feeling sick,
- more saliva in mouth than normal,
- vomiting,
- feeling tired.

Uncommon side effects (may affect up to 1 in 100 people):

- increased or decreased blood levels of the hormone prolactin,
- too much sugar in the blood,
- depression,
- altered or increased sexual interest,
- uncontrollable movements of mouth, tongue and limbs (tardive dyskinesia),
- muscle disorder causing twisting movements (dystonia),
- restless legs,
- double vision,
- eye sensitivity to light,
- fast heartbeat,
- a fall in blood pressure on standing up which causes dizziness, light-headedness or fainting,
- hiccups.

The following side effects have been reported since the marketing of oral aripiprazole but the frequency for them to occur is not known:

- low levels of white blood cells,
- low levels of blood platelets,
- allergic reaction (e.g. swelling in the mouth, tongue, face and throat, itching, hives),
- onset or worsening of diabetes, ketoacidosis (ketones in the blood and urine) or coma,
- high blood sugar,
- not enough sodium in the blood,
- loss of appetite (anorexia),
- weight loss,
- weight gain,
- thoughts of suicide, suicide attempt and suicide,
- feeling aggressive,
- agitation,
- nervousness,

- combination of fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and heart rate, fainting (neuroleptic malignant syndrome),
- seizure,
- serotonin syndrome (a reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles),
- speech disorder,
- fixation of the eyeballs in one position,
- sudden unexplained death,
- life-threatening irregular heartbeat,
- heart attack,
- slower heartbeat,
- 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),
- high blood pressure,
- fainting,
- accidental inhalation of food with risk of pneumonia (lung infection),
- spasm of the muscles around the voice box,
- inflammation of the pancreas,
- difficulty swallowing,
- diarrhoea,
- abdominal discomfort,
- stomach discomfort,
- liver failure,
- inflammation of the liver,
- yellowing of the skin and white part of eyes,
- reports of abnormal liver tests values,
- skin rash,
- skin sensitivity to light,
- baldness,
- excessive sweating,
- 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 in blood tests and an increase in a type of white blood cell (eosinophilia),
- abnormal muscle breakdown which can lead to kidney problems,
- muscle pain,
- stiffness,
- involuntary loss of urine (incontinence),
- difficulty in passing urine,
- withdrawal symptoms in newborn babies in case of exposure during pregnancy,
- prolonged and/or painful erection,
- difficulty controlling core body temperature or overheating,
- chest pain,
- swelling of hands, ankles or feet,
- in blood tests: increased or fluctuating blood sugar, increased glycosylated haemoglobin.
- Inability to resist the impulse, drive or temptation to perform an action that could be harmful to you or others, which may include:
  - strong impulse to gamble excessively despite serious personal or family consequences
  - altered or increased sexual interest and behaviour of significant concern to you or to others, for example, an increased sexual drive
  - uncontrollable excessive shopping
  - binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger)
  - a tendency to wander away.

  Tell your doctor if you experience any of these behaviours; he/she will discuss ways of managing or reducing the symptoms.

In elderly patients with dementia, more fatal cases have been reported while taking aripiprazole. In addition, cases of stroke or "mini" stroke have been reported.

Additional side effects in children and adolescents
Adolescents aged 13 years and older experienced side effects that were similar in frequency and type to those in adults except that sleepiness, uncontrollable twitching or jerking movements, restlessness, and tiredness were very common (greater than 1 in 10 patients) and upper abdominal pain, dry mouth, increased heart rate, weight gain, increased appetite, muscle twitching, uncontrolled movements of the limbs, and feeling dizzy, especially when getting up from a lying or sitting position, were common (greater than 1 in 100 patients).

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 ABILIFY

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 bottle and on the carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.
Use within 6 months after first opening.

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 ABILIFY contains
- The active substance is aripiprazole.
  Each mL contains 1 mg of aripiprazole.

- The other ingredients are disodium edetate, fructose, glycerin, lactic acid, methyl parahydroxybenzoate (E218), propylene glycol, propyl parahydroxybenzoate (E216), sodium hydroxide, sucrose, purified water, and orange flavour.

What ABILIFY looks like and contents of the pack
ABILIFY 1 mg/mL oral solution is a clear, colourless to light yellow liquid supplied in bottles with polypropylene child-resistant closure containing 50 mL, 150 mL or 480 mL per bottle.

Each carton contains one bottle and both a calibrated polypropylene measuring cup and a calibrated polypropylene low-density polyethylene dropping pipette.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

Manufacturer
Elaiapharm
2881 Route des Crêtes, Z.I. Les Bouilides-Sophia Antipolis,
06560 Valbonne
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

България
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Česká republika
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Danmark
Otsuka Pharma Scandinavia AB
Tlf: +46 (0) 8 545 286 60

Deutschland
Otsuka Pharma GmbH
Tel: +49 (0) 69 1700 860

Eesti
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Ελλάδα
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

España
Otsuka Pharmaceutical, S.A.
Tel: +34 93 550 01 00

France
Otsuka Pharmaceutical France SAS
Tél: +33 (0)1 47 08 00 00

Hrvatska
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Ireland
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Lietuva
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Luxembourg/Luxemburg
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Magyarország
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Malta
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Nederland
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Norge
Otsuka Pharma Scandinavia AB
Tlf: +46 (0) 8 545 286 60

Österreich
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Polska
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Portugal
Lundbeck Portugal Lda
Tel: +351 (0) 21 00 45 900

România
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Slovenija
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Ísland
Vistor hf.
Sími: +354 (0) 535 7000

Italia
Otsuka Pharmaceutical Italy S.r.l.
Tel: +39 (0) 2 0063 2710

Κύπρος
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Latvija
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Slovenská republika
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Suomi/Finland
Otsuka Pharma Scandinavia AB
Puh/Tel: +46 (0) 8 545 286 60

Sverige
Otsuka Pharma Scandinavia AB
Tel: +46 (0) 8 545 286 60

United Kingdom (Northern Ireland)
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

This leaflet was last revised in {MM/YYYY}

Other sources of information

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

ABILIFY 7.5 mg/mL solution for injection
aripiprazole

Read all of this leaflet carefully before you receive 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 ABILIFY is and what it is used for

ABILIFY contains the active substance aripiprazole and belongs to a group of medicines called antipsychotics. ABILIFY is used to treat quickly symptoms of agitation and distressing behaviour that may occur in a disease characterised by symptoms such as:
- hearing, seeing or sensing things which are not there, suspiciousness, mistaken beliefs, incoherent speech and behaviour and emotional flatness. People with this condition may also feel depressed, guilty, anxious or tense.
- feeling "high", having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas and sometimes severe irritability.

ABILIFY is given when treatment with oral formulations is not appropriate. Your doctor will change your treatment to oral ABILIFY as soon as appropriate.

2. What you need to know before you are given ABILIFY

Do not use ABILIFY
- if you are allergic to aripiprazole or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor before you are given ABILIFY.

Suicidal thoughts and behaviours have been reported during aripiprazole treatment. Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself.

Before treatment with ABILIFY, tell your doctor if you suffer from
- high blood sugar (characterised by symptoms such as excessive thirst, passing of large amounts of urine, increase in appetite and feeling weak) or family history of diabetes
- fits (seizures) since your doctor may want to monitor you more closely
- involuntary, irregular muscle movements, especially in the face
- cardiovascular diseases (diseases of the heart and circulation), family history of cardiovascular disease, stroke or "mini" stroke, abnormal blood pressure

- blood clots, or family history of blood clots, as antipsychotics have been associated with formation of blood clots
- past experience with excessive gambling

If you notice you are gaining weight, develop unusual movements, experience somnolence that interferes with normal daily activities, any difficulty in swallowing or allergic symptoms, please tell your doctor.

If you are an elderly patient suffering from dementia (loss of memory and other mental abilities), you or your carer/relative should tell your doctor if you have ever had a stroke or "mini" stroke.

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 may also want to measure your blood pressure and pulse.

Tell your doctor immediately if you are having any thoughts or feelings about hurting yourself. Suicidal thoughts and behaviours have been reported during aripiprazole treatment.

Tell your doctor immediately if you suffer from muscle stiffness or inflexibility with high fever, sweating, altered mental status, or very rapid or irregular heartbeat.

Tell your doctor if you or your family/carer notices that you are developing urges or cravings to behave in ways that are unusual for you and you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These are called impulse control disorders and can include behaviours such as addictive gambling, excessive eating or spending, an abnormally high sex drive or preoccupation with an increase in sexual thoughts or feelings.
Your doctor may need to adjust or stop your dose.

Aripiprazole may cause sleepiness, fall in blood pressure when standing up, dizziness and changes in your ability to move and balance, which may lead to falls. Caution should be taken, particularly if you are an elderly patient or have some debility.

Children and adolescents
Do not use this medicine in children and adolescents under 18 years of age. It is not known if it is safe and effective in these patients.

Other medicines and ABILIFY
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Blood pressure-lowering medicines: ABILIFY may increase the effect of medicines used to lower the blood pressure. Be sure to tell your doctor if you take a medicine to keep your blood pressure under control.

Receiving ABILIFY with some medicines may mean the doctor will need to change your dose of ABILIFY or the other medicines. It is especially important to mention the following to your doctor:

- medicines to correct heart rhythm (such as quinidine, amiodarone, flecainide)
- antidepressants or herbal remedy used to treat depression and anxiety (such as fluoxetine, paroxetine, venlafaxine, St. John's Wort)
- antifungal medicines (such as ketoconazole, itraconazole)
- certain medicines to treat HIV infection (such as efavirenz, nevirapine, an protease inhibitors e.g. indinavir, ritonavir)
- anticonvulsants used to treat epilepsy (such as carbamazepine, phenytoin, phenobarbital)
- certain antibiotics used to treat tuberculosis (rifabutin, rifampicin)

These medicines may increase the risk of side effects or reduce the effect of ABILIFY; if you get any unusual symptom taking any of these medicines together with ABILIFY you should see your doctor.

Medicines that increase the level of serotonin are typically used in conditions including depression, generalised anxiety disorder, obsessive-compulsive disorder (OCD) and social phobia as well as migraine and pain:

- triptans, tramadol and tryptophan used for conditions including depression, generalised anxiety disorder, obsessive compulsive disorder (OCD) and social phobia as well as migraine and pain
- selective-serotonin-reuptake-inhibitors (SSRIs) (such as paroxetine and fluoxetine) used for depression, OCD, panic and anxiety
- other anti-depressants (such as venlafaxine and tryptophan) used in major depression
- tricyclic's (such as clomipramine and amitriptyline) used for depressive illness
- St John's Wort (*Hypericum perforatum*) used as a herbal remedy for mild depression
- pain killers (such as tramadol and pethidine) used for pain relief
- triptans (such as sumatriptan and zolmitripitan) used for treating migraine

These medicines may increase the risk of side effects; if you get any unusual symptom taking any of these medicines together with ABILIFY, you should see your doctor.

A combination of ABILIFY with medicines taken for anxiety might make you feel drowsy or dizzy. Only take other medicines while you are on ABILIFY if your doctor tells you that you can.

ABILIFY with food, drink and alcohol
This medicine can be given regardless of meals.
Alcohol should be avoided.

Pregnancy, breast-feeding and fertility
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.

The following symptoms may occur in newborn babies, of mothers that have used ABILIFY 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.

If you are receiving ABILIFY, your doctor will discuss with you whether you should breast-feed considering the benefit to you of your therapy and the benefit to your baby of breast-feeding. You should not do both. Talk to your doctor about the best way to feed your baby if you are receiving this medicine.

Driving and using machines
Dizziness and vision problems may occur during treatment with this medicine (see section 4).
This should be considered in cases where full alertness is required, e.g. when driving a car or handling machines.

ABILIFY contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

3. How ABILIFY is given

Your doctor will decide how much ABILIFY you need and how long you need it for. The recommended dose is 9.75 mg (1.3 mL) for the first injection. Up to three injections in 24 hours may be given. The total dose of ABILIFY (all formulations) should not exceed 30 mg per day.

ABILIFY is ready to use. The correct amount of solution will be injected into your muscle by your doctor or nurse.

If you are given more ABILIFY than you need
This medicine will be given to you under medical supervision; it is therefore unlikely that you will be given too much. If you see more than one doctor, be sure to tell them that you are receiving ABILIFY.

Patients who have been given too much aripiprazole have experienced the following symptoms:
- rapid heartbeat, 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, slower breathing, choking, high or low blood pressure, abnormal rhythms of the heart.

Contact your doctor or hospital immediately if you experience any of the above.

If you miss an injection of ABILIFY
It is important not to miss your dose. If you miss an injection, you should contact your doctor to arrange your next injection as soon as you can.

If you stop receiving ABILIFY
Do not stop your treatment just because you feel better. It is important that you carry on receiving ABILIFY solution for injection for as long as your doctor has told you to.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Common side effects (may affect up to 1 in 10 people):

- diabetes mellitus,
- difficulty sleeping,
- feeling anxious,
- feeling restless and unable to keep still, difficulty sitting still,
- akathisia (an uncomfortable feeling of inner restlessness and a compelling need to move constantly),
- uncontrollable twitching, jerking or writhing movements,
- trembling,
- headache,
- tiredness,
- sleepiness,
- light-headedness,
- shaking and blurred vision,
- decreased number of or difficulty making bowel movements,
- indigestion,
- feeling sick,
- more saliva in mouth than normal,
- vomiting,
- feeling tired.

Uncommon side effects (may affect up to 1 in 100 people):

- increased or decreased blood levels of the hormone prolactin,
- too much sugar in the blood,

- depression,
- altered or increased sexual interest,
- uncontrollable movements of mouth, tongue and limbs (tardive dyskinesia),
- muscle disorder causing twisting movements (dystonia),
- restless legs,
- double vision,
- eye sensitivity to light,
- fast heartbeat,
- increased diastolic blood pressure,
- a fall in blood pressure on standing up which causes dizziness, light-headedness or fainting,
- hiccups,
- dry mouth.

The following side effects have been reported since the marketing of oral aripiprazole but the frequency for them to occur is not known:

- low levels of white blood cells,
- low levels of blood platelets,
- allergic reaction (e.g. swelling in the mouth, tongue, face and throat, itching, hives),
- onset or worsening of diabetes, ketoacidosis (ketones in the blood and urine) or coma,
- high blood sugar,
- not enough sodium in the blood,
- loss of appetite (anorexia),
- weight loss,
- weight gain,
- thoughts of suicide, suicide attempt and suicide,
- feeling aggressive,
- agitation,
- nervousness,
- combination of fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and heart rate, fainting (neuroleptic malignant syndrome),
- seizure,
- serotonin syndrome (a reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles),
- speech disorder,
- fixation of the eyeballs in one position,
- sudden unexplained death,
- life-threatening irregular heartbeat,
- heart attack,
- slower heartbeat,
- 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),
- high blood pressure,
- fainting,
- accidental inhalation of food with risk of pneumonia (lung infection),
- spasm of the muscles around the voice box,
- inflammation of the pancreas,
- difficulty swallowing,
- diarrhoea,
- abdominal discomfort,
- stomach discomfort,
- liver failure,
- inflammation of the liver,
- yellowing of the skin and white part of eyes,
- reports of abnormal liver tests values,
- skin rash,

- skin sensitivity to light,
- baldness,
- excessive sweating,
- 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 in blood tests and an increase in a type of white blood cell (eosinophilia),
- abnormal muscle breakdown which can lead to kidney problems,
- muscle pain,
- stiffness,
- involuntary loss of urine (incontinence),
- difficulty in passing urine,
- withdrawal symptoms in newborn babies in case of exposure during pregnancy,
- prolonged and/or painful erection,
- difficulty controlling core body temperature or overheating,
- chest pain,
- swelling of hands, ankles or feet,
- in blood tests: increased or fluctuating blood sugar, increased glycosylated haemoglobin.
- Inability to resist the impulse, drive or temptation to perform an action that could be harmful to you or others, which may include:
  - strong impulse to gamble excessively despite serious personal or family consequences
  - altered or increased sexual interest and behaviour of significant concern to you or to others, for example, an increased sexual drive
  - uncontrollable excessive shopping
  - binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger)
  - a tendency to wander away.

  Tell your doctor if you experience any of these behaviours; he/she will discuss ways of managing or reducing the symptoms.

In elderly patients with dementia, more fatal cases have been reported while taking aripiprazole. In addition, cases of stroke or "mini" stroke have been reported.

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 ABILIFY

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 on the vial after EXP. The expiry date refers to the last day of that month.

Keep the vial in the outer carton 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 ABILIFY contains

- The active substance is aripiprazole.
  Each mL contains 7.5 mg aripiprazole.
  A vial contains 9.75 mg (1.3 mL) aripiprazole.

- The other ingredients are sulfobutylether β-cyclodextrin (SBECD), tartaric acid, sodium hydroxide, and water for injections.

What ABILIFY looks like and contents of the pack
The ABILIFY solution for injection is a clear, colourless, aqueous solution.

Each carton contains one single-use type I glass vial with a rubber butyl stopper and a "tear-off" aluminium seal.

Marketing Authorisation Holder
Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

Manufacturer
Zambon S.p.A.
Via della Chimica, 9
I-36100 Vicenza(VI)
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

България
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Česká republika
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Danmark
Otsuka Pharma Scandinavia AB
Tlf: +46 (0) 8 545 286 60

Deutschland
Otsuka Pharma GmbH
Tel: +49 (0) 69 1700 860

Eesti
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Lietuva
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Luxembourg/Luxemburg
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Magyarország
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Malta
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Nederland
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Norge
Otsuka Pharma Scandinavia AB
Tlf: +46 (0) 8 545 286 60

Ελλάδα
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

España
Otsuka Pharmaceutical, S.A.
Tel: +34 93 550 01 00

France
Otsuka Pharmaceutical France SAS
Tél: +33 (0)1 47 08 00 00

Hrvatska
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Ireland
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Ísland
Vistor hf.
Sími: +354 (0) 535 7000

Italia
Otsuka Pharmaceutical Italy S.r.l.
Tel: +39 (0) 2 0063 2710

Κύπρος
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Latvija
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Österreich
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Polska
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Portugal
Lundbeck Portugal Lda
Tel: +351 (0) 21 00 45 900

România
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Slovenija
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Slovenská republika
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

Suomi/Finland
Otsuka Pharma Scandinavia AB
Puh/Tel: +46 (0) 8 545 286 60

Sverige
Otsuka Pharma Scandinavia AB
Tel: +46 (0) 8 545 286 60

United Kingdom (Northern Ireland)
Otsuka Pharmaceutical Netherlands B.V.
Tel: +31 (0) 20 85 46 555

This leaflet was last revised in {MM/YYYY}

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Asenapine

EMA

ANNEX I

SUMMARY OF kkllllllPRODUCT

CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sycrest 5 mg sublingual tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sublingual tablet contains 5 mg asenapine (as maleate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sublingual tablet
Round, white to off-white, sublingual tablets debossed with "5" on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sycrest is indicated for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults.

4.2 Posology and method of administration

Posology

The recommended starting dose of Sycrest as monotherapy is 5 mg twice daily. One dose should be taken in the morning and one dose should be taken in the evening. The dose can be increased to 10 mg twice daily based on individual clinical response and tolerability. See section 5.1. For combination therapy a starting dose of 5 mg twice daily is recommended. Depending on the clinical response and tolerability in the individual patient, the dose can be increased to 10 mg twice daily.

Special populations

Elderly
Sycrest should be used with care in the elderly. Limited data on efficacy in patients 65 years of age and older are available. Available pharmacokinetic data are described in section 5.2.

Renal impairment
No dose adjustment is required for patients with renal impairment. There is no experience with asenapine in patients with severe renal impairment who have a creatinine clearance less than 15 mL/min.

Hepatic impairment
No dose adjustment is required for patients with mild hepatic impairment. The possibility of elevated asenapine plasma levels cannot be excluded in some patients with moderate hepatic impairment (Child-Pugh B) and caution is advised. In subjects with severe hepatic impairment (Child-Pugh C), a 7-fold increase in asenapine exposure was observed. Thus, Sycrest is not recommended in patients with severe hepatic impairment.

Paediatric population
A pharmacokinetic study and a short term efficacy and safety study were performed in a paediatric population (ages 10-17 years) with manic or mixed episodes associated with bipolar I disorder. Long term safety in this population was explored in a 50-week, open-label, uncontrolled extension study.

Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

The tablet should not be removed from the blister until ready to take it. Dry hands should be used when touching the tablet. The tablet should not be pushed through the tablet pack. The tablet pack should not be cut or torn. The coloured tab should be peeled back and the tablet should be removed gently. The tablet should not be crushed.

To ensure optimal absorption, the Sycrest sublingual tablet should be placed under the tongue and allowed to dissolve completely. The tablet will dissolve in saliva within seconds. Sycrest sublingual tablets should not be chewed or swallowed. Eating and drinking should be avoided for 10 minutes after administration.
When used in combination with other medicinal products, Sycrest should be taken last.

Treatment with Sycrest is not advised in patients who are unable to comply with this method of administration, as the bioavailability of asenapine when swallowed is low (< 2 % with an oral tablet formulation).

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-related psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic substances are at an increased risk of death.

Sycrest is not approved for the treatment of patients with dementia-related psychosis and is not recommended for use in this particular group of patients.

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 antipsychotics, including asenapine. Additional clinical signs may include myoglobinuria (rhabdomyolysis) and acute renal failure.

If a patient develops signs and symptoms indicative of NMS Sycrest must be discontinued.

Seizures
In clinical trials, cases of seizure were occasionally reported during treatment with asenapine. Therefore, Sycrest should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures.

Suicide
The possibility of a suicide attempt is inherent in psychotic illnesses and bipolar disorder and close supervision of high-risk patients should accompany treatment.

Orthostatic hypotension
Asenapine may induce orthostatic hypotension and syncope, especially early in treatment, probably reflecting its α1-adrenergic antagonist properties. Elderly patients are particularly at risk for experiencing orthostatic hypotension (see section 4.8). In clinical trials, cases of syncope were occasionally reported during treatment with Sycrest. Sycrest should be used with caution in elderly patients and in patients with known cardiovascular disease (e.g., heart failure, myocardial infarction or

ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration and hypovolemia).

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. In clinical trials, cases of tardive dyskinesia were occasionally reported during treatment with asenapine. The onset of extrapyramidal symptoms is a risk factor for tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear in a patient on Sycrest, discontinuation of treatment should be considered.

Hyperprolactinaemia
Increases in prolactin levels were observed in some patients with Sycrest. In clinical trials, there were few adverse reactions related to abnormal prolactin levels reported.

QT interval
Clinically relevant QT prolongation does not appear to be associated with asenapine. Caution should be exercised when Sycrest is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products thought to prolong the QT interval.

Hyperglycaemia and diabetes mellitus
Hyperglycaemia or exacerbation of pre-existing diabetes has occasionally been reported during treatment with asenapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia or bipolar disorder and the increasing incidence of diabetes mellitus in the general population. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Dysphagia
Esophageal dysmotility and aspiration have been associated with antipsychotic treatment. Cases of dysphagia were occasionally reported in patients treated with Sycrest.

Body temperature regulation
Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicinal products. From the clinical trials, it is concluded that clinically relevant body temperature dysregulation does not appear to be associated with asenapine. Appropriate care is advised when prescribing Sycrest for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g. exercising strenuously, exposure to extreme heat, receiving concomitant medicinal products with anticholinergic activity or being subject to dehydration.

Patients with severe hepatic impairment
Asenapine exposure is increased 7-fold in patients with severe hepatic impairment (Child-Pugh C). Therefore, Sycrest is not recommended in such patients.

Parkinson's disease and dementia with Lewy bodies
Physicians should weigh the risks versus the benefits when prescribing Sycrest 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.

Falls
Asenapine may cause adverse effects such as somnolence, orthostatic hypotension, dizziness and extrapyramidal symptoms, which may lead to falls and, consequently, fractures or other injuries. Patients at risk for fall should be evaluated prior to prescribing asenapine.

4.5 Interaction with other medicinal products and other forms of interaction

Given the primary effects of asenapine on the central nervous system (CNS) (see section 4.8), caution should be used when it is taken in combination with other centrally acting medicinal products. Patients should be advised to avoid alcohol while taking Sycrest.

Potential for other medicinal products to affect Sycrest
Asenapine is cleared primarily through direct glucuronidation by UGT1A4 and oxidative metabolism by cytochrome P450 isoenzymes (predominantly CYP1A2). The potential effects of inhibitors and an inducer of several of these enzyme pathways on asenapine pharmacokinetics were studied, specifically fluvoxamine (CYP1A2 inhibitor), paroxetine (CYP2D6 inhibitor), imipramine (CYP1A2/2C19/3A4 inhibitor), cimetidine (CYP3A4/2D6/1A2 inhibitor), carbamazepine (CYP3A4/1A2 inducer) and valproate (UGT inhibitor). Except for fluvoxamine, none of the interacting medicinal products resulted in clinically relevant alterations in asenapine pharmacokinetics.

During combined administration with a single dose of asenapine 5 mg, fluvoxamine 25 mg twice daily resulted in a 29 % increase in asenapine AUC. The full therapeutic dose of fluvoxamine would be expected to produce a greater increase in asenapine plasma concentrations. Therefore, co-administration of asenapine and fluvoxamine should be approached with caution.

Potential for Sycrest to affect other medicinal products
Because of its α1-adrenergic antagonism with potential for inducing orthostatic hypotension (see section 4.4), Sycrest may enhance the effects of certain antihypertensive agents.

Asenapine may antagonise the effect of levodopa and dopamine agonists. If this combination is deemed necessary, the lowest effective dose of each treatment should be prescribed.

In vitro studies indicate that asenapine weakly inhibits CYP2D6. Clinical drug interaction studies investigating the effects of CYP2D6 inhibition by asenapine showed the following results:

- Following co-administration of dextromethorphan and asenapine in healthy subjects, the ratio of dextrorphan/dextromethorphan (DX/DM) as a marker of CYP2D6 activity was measured. Indicative of CYP2D6 inhibition, treatment with asenapine 5 mg twice daily resulted in a fractional decrease in DX/DM ratio to 0.43. In the same study, treatment with paroxetine 20 mg daily decreased the DX/DM ratio to 0.032.

- In a separate study, co-administration of a single 75 mg dose of imipramine with a single 5 mg dose of asenapine did not affect the plasma concentrations of the metabolite desipramine (a CYP2D6 substrate).

- Co-administration of a single 20 mg dose of paroxetine (a CYP2D6 substrate and inhibitor) during treatment with 5 mg asenapine twice daily in 15 healthy male subjects resulted in an almost 2-fold increase in paroxetine exposure.

In vivo asenapine appears to be at most a weak inhibitor of CYP2D6. However, asenapine may enhance the inhibitory effects of paroxetine on its own metabolism.

Therefore, Sycrest should be co-administered cautiously with medicinal products that are both substrates and inhibitors for CYP2D6.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of Sycrest in pregnant women. Asenapine was not teratogenic in animal studies. Maternal and embryo toxic effects were found in animal studies (see section 5.3).

Newborn infants exposed to antipsychotics (including Sycrest) 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 in newborn infants. Consequently, newborn infants should be monitored carefully.

Sycrest should not be used during pregnancy unless the clinical condition of the woman requires treatment with asenapine and only if the potential benefit outweighs the potential risk to the foetus.

Breast-feeding
Asenapine was excreted in milk of rats during lactation. It is not known whether asenapine or its metabolites are excreted in human milk. Breast-feeding should be discontinued during treatment with Sycrest.

Fertility
No impairment of fertility has been observed in nonclinical studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Asenapine may cause somnolence and sedation. Therefore, patients should be cautioned about driving and using machines until they are reasonably certain that Sycrest therapy does not affect them adversely.

4.8 Undesirable effects

Summary of safety profile
The most frequently reported adverse drug reactions (ADRs) associated with the use of asenapine in clinical trials were somnolence and anxiety. Serious hypersensitivity reactions have been reported. Other serious ADRs are discussed in more detail in section 4.4.

Tabulated list of adverse reactions
The incidences of the ADRs associated with asenapine therapy are tabulated below. The table is based on adverse reactions reported during clinical trials and/or post-marketing use.
All ADRs are listed by system organ 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) and not known (cannot be estimated from the available data). Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon	Rare	Not known
Blood and lymphatic disorders				Neutropenia	
Immune system disorders			Allergic reactions		
Metabolism and nutrition disorders		Weight increased Increased appetite	Hyperglycaemia		
Psychiatric disorders	Anxiety				

System organ class	Very common	Common	Uncommon	Rare	Not known
Nervous system disorders	Somnolence	Dystonia Akathisia Dyskinesia Parkinsonism Sedation Dizziness Dysgeusia	Syncope Seizure Extrapyramidal disorder Dysarthria Restless legs syndrome	Neuroleptic malignant syndrome	
Eye disorders				Accommodation disorder	
Cardiac disorders			Sinus bradycardia Bundle branch block Electrocardio-gram QT prolonged Sinus tachycardia		
Vascular disorders			Orthostatic hypotension Hypotension		
Respiratory, thoracic and mediastinal disorders				Pulmonary embolism	
Gastrointestinal disorders		Hypoaesthesia oral Nausea Salivary hypersecretion	Swollen tongue Dysphagia Glossodynia Paraesthesia oral Oral mucosal lesions (ulcerations, blistering and inflammation)		
Hepatobiliary disorders		Alanine aminotransferase increased			
Injury, poisoning and procedural complications					Falls*
Musculoskeletal and connective tissue disorders		Muscle rigidity		Rhabdomyolysis	
Pregnancy, puerperium and perinatal conditions					Drug withdrawal syndrome neonatal (see 4.6)

System organ class	Very common	Common	Uncommon	Rare	Not known
Reproductive system and breast disorders			Sexual dysfunction Amenorrhoea	Gynaecomastia Galactorrhoea	
General disorders and administration site conditions		Fatigue			

* See subsection "*Falls*" below

Description of selected adverse reactions

Extrapyramidal Symptoms (EPS)
In clinical trials, the incidence of extrapyramidal symptoms in asenapine-treated patients was higher than placebo (15.4 % vs 11.0 %).

From the short-term (6 weeks) schizophrenia trials there appears to be a dose-response relationship for akathisia in patients treated with asenapine, and for parkinsonism there was an increasing trend with higher doses.

Based on a small pharmacokinetic study, paediatric patients appeared to be more sensitive to dystonia with initial dosing with asenapine when a gradual up-titration schedule was not followed (see section 5.2). The incidence of dystonia in paediatric clinical trials using a gradual up-titration was similar to that seen in adult trials.

Weight increase
In the combined short-term and long-term schizophrenia and bipolar mania trials in adults, the mean change in body weight for asenapine was 0.8 kg. The proportion of subjects with clinically significant weight gain (≥ 7 % weight gain from baseline at endpoint) in the short-term schizophrenia trials was 5.3 % for asenapine compared to 2.3 % for placebo. The proportion of subjects with clinically significant weight gain (≥ 7 % weight gain from baseline at endpoint) in the short-term, flexible-dose bipolar mania trials was 6.5 % for asenapine compared to 0.6 % for placebo.

In a 3-week, placebo-controlled, randomized, fixed-dose efficacy and safety trial in paediatric patients 10 to 17 years of age with bipolar I disorder, the mean change from baseline to endpoint in weight for placebo and asenapine 2.5 mg, 5 mg, and 10 mg twice daily, was 0.48, 1.72, 1.62, and 1.44 kg, respectively. The proportion of subjects with clinically significant weight gain (≥ 7 % weight gain from baseline at Day 21) was 14.1 % for asenapine 2.5 mg twice daily, 8.9 % for asenapine 5 mg twice daily, and 9.2 % for asenapine 10 mg twice daily, compared to 1.1 % for placebo. In the long-term extension trial (50 weeks), a total of 34.8 % of subjects experienced clinically significant weight increase (i.e., ≥ 7 % increase in body weight at endpoint). Overall mean (SD) weight gain at study endpoint was 3.5 (5.76) kg.

Orthostatic hypotension
The incidence of orthostatic hypotension in elderly subjects was 4.1 % compared to 0.3 % in the combined phase 2/3 trial population.

Falls
Falls may occur as a result of one or more adverse events such as the following: Somnolence, Orthostatic hypotension, Dizziness, Extrapyramidal symptoms.

Hepatic enzymes
Transient, asymptomatic elevations of hepatic transaminases, alanine transferase (ALT), aspartate transferase (AST) have been seen commonly, especially in early treatment.

Other findings
Cerebrovascular events have been reported in patients treated with asenapine but there is no evidence of any excess incidence over what is expected in adults between 18 and 65 years of age.

Asenapine has anaesthetic properties. Oral hypoaesthesia and oral paraesthesia may occur directly after administration and usually resolves within 1 hour.

There have been post-marketing reports of serious hypersensitivity reactions in patients treated with asenapine, including anaphylactic/anaphylactoid reactions, angioedema, swollen tongue and swollen throat (pharyngeal oedema).

Paediatric population
Asenapine is not indicated for the treatment of children and adolescent patients below 18 years (see section 4.2).

The clinically relevant adverse experiences identified in the paediatric bipolar and schizophrenia trials were similar to those observed in adult bipolar and schizophrenia trials.

The most common adverse reactions (≥ 5 % and at least twice the rate of placebo) reported in paediatric patients with bipolar I disorder were somnolence, sedation, dizziness, dysgeusia, hypoaesthesia oral, paraesthesia oral, nausea, increased appetite, fatigue, and weight increased (see *Weight increase* above).

The most common adverse reactions (proportion of patients ≥ 5 % and at least twice placebo) reported in paediatric patients with schizophrenia were somnolence, sedation, akathisia, dizziness, and hypoaesthesia oral. There was a statistically significant higher incidence of patients with ≥ 7 % weight gain (from baseline to endpoint) compared to placebo (3.1 %) for Sycrest 2.5 mg twice daily (9.5 %) and Sycrest 5 mg twice daily (13.1 %).

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 national reporting system listed in Appendix V.

4.9 Overdose

Few cases of overdose were reported in the asenapine program. Reported estimated doses were between 15 and 400 mg. In most cases it was not clear if asenapine had been taken sublingually. Treatment-related adverse reactions included agitation and confusion, akathisia, orofacial dystonia, sedation, and asymptomatic ECG findings (bradycardia, supraventricular complexes, intraventricular conduction delay).

No specific information is available on the treatment of overdose with Sycrest. There is no specific antidote to Sycrest. The possibility of multiple medicinal product involvement should be considered. Cardiovascular monitoring is necessary to detect possible arrhythmias and management of overdose should concentrate on supportive therapy, maintaining an adequate airway oxygenation and ventilation, and management of symptoms. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulations may worsen hypotension in the setting of Sycrest-induced alpha blockade). In case of severe extrapyramidal symptoms, anticholinergic medicinal products should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, antipsychotics, ATC code: N05AH05

Mechanism of action
The mechanism of action of asenapine is not fully understood. However, based on its receptor pharmacology, it is proposed that the efficacy of asenapine is mediated through a combination of antagonist activity at D2 and 5-HT2A receptors. Actions at other receptors e.g., 5-HT1A, 5-HT1B, 5-HT2C, 5-HT6, 5-HT7, D3, and α2-adrenergic receptors, may also contribute to the clinical effects of asenapine.

Pharmacodynamic effects
Asenapine exhibits high affinity for serotonin 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT5, 5-HT6, and 5-HT7 receptors, dopamine D2, D3, D4, and D1 receptors, α1 and α2-adrenergic receptors, and histamine H1 receptors, and moderate affinity for H2 receptors. In *in vitro* assays asenapine acts as an antagonist at these receptors. Asenapine has no appreciable affinity for muscarinic cholinergic receptors.

Clinical efficacy

Clinical efficacy in bipolar I disorder
The efficacy of asenapine in the treatment of a DSM-IV manic or mixed episode of bipolar I disorder with or without psychotic features was evaluated in two similarly designed 3-week, randomized, double-blind, flexible-dose, placebo- and active controlled (olanzapine) monotherapy trials involving 488 and 489 patients, respectively. All patients met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnostic criteria for bipolar I disorder, current episode manic (DSM-IV 296.4x), or mixed (DSM-IV 296.6x) and had a Young Mania Rating Scale (Y-MRS) score of $\geq$ 20 at screening and baseline. Patients with rapid cycling were excluded from these studies. Asenapine demonstrated superior efficacy to placebo in the reduction of manic symptoms over 3 weeks. Point estimates [95 % CI] for the change from baseline to endpoint in YMRS using LOCF analysis in the two studies were as follows:
-11.5 [-13.0, -10.0] for asenapine vs -7.8 [-10.0, -5.6] for placebo and
-10.8 [-12.3, -9.3] for asenapine vs -5.5 [-7.5, -3.5] for placebo.
A statistically significant difference between asenapine and placebo was seen as early as day 2.

Patients from the two pivotal 3 week trials were studied for a further 9 weeks an extension trial. Maintenance of effect during the episode after 12 weeks of randomised treatment was demonstrated in this trial.

In one double-blind, fixed-dose, parallel-group, 3-week placebo controlled trial in subjects with bipolar I disorder experiencing an acute manic or mixed episode involving 367 patients of which 126 received placebo, 122 received asenapine 5 mg twice daily (BID), and 119 received asenapine 10 mg BID, the primary efficacy hypothesis was met. Both asenapine doses (5 mg BID and 10 mg BID) were superior to placebo and showed statistically significant improvement in change from baseline in Y-MRS total score at Day 21 compared with placebo. Based upon a LOCF analysis including all patients treated, the difference in least squares (LS) mean change from baseline to Day 21 in the Y-MRS total score between asenapine 5 mg BID and placebo was -3.1 points (95 % CI [-5.7, -0.5]; p-value = 0.0183). The difference in LS mean change from baseline to Day 21 in the Y-MRS total score between asenapine 10 mg BID and placebo was -3.0 points (95 % CI [-5.6, -0.4]; p-value = 0.0244). A statistically significant difference between asenapine and placebo was seen as early as day 2. In this short-term, fixed-dose controlled trial there was no evidence of added benefit with a 10 mg twice daily dose compared to 5 mg twice daily.

In a 12-week, placebo-controlled trial involving 326 patients with a manic or mixed episode of bipolar I disorder, with or without psychotic features, who were partially non-responsive to lithium or

valproate monotherapy for 2 weeks at therapeutic serum levels, the addition of asenapine as adjunctive therapy resulted in superior efficacy to lithium or valproate monotherapy at week 3 (point estimates [95 % CI] for the change from baseline to endpoint in YMRS using LOCF analysis were -10.3 [-11.9, -8.8] for asenapine and -7.9 [-9.4, -6.4] for placebo) and at week 12 (-12.7 [-14.5, -10.9] for asenapine and -9.3 [-11.8, -7.6] for placebo) in the reduction of manic symptoms.

Paediatric population
Asenapine is not indicated for the treatment of children and adolescent patients below 18 years (see section 4.2).

The safety and efficacy of Sycrest was evaluated in 403 paediatric patients with bipolar I disorder who participated in a single, 3-week, placebo-controlled, double-blind trial, of whom 302 patients received Sycrest at fixed doses ranging from 2.5 mg to 10 mg twice daily. Study results showed statistically significant superiority for all three Sycrest doses in improving the Young Mania Rating Scale (YMRS) total score as measured by the change from baseline to Day 21, as compared with placebo. Long term efficacy could not be established in a 50-week, uncontrolled, open-label extension trial. The clinically relevant adverse reactions identified in the paediatric trials were generally similar to those observed in the adult trials. However, adverse effects of treatment on weight gain and on plasma lipid profile appeared to be greater than effects observed in the adult trials.

Efficacy of Sycrest was not demonstrated in an 8-week, placebo-controlled, double-blind, randomized, fixed-dose trial in 306 adolescent patients aged 12-17 years with schizophrenia at doses of 2.5 and 5 mg twice daily.

Paediatric studies with Sycrest were performed using flavoured sublingual tablets. The European Medicines Agency has deferred the obligation to submit the results of studies with Sycrest in one or more subsets of the paediatric population in bipolar I disorder (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Following sublingual administration, asenapine is rapidly absorbed with peak plasma concentrations occurring within 0.5 to 1.5 hours. The absolute bioavailability of sublingual asenapine at 5 mg is 35 %. The absolute bioavailability of asenapine when swallowed is low (< 2 % with an oral tablet formulation). The intake of water several (2 or 5) minutes after asenapine administration resulted in decreased (19 % and 10 %, respectively) asenapine exposure. Therefore, eating and drinking should be avoided for 10 minutes after administration (see section 4.2).

Distribution
Asenapine is rapidly distributed and has a large volume of distribution (approximately 20-25 L/kg), indicating extensive extravascular distribution. Asenapine is highly bound (95 %) to plasma proteins, including albumin and α1-acid glycoprotein.

Biotransformation
Asenapine is extensively metabolized. Direct glucuronidation (mediated by UGT1A4) and cytochrome P450 (primarily CYP1A2, with contributions of 2D6 and 3A4) mediated oxidation and demethylation are the primary metabolic pathways for asenapine. In an *in vivo* study in humans with radio-labelled asenapine, the predominant drug-related entity in plasma was asenapine N^+-glucuronide; others included N-desmethylasenapine, N-desmethylasenapine N-carbamoyl glucuronide, and unchanged asenapine in smaller amounts. Sycrest activity is primarily due to the parent compound.

Asenapine is a weak inhibitor of CYP2D6. Asenapine does not cause induction of CYP1A2 or CYP3A4 activities in cultured human hepatocytes. Co-administration of asenapine with known inhibitors, inducers or substrates of these metabolic pathways has been studied in a number of drug-drug interaction studies (see section 4.5).

Elimination
Asenapine is a high clearance compound, with a clearance after intravenous administration of 52 L/h. In a mass balance study, the majority of the radioactive dose was recovered in urine (about 50 %) and faeces (about 40 %), with only a small amount excreted in faeces (5-16 %) as unchanged compound. Following an initial more rapid distribution phase, the terminal half-life of asenapine is approximately 24 h.

Linearity/non-linearity
Increasing the dose from 5 to 10 mg twice daily (a two-fold increase) results in less than linear (1.7 times) increases in both the extent of exposure and maximum concentration. The less than proportional increase of Cmax and AUC with dose may be attributed to limitations in the absorption capacity from the oral mucosa following sublingual administration.
During twice-daily dosing, steady-state is attained within 3 days. Overall, steady-state asenapine pharmacokinetics are similar to single-dose pharmacokinetics.

Pharmacokinetics in special populations

Hepatic impairment
The pharmacokinetics of asenapine were similar among subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment and subjects with normal hepatic function. In subjects with severe hepatic impairment (Child-Pugh C), a 7-fold increase in asenapine exposure was observed (see section 4.2).

Renal impairment
The pharmacokinetics of asenapine following a single dose of 5 mg asenapine were similar among subjects with varying degrees of renal impairment and subjects with normal renal function.
There is no experience with asenapine in severe renal impairment patients with a creatinine clearance less than 15 mL/min.

Elderly
In elderly patients (between 65 and 85 years of age), exposure to asenapine is approximately 30 % higher than in younger adults.

Paediatric population (children and adolescents)
In a PK study using unflavoured sublingual tablets, at the 5 mg twice daily dose level, asenapine pharmacokinetics in adolescent patients (12 to 17 years of age, inclusive) are similar to those observed in adults. In adolescents, the 10 mg twice daily dose did not result in increased exposure compared to 5 mg twice daily.

In a second PK study using flavoured sublingual tablets, the 10 mg twice daily dose in a paediatric population (10 to 17 years of age, inclusive) resulted in an approximate dose-proportional increase in asenapine exposure compared to 5 mg twice daily.

Gender
A population pharmacokinetic analysis indicated that there is no evidence of gender-related differences in the pharmacokinetics of asenapine.

Race
In a population pharmacokinetic analysis, no clinical relevant effects of race on the pharmacokinetics of asenapine were found.

Smoking status
A population pharmacokinetic analysis indicated that smoking, which induces CYP1A2, has no effect on the clearance of asenapine. In a dedicated study, concomitant smoking during administration of a single 5 mg sublingual dose had no effect on the pharmacokinetics of asenapine.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology. Repeat-dose toxicity studies in rat and dog showed mainly dose-limiting pharmacological effects, such as sedation. Furthermore, prolactin-mediated effects on mammary glands and oestrus cycle disturbances were observed. In dogs high oral doses resulted in hepatotoxicity that was not observed after chronic intravenous administration. Asenapine has some affinity to melanin-containing tissues. However, when tested *in vitro* it was devoid of phototoxicity. In addition, histopathological examination of the eyes from dogs treated chronically with asenapine did not reveal any signs of ocular toxicity, demonstrating the absence of a phototoxic hazard. Asenapine was not genotoxic in a battery of tests. In subcutaneous carcinogenicity studies in rats and mice, no increases in tumour incidences were observed. Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Asenapine did not impair fertility in rats and was not teratogenic in rat and rabbit. Embryotoxicity was found in reproduction toxicology studies using rats and rabbits. Asenapine caused mild maternal toxicity and slight retardation of foetal skeletal development. Following oral administration to pregnant rabbits during the period of organogenesis, asenapine adversely affected body weight at the high dose of 15 $mg.kg^{-1}$ twice daily. At this dose foetal body weight decreased. When asenapine was administered intravenously to pregnant rabbits, no signs of embryotoxicity were observed. In rats, embryofoetal toxicity (increased post-implantation loss, decreased foetal weights, and delayed ossification) was observed following oral or intravenous administration during organogenesis or throughout gestation. Increased neonatal mortality was observed among the offspring of female rats treated during gestation and lactation. From a cross-fostering study it was concluded that asenapine induced peri- and postnatal losses are caused by impairment of the pups rather than altered nursing behaviour of the dams.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin
Mannitol (E421)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Peelable aluminium/aluminium blisters in cartons of 20, 60 or 100 sublingual tablets per carton.
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

N.V. Organon, Kloosterstraat 6, NL-5349 AB Oss, The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/640/001
EU/1/10/640/002
EU/1/10/640/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 September 2010
Date of latest renewal: 05 May 2015

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.

1. NAME OF THE MEDICINAL PRODUCT

Sycrest 10 mg sublingual tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each sublingual tablet contains 10 mg asenapine (as maleate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sublingual tablet
Round, white to off-white, sublingual tablets debossed with ”10” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sycrest is indicated for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults.

4.2 Posology and method of administration

Posology

The recommended starting dose of Sycrest as monotherapy is 5 mg twice daily. One dose should be taken in the morning and one dose should be taken in the evening. The dose can be increased to 10 mg twice daily based on individual clinical response and tolerability. See section 5.1. For combination therapy a starting dose of 5 mg twice daily is recommended. Depending on the clinical response and tolerability in the individual patient, the dose can be increased to 10 mg twice daily.

Special populations

Elderly
Sycrest should be used with care in the elderly. Limited data on efficacy in patients 65 years of age and older are available. Available pharmacokinetic data are described in section 5.2.

Renal impairment
No dose adjustment is required for patients with renal impairment. There is no experience with asenapine in patients with severe renal impairment who have a creatinine clearance less than 15 mL/min.

Hepatic impairment
No dose adjustment is required for patients with mild hepatic impairment. The possibility of elevated asenapine plasma levels cannot be excluded in some patients with moderate hepatic impairment (Child-Pugh B) and caution is advised. In subjects with severe hepatic impairment (Child-Pugh C), a 7-fold increase in asenapine exposure was observed. Thus, Sycrest is not recommended in patients with severe hepatic impairment.

Paediatric population
A pharmacokinetic study and a short term efficacy and safety study were performed in a paediatric population (ages 10-17 years) with manic or mixed episodes associated with bipolar I disorder. Long term safety in this population was explored in a 50-week, open-label, uncontrolled extension study.

Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

The tablet should not be removed from the blister until ready to take it. Dry hands should be used when touching the tablet. The tablet should not be pushed through the tablet pack. The tablet pack should not be cut or torn. The coloured tab should be peeled back and the tablet should be removed gently. The tablet should not be crushed.

To ensure optimal absorption, the Sycrest sublingual tablet should be placed under the tongue and allowed to dissolve completely. The tablet will dissolve in saliva within seconds. Sycrest sublingual tablets should not be chewed or swallowed. Eating and drinking should be avoided for 10 minutes after administration.

When used in combination with other medicinal products, Sycrest should be taken last.

Treatment with Sycrest is not advised in patients who are unable to comply with this method of administration, as the bioavailability of asenapine when swallowed is low (< 2 % with an oral tablet formulation).

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-related psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic substances are at an increased risk of death.

Sycrest is not approved for the treatment of patients with dementia-related psychosis and is not recommended for use in this particular group of patients.

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 antipsychotics, including asenapine. Additional clinical signs may include myoglobinuria (rhabdomyolysis) and acute renal failure.

If a patient develops signs and symptoms indicative of NMS Sycrest must be discontinued.

Seizures
In clinical trials, cases of seizure were occasionally reported during treatment with asenapine. Therefore, Sycrest should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures.

Suicide
The possibility of a suicide attempt is inherent in psychotic illnesses and bipolar disorder and close supervision of high-risk patients should accompany treatment.

Orthostatic hypotension
Asenapine may induce orthostatic hypotension and syncope, especially early in treatment, probably reflecting its α1-adrenergic antagonist properties. Elderly patients are particularly at risk for experiencing orthostatic hypotension (see section 4.8). In clinical trials, cases of syncope were occasionally reported during treatment with Sycrest. Sycrest should be used with caution in elderly patients and in patients with known cardiovascular disease (e.g., heart failure, myocardial infarction or

ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration and hypovolemia).

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. In clinical trials, cases of tardive dyskinesia were occasionally reported during treatment with asenapine. The onset of extrapyramidal symptoms is a risk factor for tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear in a patient on Sycrest, discontinuation of treatment should be considered.

Hyperprolactinaemia
Increases in prolactin levels were observed in some patients with Sycrest. In clinical trials, there were few adverse reactions related to abnormal prolactin levels reported.

QT interval
Clinically relevant QT prolongation does not appear to be associated with asenapine. Caution should be exercised when Sycrest is prescribed in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with other medicinal products thought to prolong the QT interval.

Hyperglycaemia and diabetes mellitus
Hyperglycaemia or exacerbation of pre-existing diabetes has occasionally been reported during treatment with asenapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia or bipolar disorder and the increasing incidence of diabetes mellitus in the general population. Appropriate clinical monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus.

Dysphagia
Esophageal dysmotility and aspiration have been associated with antipsychotic treatment. Cases of dysphagia were occasionally reported in patients treated with Sycrest.

Body temperature regulation
Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicinal products. From the clinical trials, it is concluded that clinically relevant body temperature dysregulation does not appear to be associated with asenapine. Appropriate care is advised when prescribing Sycrest for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g. exercising strenuously, exposure to extreme heat, receiving concomitant medicinal products with anticholinergic activity or being subject to dehydration.

Patients with severe hepatic impairment
Asenapine exposure is increased 7-fold in patients with severe hepatic impairment (Child-Pugh C). Therefore, Sycrest is not recommended in such patients.

Parkinson's disease and dementia with Lewy bodies
Physicians should weigh the risks versus the benefits when prescribing Sycrest 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.

Falls
Asenapine may cause adverse effects such as somnolence, orthostatic hypotension, dizziness and extrapyramidal symptoms, which may lead to falls and, consequently, fractures or other injuries. Patients at risk for fall should be evaluated prior to prescribing asenapine.

4.5 Interaction with other medicinal products and other forms of interaction

Given the primary effects of asenapine on the central nervous system (CNS) (see section 4.8), caution should be used when it is taken in combination with other centrally acting medicinal products. Patients should be advised to avoid alcohol while taking Sycrest.

Potential for other medicinal products to affect Sycrest
Asenapine is cleared primarily through direct glucuronidation by UGT1A4 and oxidative metabolism by cytochrome P450 isoenzymes (predominantly CYP1A2). The potential effects of inhibitors and an inducer of several of these enzyme pathways on asenapine pharmacokinetics were studied, specifically fluvoxamine (CYP1A2 inhibitor), paroxetine (CYP2D6 inhibitor), imipramine (CYP1A2/2C19/3A4 inhibitor), cimetidine (CYP3A4/2D6/1A2 inhibitor), carbamazepine (CYP3A4/1A2 inducer) and valproate (UGT inhibitor). Except for fluvoxamine, none of the interacting medicinal products resulted in clinically relevant alterations in asenapine pharmacokinetics.

During combined administration with a single dose of asenapine 5 mg, fluvoxamine 25 mg twice daily resulted in a 29 % increase in asenapine AUC. The full therapeutic dose of fluvoxamine would be expected to produce a greater increase in asenapine plasma concentrations. Therefore, co-administration of asenapine and fluvoxamine should be approached with caution.

Potential for Sycrest to affect other medicinal products
Because of its α1-adrenergic antagonism with potential for inducing orthostatic hypotension (see section 4.4), Sycrest may enhance the effects of certain antihypertensive agents.

Asenapine may antagonise the effect of levodopa and dopamine agonists. If this combination is deemed necessary, the lowest effective dose of each treatment should be prescribed.

In vitro studies indicate that asenapine weakly inhibits CYP2D6. Clinical drug interaction studies investigating the effects of CYP2D6 inhibition by asenapine showed the following results:

- Following co-administration of dextromethorphan and asenapine in healthy subjects, the ratio of dextrorphan/dextromethorphan (DX/DM) as a marker of CYP2D6 activity was measured. Indicative of CYP2D6 inhibition, treatment with asenapine 5 mg twice daily resulted in a fractional decrease in DX/DM ratio to 0.43. In the same study, treatment with paroxetine 20 mg daily decreased the DX/DM ratio to 0.032.

- In a separate study, co-administration of a single 75 mg dose of imipramine with a single 5 mg dose of asenapine did not affect the plasma concentrations of the metabolite desipramine (a CYP2D6 substrate).

- Co-administration of a single 20 mg dose of paroxetine (a CYP2D6 substrate and inhibitor) during treatment with 5 mg asenapine twice daily in 15 healthy male subjects resulted in an almost 2-fold increase in paroxetine exposure.

In vivo asenapine appears to be at most a weak inhibitor of CYP2D6. However, asenapine may enhance the inhibitory effects of paroxetine on its own metabolism.

Therefore, Sycrest should be co-administered cautiously with medicinal products that are both substrates and inhibitors for CYP2D6.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of Sycrest in pregnant women. Asenapine was not teratogenic in animal studies. Maternal and embryo toxic effects were found in animal studies (see section 5.3).

Newborn infants exposed to antipsychotics (including Sycrest) 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 in newborn infants. Consequently, newborn infants should be monitored carefully.

Sycrest should not be used during pregnancy unless the clinical condition of the woman requires treatment with asenapine and only if the potential benefit outweighs the potential risk to the foetus.

Breast-feeding
Asenapine was excreted in milk of rats during lactation. It is not known whether asenapine or its metabolites are excreted in human milk. Breast-feeding should be discontinued during treatment with Sycrest.

Fertility
No impairment of fertility has been observed in nonclinical studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Asenapine may cause somnolence and sedation. Therefore, patients should be cautioned about driving and using machines until they are reasonably certain that Sycrest therapy does not affect them adversely.

4.8 Undesirable effects

Summary of safety profile
The most frequently reported adverse drug reactions (ADRs) associated with the use of asenapine in clinical trials were somnolence and anxiety. Serious hypersensitivity reactions have been reported. Other serious ADRs are discussed in more detail in section 4.4.

Tabulated list of adverse reactions
The incidences of the ADRs associated with asenapine therapy are tabulated below. The table is based on adverse reactions reported during clinical trials and/or post-marketing use.

All ADRs are listed by system organ 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) and not known (cannot be estimated from the available data). Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

System organ class	Very common	Common	Uncommon	Rare	Not known
Blood and lymphatic disorders				Neutropenia	
Immune system disorders			Allergic reactions		
Metabolism and nutrition disorders		Weight increased Increased appetite	Hyperglycaemia		
Psychiatric disorders	Anxiety				

System organ class	Very common	Common	Uncommon	Rare	Not known
Nervous system disorders	Somnolence	Dystonia Akathisia Dyskinesia Parkinsonism Sedation Dizziness Dysgeusia	Syncope Seizure Extrapyramidal disorder Dysarthria Restless legs syndrome	Neuroleptic malignant syndrome	
Eye disorders				Accommodation disorder	
Cardiac disorders			Sinus bradycardia Bundle branch block Electrocardio-gram QT prolonged Sinus tachycardia		
Vascular disorders			Orthostatic hypotension Hypotension		
Respiratory, thoracic and mediastinal disorders				Pulmonary embolism	
Gastrointestinal disorders		Hypoaesthesia oral Nausea Salivary hypersecretion	Swollen tongue Dysphagia Glossodynia Paraesthesia oral Oral mucosal lesions (ulcerations, blistering and inflammation)		
Hepatobiliary disorders		Alanine aminotransferase increased			
Injury, poisoning and procedural complications					Falls*
Musculoskeletal and connective tissue disorders		Muscle rigidity		Rhabdomyolysis	
Pregnancy, puerperium and perinatal conditions					Drug withdrawal syndrome neonatal (see 4.6)

System organ class	Very common	Common	Uncommon	Rare	Not known
Reproductive system and breast disorders			Sexual dysfunction Amenorrhoea	Gynaecomastia Galactorrhoea	
General disorders and administration site conditions		Fatigue			

* See subsection "*Falls*" below

Description of selected adverse reactions

Extrapyramidal Symptoms (EPS)
In clinical trials, the incidence of extrapyramidal symptoms in asenapine-treated patients was higher than placebo (15.4 % vs 11.0 %).

From the short-term (6 weeks) schizophrenia trials there appears to be a dose-response relationship for akathisia in patients treated with asenapine, and for parkinsonism there was an increasing trend with higher doses.

Based on a small pharmacokinetic study, paediatric patients appeared to be more sensitive to dystonia with initial dosing with asenapine when a gradual up-titration schedule was not followed (see section 5.2). The incidence of dystonia in paediatric clinical trials using a gradual up-titration was similar to that seen in adult trials.

Weight increase
In the combined short-term and long-term schizophrenia and bipolar mania trials in adults, the mean change in body weight for asenapine was 0.8 kg. The proportion of subjects with clinically significant weight gain (≥ 7 % weight gain from baseline at endpoint) in the short-term schizophrenia trials was 5.3 % for asenapine compared to 2.3 % for placebo. The proportion of subjects with clinically significant weight gain (≥ 7 % weight gain from baseline at endpoint) in the short-term, flexible-dose bipolar mania trials was 6.5 % for asenapine compared to 0.6 % for placebo.

In a 3-week, placebo-controlled, randomized, fixed-dose efficacy and safety trial in paediatric patients 10 to 17 years of age with bipolar I disorder, the mean change from baseline to endpoint in weight for placebo and asenapine 2.5 mg, 5 mg, and 10 mg twice daily, was 0.48, 1.72, 1.62, and 1.44 kg, respectively. The proportion of subjects with clinically significant weight gain (≥ 7 % weight gain from baseline at Day 21) was 14.1 % for asenapine 2.5 mg twice daily, 8.9 % for asenapine 5 mg twice daily, and 9.2 % for asenapine 10 mg twice daily, compared to 1.1 % for placebo. In the long-term extension trial (50 weeks), a total of 34.8 % of subjects experienced clinically significant weight increase (i.e., ≥ 7 % increase in body weight at endpoint). Overall mean (SD) weight gain at study endpoint was 3.5 (5.76) kg.

Orthostatic hypotension
The incidence of orthostatic hypotension in elderly subjects was 4.1 % compared to 0.3 % in the combined phase 2/3 trial population.

Falls
Falls may occur as a result of one or more adverse events such as the following: Somnolence, Orthostatic hypotension, Dizziness, Extrapyramidal symptoms.

Hepatic enzymes
Transient, asymptomatic elevations of hepatic transaminases, alanine transferase (ALT), aspartate transferase (AST) have been seen commonly, especially in early treatment.

Other findings
Cerebrovascular events have been reported in patients treated with asenapine but there is no evidence of any excess incidence over what is expected in adults between 18 and 65 years of age.

Asenapine has anaesthetic properties. Oral hypoaesthesia and oral paraesthesia may occur directly after administration and usually resolves within 1 hour.

There have been post-marketing reports of serious hypersensitivity reactions in patients treated with asenapine, including anaphylactic/anaphylactoid reactions, angioedema, swollen tongue and swollen throat (pharyngeal oedema).

Paediatric population
Asenapine is not indicated for the treatment of children and adolescent patients below 18 years (see section 4.2).

The clinically relevant adverse experiences identified in the paediatric bipolar and schizophrenia trials were similar to those observed in adult bipolar and schizophrenia trials.

The most common adverse reactions (≥ 5 % and at least twice the rate of placebo) reported in paediatric patients with bipolar I disorder were somnolence, sedation, dizziness, dysgeusia, hypoaesthesia oral, paraesthesia oral, nausea, increased appetite, fatigue, and weight increased (see *Weight increase* above).

The most common adverse reactions (proportion of patients ≥ 5 % and at least twice placebo) reported in paediatric patients with schizophrenia were somnolence, sedation, akathisia, dizziness, and hypoaesthesia oral. There was a statistically significant higher incidence of patients with ≥ 7 % weight gain (from baseline to endpoint) compared to placebo (3.1 %) for Sycrest 2.5 mg twice daily (9.5 %) and Sycrest 5 mg twice daily (13.1 %).

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 national reporting system listed in Appendix V.

4.9 Overdose

Few cases of overdose were reported in the asenapine program. Reported estimated doses were between 15 and 400 mg. In most cases it was not clear if asenapine had been taken sublingually. Treatment-related adverse reactions included agitation and confusion, akathisia, orofacial dystonia, sedation, and asymptomatic ECG findings (bradycardia, supraventricular complexes, intraventricular conduction delay).

No specific information is available on the treatment of overdose with Sycrest. There is no specific antidote to Sycrest. The possibility of multiple medicinal product involvement should be considered. Cardiovascular monitoring is necessary to detect possible arrhythmias and management of overdose should concentrate on supportive therapy, maintaining an adequate airway oxygenation and ventilation, and management of symptoms. Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulations may worsen hypotension in the setting of Sycrest-induced alpha blockade). In case of severe extrapyramidal symptoms, anticholinergic medicinal products should be administered. Close medical supervision and monitoring should continue until the patient recovers.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, antipsychotics, ATC code: N05AH05

Mechanism of action
The mechanism of action of asenapine is not fully understood. However, based on its receptor pharmacology, it is proposed that the efficacy of asenapine is mediated through a combination of antagonist activity at D2 and 5-HT2A receptors. Actions at other receptors e.g., 5-HT1A, 5-HT1B, 5-HT2C, 5-HT6, 5-HT7, D3, and α2-adrenergic receptors, may also contribute to the clinical effects of asenapine.

Pharmacodynamic effects
Asenapine exhibits high affinity for serotonin 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT5, 5-HT6, and 5-HT7 receptors, dopamine D2, D3, D4, and D1 receptors), α1 and α2-adrenergic receptors, and histamine H1 receptors, and moderate affinity for H2 receptors. In *in vitro* assays asenapine acts as an antagonist at these receptors. Asenapine has no appreciable affinity for muscarinic cholinergic receptors.

Clinical efficacy

Clinical efficacy in bipolar I disorder
The efficacy of asenapine in the treatment of a DSM-IV manic or mixed episode of bipolar I disorder with or without psychotic features was evaluated in two similarly designed 3-week, randomized, double-blind, flexible-dose, placebo- and active controlled (olanzapine) monotherapy trials involving 488 and 489 patients, respectively. All patients met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnostic criteria for bipolar I disorder, current episode manic (DSM-IV 296.4x), or mixed (DSM-IV 296.6x) and had a Young Mania Rating Scale (Y-MRS) score of $\geq$ 20 at screening and baseline. Patients with rapid cycling were excluded from these studies. Asenapine demonstrated superior efficacy to placebo in the reduction of manic symptoms over 3 weeks. Point estimates [95 % CI] for the change from baseline to endpoint in YMRS using LOCF analysis in the two studies were as follows:
-11.5 [-13.0, -10.0] for asenapine vs -7.8 [-10.0, -5.6] for placebo and
-10.8 [-12.3, -9.3] for asenapine vs -5.5 [-7.5, -3.5] for placebo.
A statistically significant difference between asenapine and placebo was seen as early as day 2.

Patients from the two pivotal 3 week trials were studied for a further 9 weeks an extension trial. Maintenance of effect during the episode after 12 weeks of randomised treatment was demonstrated in this trial.

In one double-blind, fixed-dose, parallel-group, 3-week placebo controlled trial in subjects with bipolar I disorder experiencing an acute manic or mixed episode involving 367 patients of which 126 received placebo, 122 received asenapine 5 mg twice daily (BID), and 119 received asenapine 10 mg BID, the primary efficacy hypothesis was met. Both asenapine doses (5 mg BID and 10 mg BID) were superior to placebo and showed statistically significant improvement in change from baseline in Y-MRS total score at Day 21 compared with placebo. Based upon a LOCF analysis including all patients treated, the difference in least squares (LS) mean change from baseline to Day 21 in the Y-MRS total score between asenapine 5 mg BID and placebo was -3.1 points (95 % CI [-5.7, -0.5]; p-value = 0.0183). The difference in LS mean change from baseline to Day 21 in the Y-MRS total score between asenapine 10 mg BID and placebo was -3.0 points (95 % CI [-5.6, -0.4]; p-value = 0.0244). A statistically significant difference between asenapine and placebo was seen as early as day 2. In this short-term, fixed-dose controlled trial there was no evidence of added benefit with a 10 mg twice daily dose compared to 5 mg twice daily.

In a 12-week, placebo-controlled trial involving 326 patients with a manic or mixed episode of bipolar I disorder, with or without psychotic features, who were partially non-responsive to lithium or

valproate monotherapy for 2 weeks at therapeutic serum levels, the addition of asenapine as adjunctive therapy resulted in superior efficacy to lithium or valproate monotherapy at week 3 (point estimates [95 % CI] for the change from baseline to endpoint in YMRS using LOCF analysis were -10.3 [-11.9, -8.8] for asenapine and -7.9 [-9.4, -6.4] for placebo) and at week 12 (-12.7 [-14.5, -10.9] for asenapine and -9.3 [-11.8, -7.6] for placebo) in the reduction of manic symptoms.

Paediatric population
Asenapine is not indicated for the treatment of children and adolescent patients below 18 years (see section 4.2).

The safety and efficacy of Sycrest was evaluated in 403 paediatric patients with bipolar I disorder who participated in a single, 3-week, placebo-controlled, double-blind trial, of whom 302 patients received Sycrest at fixed doses ranging from 2.5 mg to 10 mg twice daily. Study results showed statistically significant superiority for all three Sycrest doses in improving the Young Mania Rating Scale (YMRS) total score as measured by the change from baseline to Day 21, as compared with placebo. Long term efficacy could not be established in a 50-week, uncontrolled, open-label extension trial. The clinically relevant adverse reactions identified in the paediatric trials were generally similar to those observed in the adult trials. However, adverse effects of treatment on weight gain and on plasma lipid profile appeared to be greater than effects observed in the adult trials.

Efficacy of Sycrest was not demonstrated in an 8-week, placebo-controlled, double-blind, randomized, fixed-dose trial in 306 adolescent patients aged 12-17 years with schizophrenia at doses of 2.5 and 5 mg twice daily.

Paediatric studies with Sycrest were performed using flavoured sublingual tablets. The European Medicines Agency has deferred the obligation to submit the results of studies with Sycrest in one or more subsets of the paediatric population in bipolar I disorder (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption
Following sublingual administration, asenapine is rapidly absorbed with peak plasma concentrations occurring within 0.5 to 1.5 hours. The absolute bioavailability of sublingual asenapine at 5 mg is 35 %. The absolute bioavailability of asenapine when swallowed is low (< 2 % with an oral tablet formulation). The intake of water several (2 or 5) minutes after asenapine administration resulted in decreased (19 % and 10 %, respectively) asenapine exposure. Therefore, eating and drinking should be avoided for 10 minutes after administration (see section 4.2).

Distribution
Asenapine is rapidly distributed and has a large volume of distribution (approximately 20-25 L/kg), indicating extensive extravascular distribution. Asenapine is highly bound (95 %) to plasma proteins, including albumin and α1-acid glycoprotein.

Biotransformation
Asenapine is extensively metabolized. Direct glucuronidation (mediated by UGT1A4) and cytochrome P450 (primarily CYP1A2, with contributions of 2D6 and 3A4) mediated oxidation and demethylation are the primary metabolic pathways for asenapine. In an *in vivo* study in humans with radio-labelled asenapine, the predominant drug-related entity in plasma was asenapine N^+-glucuronide; others included N-desmethylasenapine, N-desmethylasenapine N-carbamoyl glucuronide, and unchanged asenapine in smaller amounts. Sycrest activity is primarily due to the parent compound.

Asenapine is a weak inhibitor of CYP2D6. Asenapine does not cause induction of CYP1A2 or CYP3A4 activities in cultured human hepatocytes. Co-administration of asenapine with known inhibitors, inducers or substrates of these metabolic pathways has been studied in a number of drug-drug interaction studies (see section 4.5).

Elimination
Asenapine is a high clearance compound, with a clearance after intravenous administration of 52 L/h. In a mass balance study, the majority of the radioactive dose was recovered in urine (about 50 %) and faeces (about 40 %), with only a small amount excreted in faeces (5-16 %) as unchanged compound. Following an initial more rapid distribution phase, the terminal half-life of asenapine is approximately 24 h.

Linearity/non-linearity
Increasing the dose from 5 to 10 mg twice daily (a two-fold increase) results in less than linear (1.7 times) increases in both the extent of exposure and maximum concentration. The less than proportional increase of Cmax and AUC with dose may be attributed to limitations in the absorption capacity from the oral mucosa following sublingual administration.

During twice-daily dosing, steady-state is attained within 3 days. Overall, steady-state asenapine pharmacokinetics are similar to single-dose pharmacokinetics.

Pharmacokinetics in special populations

Hepatic impairment
The pharmacokinetics of asenapine were similar among subjects with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment and subjects with normal hepatic function. In subjects with severe hepatic impairment (Child-Pugh C), a 7-fold increase in asenapine exposure was observed (see section 4.2).

Renal impairment
The pharmacokinetics of asenapine following a single dose of 5 mg asenapine were similar among subjects with varying degrees of renal impairment and subjects with normal renal function.
There is no experience with asenapine in severe renal impairment patients with a creatinine clearance less than 15 mL/min.

Elderly
In elderly patients (between 65 and 85 years of age), exposure to asenapine is approximately 30 % higher than in younger adults.

Paediatric population (children and adolescents)
In a PK study using unflavoured sublingual tablets, at the 5 mg twice daily dose level, asenapine pharmacokinetics in adolescent patients (12 to 17 years of age, inclusive) are similar to those observed in adults. In adolescents, the 10 mg twice daily dose did not result in increased exposure compared to 5 mg twice daily.

In a second PK study using flavoured sublingual tablets, the 10 mg twice daily dose in a paediatric population (10 to 17 years of age, inclusive) resulted in an approximate dose-proportional increase in asenapine exposure compared to 5 mg twice daily.

Gender
A population pharmacokinetic analysis indicated that there is no evidence of gender-related differences in the pharmacokinetics of asenapine.

Race
In a population pharmacokinetic analysis, no clinical relevant effects of race on the pharmacokinetics of asenapine were found.

Smoking status
A population pharmacokinetic analysis indicated that smoking, which induces CYP1A2, has no effect on the clearance of asenapine. In a dedicated study, concomitant smoking during administration of a single 5 mg sublingual dose had no effect on the pharmacokinetics of asenapine.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology. Repeat-dose toxicity studies in rat and dog showed mainly dose-limiting pharmacological effects, such as sedation. Furthermore, prolactin-mediated effects on mammary glands and oestrus cycle disturbances were observed. In dogs high oral doses resulted in hepatotoxicity that was not observed after chronic intravenous administration. Asenapine has some affinity to melanin-containing tissues. However, when tested *in vitro* it was devoid of phototoxicity. In addition, histopathological examination of the eyes from dogs treated chronically with asenapine did not reveal any signs of ocular toxicity, demonstrating the absence of a phototoxic hazard. Asenapine was not genotoxic in a battery of tests. In subcutaneous carcinogenicity studies in rats and mice, no increases in tumour incidences were observed. Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Asenapine did not impair fertility in rats and was not teratogenic in rat and rabbit. Embryotoxicity was found in reproduction toxicology studies using rats and rabbits. Asenapine caused mild maternal toxicity and slight retardation of foetal skeletal development. Following oral administration to pregnant rabbits during the period of organogenesis, asenapine adversely affected body weight at the high dose of 15 $mg.kg^{-1}$ twice daily. At this dose foetal body weight decreased. When asenapine was administered intravenously to pregnant rabbits, no signs of embryotoxicity were observed. In rats, embryofoetal toxicity (increased post-implantation loss, decreased foetal weights, and delayed ossification) was observed following oral or intravenous administration during organogenesis or throughout gestation. Increased neonatal mortality was observed among the offspring of female rats treated during gestation and lactation. From a cross-fostering study it was concluded that asenapine induced peri- and postnatal losses are caused by impairment of the pups rather than altered nursing behaviour of the dams.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatin
Mannitol (E421)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Peelable aluminium/aluminium blisters in cartons of 20, 60 or 100 sublingual tablets per carton.
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

N.V. Organon, Kloosterstraat 6, NL-5349 AB Oss, The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/640/004
EU/1/10/640/005
EU/1/10/640/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 September 2010
Date of latest renewal: 05 May 2015

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(S) 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(S) RESPONSIBLE FOR BATCH RELEASE

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

Organon Heist bv
Industriepark 30
2220 Heist-op-den-Berg, Belgium

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

OUTER CARTON (5 mg)

1. NAME OF THE MEDICINAL PRODUCT

Sycrest 5 mg sublingual tablets
asenapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sublingual tablet contains 5 mg asenapine (as maleate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 sublingual tablets
60 sublingual tablets
100 sublingual tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Sublingual use.
Peelable blister. Do not crush, chew or swallow.
Keep the tablet under your tongue until it dissolves.
Do not eat or drink for 10 minutes after taking the tablet.

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

N.V. Organon
Kloosterstraat 6
NL- 5349 AB Oss
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/640/001 20 sublingual tablets
EU/1/10/640/002 60 sublingual tablets
EU/1/10/640/003 100 sublingual tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sycrest 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

BLISTER (5 mg)

1. NAME OF THE MEDICINAL PRODUCT

Sycrest 5 mg sublingual tablets
asenapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

N.V. Organon

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (10 mg)

1. NAME OF THE MEDICINAL PRODUCT

Sycrest 10 mg sublingual tablets
asenapine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sublingual tablet contains 10 mg asenapine (as maleate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

20 sublingual tablets
60 sublingual tablets
100 sublingual tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Sublingual use.
Peelable blister. Do not crush, chew or swallow.
Keep the tablet under your tongue until it dissolves.
Do not eat or drink for 10 minutes after taking the tablet.

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

N.V. Organon
Kloosterstraat 6
NL- 5349 AB Oss
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/10/640/004 20 sublingual tablets
EU/1/10/640/005 60 sublingual tablets
EU/1/10/640/006 100 sublingual tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sycrest 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

BLISTER (10 mg)

1. NAME OF THE MEDICINAL PRODUCT

Sycrest 10 mg sublingual tablets
asenapine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

N.V. Organon

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Sycrest 5 mg sublingual tablets
Sycrest 10 mg sublingual tablets
asenapine

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 Sycrest is and what it is used for

Sycrest contains the active substance asenapine. This medicine belongs to a group of medicines called antipsychotics. Sycrest is used to treat moderate to severe manic episodes associated with bipolar I disorder in adults. Antipsychotic medicines affect the chemicals that allow communication between nerve cells (neurotransmitters). Illnesses that affect the brain, such as bipolar I disorder, may be due to certain chemicals in the brain, such as dopamine and serotonin, being out of balance and these imbalances may cause some of the symptoms you may be experiencing. Exactly how this medicine works is unknown, however, it is believed to adjust the balance of these chemicals.

Manic episodes associated with bipolar I disorder is a condition with symptoms such as feeling “high”, having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas and sometimes severe irritability.

2. What you need to know before you take Sycrest

Do not take Sycrest
If you are allergic to asenapine 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 Sycrest.

Sycrest 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. Sycrest is not approved for the treatment of elderly patients with dementia and is not recommended for use in this particular group of patients.

Sycrest may cause low blood pressure. In the early stages of treatment, some people may faint, 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. Your dose may need to be adjusted.

Asenapine may cause sleepiness, sudden drops in blood pressure when you stand up, dizziness and changes in your ability to move and balance, which may lead to falls and, consequently, fractures or other injuries. Patients at risk for fall should be evaluated prior to prescribing asenapine.

Tell your doctor immediately if you experience
- involuntary rhythmic movements of the tongue, mouth and face. Withdrawal of Sycrest may be needed.
- fever, severe muscle stiffness, sweating or a lowered level of consciousness (a disorder called "neuroleptic malignant syndrome"). Immediate medical treatment may be needed.

Check with your doctor or pharmacist before taking Sycrest:

- if you have ever been diagnosed with a condition whose symptoms include high body 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 have a heart disease or a treatment for heart disease that makes you prone to low blood pressure
- if you are diabetic or prone to diabetes
- if you have Parkinson's disease or dementia
- if you have epilepsy (seizures)
- if you experience any difficulty in swallowing (dysphagia)
- if you have severe liver problems. If you do, you should not take Sycrest
- if you have difficulty controlling core body temperature
- if you have thoughts of suicide
- if you have abnormally high levels of prolactin in the blood (hyperprolactinaemia)

Be sure to tell your doctor if you meet any of these conditions as he/she may want to adjust your dose or monitor you for a while. Also contact your doctor immediately if any of these conditions develops or worsens while using Sycrest.

Children and adolescents
Sycrest is not recommended for use in patients below the age of 18 years.

Other medicines and Sycrest
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Some medicines may reduce or increase the effect of Sycrest.

If you are taking other medicines, Sycrest should be taken last.

You should tell your doctor if you are taking antidepressant medicines (specifically fluvoxamine, paroxetine or fluoxetine), as it may be necessary to change your Sycrest or antidepressant medicine dose.

You should tell your doctor if you are taking medicines for Parkinson's disease (such as levodopa), as this medicine may make them less effective.

Since Sycrest works primarily in the brain, interference from other medicines (or alcohol) that work in the brain could occur due to an additive effect on brain function.

Since Sycrest can lower blood pressure, care should be taken when Sycrest is taken with other medicines that lower blood pressure.

Sycrest with food, drink and alcohol
Do not eat or drink for 10 minutes after taking this medicine.
You should avoid drinking alcohol 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.

Do not take Sycrest while you are pregnant, unless your doctor tells you so. If you are taking this medicine and you become pregnant or you plan to get pregnant, ask your doctor as soon as possible whether you may continue taking Sycrest.

The following symptoms may occur in newborn babies, of mothers that have used Sycrest 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.

Do not breast-feed when taking Sycrest.

Driving and using machines
Sycrest may cause sleepiness or sedation. Therefore, make sure your concentration and alertness are not affected before you drive or operate machinery.

3. How to take Sycrest

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is a sublingual tablet of 5 mg or 10 mg two times a day. One dose should be taken in the morning and one dose should be taken in the evening.

Instructions for use
Sycrest is for sublingual use.
Sycrest is not advised if you are unable to take the tablet as described below. If you are unable to take this medicine as is described below, the treatment may not be effective for you.
- Do not remove a sublingual tablet from the blister until ready to take it.
- Use dry hands when touching the tablet.
- Do not push the tablet through the blister. Do not cut or tear the blister.
- Peel back the coloured tab (Figure 1).
- Gently remove the tablet (Figure 2). Do not crush the tablet.
- To ensure optimal absorption, place the tablet under the tongue and wait until it dissolves completely (Figure 3). The tablet will dissolve in saliva within seconds.
- Do not swallow or chew on the tablet.
- Do not eat or drink for 10 minutes after taking the tablet.

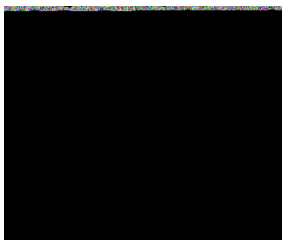
Figure 1


Figure 2


Figure 3

If you take more Sycrest than you should
If you take too much Sycrest, contact a doctor straight away. Take the medicine pack with you. In case of overdose you may feel sleepy or tired, or have abnormal body movements, problems with standing and walking, feel dizzy due to low blood pressure and feel agitated and confused.

If you forget to take Sycrest
Do not take a double dose to make up for a forgotten dose. If you miss one dose, take your next dose as usual. If you miss two or more doses, contact your doctor or pharmacist.

If you stop taking Sycrest
If you stop taking Sycrest, you will lose the effects of this medicine. You should not stop taking this medicine, unless your doctor tells you 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.

Serious side effects have been reported with this medicine. Seek medical attention immediately if you have any of the following symptoms:
- allergic reactions (These usually involve a combination of effects such as difficulty in breathing or swallowing, swollen face, lips, tongue or throat, skin rash, itching and increased heart rate.)
- sudden increase in body temperature, with sweating, fast heartbeat, severe muscle stiffness, confusion and fluctuating blood pressure which may lead to coma
- convulsions, fits or seizures
- fainting
- falls which may occur as a result of one or more adverse events such as: sleepiness, sudden drops in blood pressure when you stand up, dizziness and changes in your ability to move and balance.

Tell your doctor right away if you have:
- signs of increased blood sugar levels such as excessive thirst, hunger or urination, weakness or onset of worsening of diabetes
- worm-like movements of the tongue, or other uncontrolled movements of the tongue, mouth, cheeks, or jaw which may progress to arms and legs

Other side effects reported with this medicine include:

Very common side effects (may affect more than 1 in 10 people)
- anxiety
- sleepiness

Common side effects (may affect up to 1 in 10 people)
- weight gain
- increased appetite
- slow or sustained muscle contractions
- restlessness entered as akathisia
- involuntary muscle contractions
- slow movements, tremor
- sedation
- dizziness
- nausea
- change in taste
- numb feeling of the tongue or in the mouth
- increased saliva (drooling)
- muscle tightness
- fatigue
- increase in the level of liver proteins

Uncommon side effects (may affect up to 1 in 100 people)
- abnormal muscle movements: a collection of symptoms known as extrapyramidal symptoms (EPS) which may include one or more of the following: abnormal movements of muscles, tongue, or jaw, slow or sustained muscle contractions, muscle spasms, tremor (shaking), abnormal movements of the eyes, involuntary muscle contractions, slow movements, or restlessness
- unpleasant sensations in the legs (also called restless legs syndrome)
- speech problems
- abnormal slow or fast heartbeat
- middle heart block
- abnormal electrocardiogram (prolongation of the QT interval)
- low blood pressure upon standing
- low blood pressure
- tingling of the tongue or in the mouth
- swollen or painful tongue
- difficulty in swallowing
- ulcers, soreness, redness, swelling, and blisters within the mouth
- sexual dysfunction
- lack of regular menstrual periods

Rare side effects (may affect up to 1 in 1,000 people)
- changes in the levels of white blood cells
- difficulties in focusing with the eyes
- blood clots in blood vessels to the lungs causing chest pain and difficulty in breathing
- muscle disease presenting as unexplained aches and pains
- male breast enlargement
- leakage of milk or fluid from the breast

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 Sycrest

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 and on the carton. The expiry date refers to the last day of that month.

Store this medicine in the original package in order to protect from light and moisture.

This medicinal product does not require any special temperature storage conditions.

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 Sycrest contains
– The active substance is asenapine.
– Each Sycrest 5 mg sublingual tablet contains 5 mg asenapine.
– Each Sycrest 10 mg sublingual tablet contains 10 mg asenapine.
– The exact amount is shown on your Sycrest tablet pack.

– The other ingredients are gelatin and mannitol (E421).

What Sycrest looks like and contents of the pack
The 5 mg sublingual tablets are round white to off-white tablets marked with “5” on one side.
The 10 mg sublingual tablets are round white to off-white tablets marked with “10” on one side.

The sublingual tablets are provided in peelable blisters containing 10 tablets each. Packs may contain 20, 60 or 100 tablets.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
N.V. Organon
Kloosterstraat 6
NL-5349 AB Oss
The Netherlands

Manufacturer
Organon Heist bv
Industriepark 30
2220 Heist-op-den-Berg, Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Organon Belgium
Tél/Tel: 0080066550123 (+32 2 2418100)
dpoc.benelux@organon.com

България
Органон (И.А.) Б.В. - клон България
Тел.: +359 2 806 3030
dpoc.bulgaria@organon.com

Česká republika
Organon Czech Republic s.r.o.
Tel: +420 233 010 300
dpoc.czech@organon.com

Danmark
Organon Denmark ApS
Tlf: +45 4484 6800
info.denmark@organon.com

Deutschland
Organon Healthcare GmbH
Tel.: 0800 3384 726 (+49 (0) 89 2040022 10)
dpoc.germany@organon.com

Eesti
Organon Pharma B.V. Estonian RO
Tel: +372 66 61 300
dpoc.estonia@organon.com

Lietuva
Organon Pharma B.V. Lithuania atstovybė
Tel.: +370 52041693
dpoc.lithuania@organon.com

Luxembourg/Luxemburg
Organon Belgium
Tél/Tel: 0080066550123 (+32 2 2418100)
dpoc.benelux@organon.com

Magyarország
Organon Hungary Kft.
Tel.: +36 1 766 1963
dpoc.hungary@organon.com

Malta
Organon Pharma B.V., Cyprus branch
Tel: +356 2277 8116
dpoc.cyprus@organon.com

Nederland
N.V. Organon
Tel: 00800 66550123 (+32 2 2418100)
dpoc.benelux@organon.com

Norge
Organon Norway AS
Tlf: +47 24 14 56 60
info.norway@organon.com

Ελλάδα
BIANEΞ A.E.
Τηλ: +30 210 80091 11
Mailbox@vianex.gr

España
Organon Salud, S.L.
Tel: +34 91 591 12 79
organon_info@organon.com

France
Organon France
Tél: +33 (0) 1 57 77 32 00

Hrvatska
Organon Pharma d.o.o.
Tel: +385 1 638 4530
dpoc.croatia@organon.com

Ireland
Organon Pharma (Ireland) Limited
Tel: +353 15828260
medinfo.ROI@organon.com

Ísland
Vistor hf.
Sími: +354 535 7000

Italia
Organon Italia S.r.l.
Tel: +39 06 90259059
dpoc.italy@organon.com

Κύπρος
Organon Pharma B.V., Cyprus branch
Τηλ: +357 22866730
dpoc.cyprus@organon.com

Latvija
Ārvalsts komersanta "Organon Pharma B.V." pārstāvniecība
Tel: +371 66968876
dpoc.latvia@organon.com

Österreich
Organon Healthcare GmbH
Tel: 0800 3384 726 (+49 (0) 89 2040022 10)
dpoc.austria@organon.com

Polska
Organon Polska Sp. z o.o.
Tel.: +48 22 105 50 01
organonpolska@organon.com

Portugal
Organon Portugal, Sociedade Unipessoal Lda.
Tel: +351 218705500
geral_pt@organon.com

România
Organon Biosciences S.R.L.
Tel: +40 21 527 29 90
dpoc.romania@organon.com

Slovenija
Organon Pharma B.V., Oss, podružnica Ljubljana
Tel: +386 1 300 10 80
dpoc.slovenia@organon.com

Slovenská republika
Organon Slovakia s. r. o.
Tel: +421 2 44 88 98 88
dpoc.slovakia@organon.com

Suomi/Finland
Organon Finland Oy
Puh/Tel: +358 (0) 29 170 3520
dpoc.finland@organon.com

Sverige
Organon Sweden AB
Tel: +46 8 502 597 00
dpoc.sweden@organon.com

United Kingdom (Northern Ireland)
Organon Pharma (UK) Limited
Tel: +44 (0) 208 159 3593
medicalinformationuk@organon.com

This leaflet was last revised in {month/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

RXULTI 0.25 mg film-coated tablets
RXULTI 0.5 mg film-coated tablets
RXULTI 1 mg film-coated tablets
RXULTI 2 mg film-coated tablets
RXULTI 3 mg film-coated tablets
RXULTI 4 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RXULTI 0.25 mg film-coated tablets

Each film-coated tablet contains 0.25 mg brexpiprazole.

Excipient with known effect
Each film-coated tablet contains approximately 45.8 mg lactose (as monohydrate).

RXULTI 0.5 mg film-coated tablets

Each film-coated tablet contains 0.5 mg brexpiprazole.

Excipient with known effect
Each film-coated tablet contains approximately 45.5 mg lactose (as monohydrate).

RXULTI 1 mg film-coated tablets

Each film-coated tablet contains 1 mg brexpiprazole.

Excipient with known effect
Each film-coated tablet contains approximately 45 mg lactose (as monohydrate).

RXULTI 2 mg film-coated tablets

Each film-coated tablet contains 2 mg brexpiprazole.

Excipient with known effect
Each film-coated tablet contains approximately 44.1 mg lactose (as monohydrate).

RXULTI 3 mg film-coated tablets

Each film-coated tablet contains 3 mg brexpiprazole.

Excipient with known effect
Each film-coated tablet contains approximately 43.1 mg lactose (as monohydrate).

RXULTI 4 mg film-coated tablets

Each film-coated tablet contains 4 mg brexpiprazole.

Excipient with known effect
Each film-coated tablet contains approximately 42.2 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

RXULTI 0.25 mg film-coated tablets
Light brown, round, 6 mm in diameter, shallow convex and bevel-edged, debossed with BRX and 0.25 on one side.

RXULTI 0.5 mg film-coated tablets
Light orange, round, 6 mm in diameter, shallow convex and bevel-edged, debossed with BRX and 0.5 on one side.

RXULTI 1 mg film-coated tablets
Light yellow, round, 6 mm in diameter, shallow convex and bevel-edged, debossed with BRX and 1 on one side.

RXULTI 2 mg film-coated tablets
Light green, round, 6 mm in diameter, shallow convex and bevel-edged, debossed with BRX and 2 on one side.

RXULTI 3 mg film-coated tablets
Light purple, round, 6 mm in diameter, shallow convex and bevel-edged, debossed with BRX and 3 on one side.

RXULTI 4 mg film-coated tablets
White, round, 6 mm in diameter, shallow convex and bevel-edged, debossed with BRX and 4 one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RXULTI is indicated for the treatment of schizophrenia in adults and adolescents aged 13 years and older.

4.2 Posology and method of administration

Posology

Adult population
The recommended starting dose for brexpiprazole is 1 mg once daily on days 1 to 4.
Based on the patient's clinical response and tolerability, the brexpiprazole dose can be titrated to 2 mg once daily on day 5 through day 7 and then to 4 mg on day 8.
The recommended target dose range is 2 mg to 4 mg once daily. The maximum recommended daily dose is 4 mg.

Paediatric population
The recommended starting dose for brexpiprazole is 0.5 mg once daily on days 1 to 4.
The brexpiprazole dose should be titrated to 1 mg once daily on day 5 through day 7 and then to 2 mg on day 8. Weekly dose increases can be made in 1 mg increments based on clinical response and tolerability.
The recommended target dose range is 2 mg to 4 mg once daily. The maximum recommended daily dose is 4 mg.

Switching from other antipsychotics to brexpiprazole
When switching from other antipsychotics to brexpiprazole, gradual cross-titration should be considered, with gradual discontinuation of the previous treatment while brexpiprazole treatment is initiated.

Switching to other antipsychotics from brexpiprazole
When switching to other antipsychotics from brexpiprazole, no gradual cross-titration is needed. The new antipsychotic should be initiated in its lowest dose while brexpiprazole is discontinued. It should be considered that plasma concentration of brexpiprazole will decline gradually and will be completely washed out in 1 to 2 weeks.

Special populations

Elderly
The safety and efficacy of brexpiprazole in the treatment of schizophrenia in patients aged 65 years and older have not been established (see sections 4.4 and 5.2). It is not possible to advise on a minimum effective/safe dose in this population.

Renal impairment
The maximum recommended dose in patients with moderate to severe impaired renal function is reduced to 3 mg once daily (see section 5.2).

Hepatic impairment
The maximum recommended dose in patients with moderate to severe hepatic impairment (Child-Pugh score ≥ 7) is reduced to 3 mg once daily (see section 5.2).

CYP2D6 poor metabolisers
Dosing modifications to half the recommended doses is required for patients with known CYP2D6 poor metaboliser status. Further dosing modifications to a quarter of the recommended dose is required for known CYP2D6 poor metabolisers while taking strong or moderate CYP3A4 inhibitors (see sections 4.5 and 5.2).

Dose adjustments due to interactions
Dose adjustments should be made in patients taking concomitant strong CYP3A4 inhibitors/inducers or strong CYP2D6 inhibitors. If the CYP3A4 inhibitor/inducers or CYP2D6 inhibitor is withdrawn, the brexpiprazole dose may need to be returned to the dose used before the initiation of the concomitant therapy (see section 4.5). In case of adverse reactions despite dose adjustments of RXULTI, the necessity of concomitant use of RXULTI and CYP2D6 or CYP3A4 inhibitor should be reassessed.

Table 1: Dose adjustments of RXULTI in patients who are CYP2D6 poor metabolisers and for concomitant use with CYP inhibitors

Factors	**Adjusted dose**
CYP2D6 poor metabolisers	
Known CYP2D6 poor metabolisers	Administer half of the recommended dose
Known CYP2D6 poor metabolisers taking strong/moderate CYP3A4 inhibitors	Administer a quarter of the recommended dose
Patients taking CYP2D6 inhibitors and/or CYP3A4 inhibitors	
Strong CYP2D6 inhibitors	Administer half of the recommended dose
Strong CYP3A4 inhibitors	Administer half of the recommended dose
Strong/moderate CYP2D6 inhibitors with strong/moderate CYP3A4 inhibitors	Administer a quarter of the recommended dose

Patients taking strong CYP3A4 inducers
If brexpiprazole is used concomitantly with strong CYP3A4 inducers (e.g., rifampicin), in a patient stabilised on brexpiprazole it is necessary to titrate the daily dose of brexpiprazole stepwise up to

double the recommended dose over the course of 1 to 2 weeks. Thereafter, if according to the clinical response, further dose adjustments are required, the dose may be increased up to a maximum of three times the recommended daily dose. Daily dose must not exceed 12 mg when brexpiprazole is used concomitantly with strong CYP3A4 inducers. Twice daily divided dosing of brexpiprazole is preferable, as once daily dosing results in high peak to trough fluctuation (see section 4.5). 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.

Paediatric population
The safety and efficacy of brexpiprazole in children and adolescents aged less than 13 years have not been established. No data are available.

Method of administration

Oral use.
The film-coated tablets can be taken with or without food.

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

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

Suicidal ideation and behaviour
The occurrence of suicidal behaviour is inherent in psychotic illnesses and mood disorders and in some cases has been reported early after initiation or switch of antipsychotic treatment, including treatment with brexpiprazole (see section 4.8). Close supervision of high-risk patients should accompany antipsychotic treatment.

Cardiovascular disorders
Brexpiprazole has not been evaluated in patients with a history of myocardial infarction/ischaemic heart disease or clinically significant cardiovascular disease since such patients were excluded from clinical trials.

Brexpiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischaemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medicinal products) or hypertension (including accelerated or malignant).

QT prolongation
QT prolongation can develop in patients treated with antipsychotics. In clinical trials, only a few, non-serious QT prolongations have been reported with brexpiprazole. Caution should be exercised when brexpiprazole is prescribed to patients with known cardiovascular disease, family history of QT prolongation, electrolyte imbalance or in case of concomitant use with other medicinal products thought to prolong the QT interval (see sections 4.8 and 5.1).

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 brexpiprazole, and preventive measures should be undertaken.

Orthostatic hypotension and syncope
Adverse reactions related to orthostatic hypotension can include dizziness, light-headedness and tachycardia. Generally, these risks are greatest at the beginning of treatment with antipsychotics and during dose escalation. Patients at increased risk of these adverse reactions (e.g., elderly) or at increased risk of developing complications from hypotension include those with dehydration, hypovolemia, treatment with antihypertensive medicinal products, history of cardiovascular disease (e.g., heart failure, myocardial infarction, ischemia, or conduction abnormalities), history of cerebrovascular disease, as well as patients who are antipsychotic-naïve. In such patients, a lower starting dose and slower titration should be considered, and orthostatic vital signs should be monitored (see section 4.2).

Neuroleptic Malignant Syndrome (NMS)
A potentially fatal symptom complex referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic treatment, including brexpiprazole (see section 4.8). 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 increased 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, brexpiprazole must be discontinued immediately.

Extrapyramidal symptoms (EPS)
Extrapyramidal symptoms (including acute dystonia) are known class effects for antipsychotics. Brexpiprazole should be used with caution in patients with a known history of EPS.

Tardive dyskinesia
A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotics. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. If signs and symptoms of tardive dyskinesia appear in a patient on brexpiprazole, dose reduction or discontinuation should be considered. These symptoms can temporally deteriorate or can even arise after discontinuation of treatment.

Cerebrovascular adverse reactions
In placebo-controlled trials with some antipsychotics in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks), including fatalities, compared to placebo-treated subjects.

Elderly patients with dementia-related psychosis
Brexpiprazole has not been studied in elderly patients with dementia and is not recommended for the treatment of elderly patients with dementia due to increased risk of overall mortality.

Hyperglycaemia and diabetes mellitus
Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Risk factors that may predispose patients to severe complications include obesity and family history of diabetes.
Patients treated with any antipsychotics, including brexpiprazole, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness). Fasting plasma glucose should be assessed before or soon after the initiation of the antipsychotic treatment. During long term treatment the plasma glucose levels should be monitored regularly for worsening of glucose control.

Weight gain and dyslipidaemia
Antipsychotics including brexpiprazole have been associated with metabolic changes, including weight gain and dyslipidaemia. An increased frequency of weight gain has been observed with increased duration of brexpiprazole treatment (see section 4.8). At the beginning of treatment, the lipid

profile should be assessed. Clinical monitoring of weight and lipid profile is recommended at baseline and during treatment.

Seizures
As with other antipsychotics, brexpiprazole should be used with caution in patients who have a history of seizure disorder or other conditions that potentially lower the seizure threshold. Seizures have been reported during use of brexpiprazole (see section 4.8).

Body temperature regulation
Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotics. Appropriate care is advised when prescribing brexpiprazole for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medicinal products with anticholinergic activity, or being subject to dehydration.

Dysphagia
Oesophageal dysmotility and aspiration have been associated with antipsychotic use. Brexpiprazole should be used cautiously in patients at risk for aspiration pneumonia.

Impulse-control disorders
Impulse-control disorders including gambling disorder have been reported in patients treated with brexpiprazole. Patients can experience increased urges, particularly for gambling, and the inability to control these urges while taking brexpiprazole. Other reported urges include compulsive sexual behaviours, compulsive shopping, binge eating, and other impulsive and compulsive behaviours. Patients with a prior history of impulse-control disorders may be at increased risk and should be monitored carefully. Because patients may not recognise these behaviours as abnormal, it is important for prescribers to ask patients or their caregivers specifically about the development of new or increased impulse-control disorders or other compulsive behaviours while being treated with brexpiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder; however, in some cases, urges were reported to have stopped when the dose was reduced, or the medicinal product was discontinued. Compulsive behaviours may result in harm to the patient and others if not recognised. Consider dose reduction or stopping the medicinal product if a patient develops such urges while taking brexpiprazole (see section 4.8).

Leukopenia, neutropenia and agranulocytosis
Leukopenia, neutropenia and agranulocytosis (including fatal cases) have been reported during treatment with antipsychotics. Possible risk factors for leukopenia/neutropenia include pre-existing 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 brexpiprazole should be discontinued at the first sign of decline in WBC, in the absence of other causative factors. Patients with 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 < 1 000/mm^3) should discontinue brexpiprazole and have their WBC followed until recovery.

Prolactin
Brexpiprazole can elevate prolactin levels. Elevations associated with brexpiprazole treatment are generally mild and may decline during administration, however, in some infrequent cases the effect may persist during administration (see section 4.8).

Lactose
RXULTI film-coated tablets contain 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

Brexpiprazole is predominantly metabolised by CYP3A4 and CYP2D6.

Potential for other medicinal products to affect brexpiprazole

CYP3A4 inhibitors
Co-administration of ketoconazole (200 mg twice daily for 7 days), a potent inhibitor of CYP3A4, with a 2 mg single oral dose of brexpiprazole increased the AUC of brexpiprazole by 97 % and did not change the C_{max}. Based on results of interaction studies, dose adjustment of brexpiprazole to half the dose is recommended when administered concomitantly with strong CYP3A4 inhibitors (itraconazole, ketoconazole, ritonavir, and clarithromycin).

CYP3A4 inducers
Co-administration of rifampicin (600 mg twice daily for 12 days), a potent CYP3A4 inducer, with a single 4 mg oral dose of brexpiprazole resulted in an approximate 31 % and 73 % decrease in brexpiprazole C_{max} and AUC, respectively. If brexpiprazole is used concomitantly with strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, rifampicin, St. John's Wort), the total daily dose requirement of brexpiprazole is increased by approximately a factor of three times the recommended daily dose. Once daily dosing of brexpiprazole in case of co-administration with CYP3A4 inducers results in high peak to trough fluctuation (see section 4.2).

CYP2D6 inhibitors
Co-administration of a 2 mg single oral dose of brexpiprazole with quinidine (324 mg/day for 7 days), a potent inhibitor of CYP2D6, increased the AUC of brexpiprazole by 94 % and did not change the C_{max}. Based on results of interaction studies, dose adjustment of brexpiprazole to half the dose is recommended when administered concomitantly with strong CYP2D6 inhibitors (quinidine, paroxetine, and fluoxetine).

Based on estimations from the population pharmacokinetic analysis, CYP2D6 extensive metabolisers receiving both CYP3A4 and CYP2D6 inhibitors or CYP2D6 poor metabolisers receiving strong CYP3A4 inhibitors are expected to have approximately 4-fold to 5-fold increase in brexpiprazole concentrations and dose adjustment to a quarter of the dose is recommended for these subjects (see section 4.2).

Potential for brexpiprazole to affect other medicinal products

Based on results of *in vitro* studies, brexpiprazole is unlikely to cause clinically important pharmacokinetic interactions with medicinal products metabolised by cytochrome P450 enzymes. Brexpiprazole does not affect absorption of medicinal products that are substrates of Breast Cancer Resistance Protein transporter (BCRP) and P-glycoprotein (P-gp) transporter.

If brexpiprazole is administered concomitantly with medicinal products known to cause QT prolongation (e.g. moxifloxacin) or electrolyte imbalance (e.g. diuretics such as furosemide, bendroflumethiazide), caution should be used.

If brexpiprazole is administered concomitantly with medicinal products known to increase creatine phosphokinase (CPK), e.g. statins like simvastatin, the possible additive effect with CPK increase induced by brexpiprazole should be considered.

Pharmacodynamic interactions
No information on pharmacodynamic interactions of brexpiprazole is available at present. Caution should be exercised when prescribing other medicinal products concomitantly. Given the primary Central Nervous System (CNS) effects of brexpiprazole, caution should be used when brexpiprazole is taken in combination with alcohol or other CNS medicinal products with overlapping adverse reactions such as opiates like codeine or morphine (see section 4.8).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of brexpiprazole in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Brexpiprazole is not recommended during pregnancy and in women of childbearing potential not using contraception.

Neonates exposed to antipsychotics, including brexpiprazole, 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 and feeding disorder. Consequently, new-borns should be monitored carefully.

Breast-feeding

It is unknown whether brexpiprazole/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of brexpiprazole/ metabolites in milk of rats (see section 5.3). A risk to the new-borns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from brexpiprazole therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

The effect of brexpiprazole on human fertility has not been evaluated. Studies in animals have shown decreased female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Brexpiprazole has minor to moderate influence on the ability to drive and use machines due to potential nervous system effects, such as sedation and dizziness that are common adverse drug reactions (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most frequently observed adverse drug reactions (ADRs) in adults were akathisia (5.6 %) and weight gain (3.9 %) and in adolescents they were nausea (6.4%), somnolence (4.5%) and akathisia (3.6%).

Tabulated list of adverse reactions

The incidences of the ADRs associated with brexpiprazole therapy are tabulated below. The table is based on adverse reactions reported in short-term placebo-controlled phase 2 and 3 adult clinical trials with relevant therapeutic doses (2 mg to 4 mg) and short-term placebo-controlled phase 3 paediatric clinical trials with relevant therapeutic doses (1 mg to 4 mg).

All ADRs are listed by system organ class (SOC) 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) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

SOC	Very common	Common	Uncommon	Not known
Immune system disorders		Rash	Angioedema Urticaria Swelling face	
Metabolism and nutrition disorders		Weight increase		
Psychiatric disorders			Suicide attempt Suicidal ideation	Gambling disorder Impulsive behaviour Binge eating Compulsive shopping Compulsive sexual behaviour
Nervous system disorders		Akathisia Dizziness Tremor Somnolence[1]	Parkinsonism	Seizures Neuroleptic malignant syndrome (NMS)
Cardiac disorders				Electrocardiogram QT prolonged
Vascular disorders			Venous thromboembolism (including pulmonary embolism and deep vein thrombosis) Orthostatic hypotension	
Respiratory, thoracic and mediastinal disorders			Cough	
Gastrointestinal disorders		Diarrhoea Nausea Abdominal pain upper	Dental caries Flatulence	
Musculoskeletal and connective tissue disorders		Back pain Pain in extremity	Myalgia	Rhabdomyolysis
Pregnancy, puerperium and perinatal conditions				Drug withdrawal syndrome neonatal (see section 4.6)

SOC	Very common	Common	Uncommon	Not known
Investigations	Blood prolactin increased[2]	Blood creatine phosphokinase increased	Blood pressure increased Blood triglycerides increased Hepatic enzymes increased	

[1] Includes also sedation and hypersomnia

[2]The categorisation of blood prolactin increased is based on Potentially Clinically Relevant (PCR) criteria of > 1 × upper limit of normal (ULN).

Description of selected adverse reactions

Adults

Extrapyramidal Symptoms (EPS)

Akathisia was the most frequently reported EPS related ADR in the brexpiprazole 2 mg/day to 4 mg/day group (5.6 %) compared to 4.5 % in placebo, followed by tremor (2.7 %) compared to 1.2 % in placebo. The incidences of other EPS-related ADRs reported in short-term, controlled trials are dyskinesia (0.4 %), extrapyramidal disorder (1.8 %) and Parkinsonism (0.4 %). See section 4.4.

Akathisia

From fixed-dose trials there appears to be a dose-response relationship for akathisia in patients treated with brexpiprazole, with an increasing frequency with higher doses. The incidence of akathisia in the brexpiprazole 1 mg/day, 2 mg/day, and 4 mg/day groups was 3.0 %, 4.6 %, and 6.5 %, respectively, compared with 5.2 % of subjects in the placebo group.

The incidence of akathisia in the short-term, controlled trials (5.4 %) was similar to the incidence in the long-term, open-label trials (5.7 %).

Suicidal behaviour

In short-term, controlled trials, Treatment Emergent Adverse Events (TEAEs) related to suicidal behaviour were reported for 8 subjects (0.5 %, 2 serious events, 1 leading to discontinuation) in the brexpiprazole treatment group and 3 subjects (0.4 %, none-serious) in the placebo group. In long-term, open-label trials, TEAEs related to suicidal behaviour were reported for 23 subjects (1.6 %). Overall, in the brexpiprazole clinical development program for schizophrenia, one death due to suicide occurred but was not considered drug related by the investigator. Spontaneous cases reporting completed suicide and suicide attempt have been reported in the post-marketing setting. See section 4.4.

QT prolongation

In the short-term controlled trials with brexpiprazole, 3 TEAEs related to QT prolongation were reported in the 2 mg to 4 mg group (0.3 %), compared with 3 TEAEs (0.5 %) reported in subjects receiving placebo. The incidence of TEAEs in long-term trials was similar to that of the short-term trials.

The effects of brexpiprazole at therapeutic (4 mg) and supra-therapeutic (12 mg) doses on QT interval were evaluated in subjects with schizophrenia or schizoaffective disorder in a randomised, double-blind, placebo- and positive-controlled (moxifloxacin), parallel-arm trial. Subgroup analyses from this trial suggested that the QTc prolongation was larger in female subjects than in males (see sections 4.4, 4.5 and 5.1).

Weight gain

In short-term, controlled trials, the percentage of subjects with clinically significant weight gain (increase of ≥ 7 % from baseline in body weight) was 9.1 % in the brexpiprazole 2 mg/day to 4 mg/day group, compared with 3.8 % in the placebo group.

In the long-term, open-label trial, the percentage of subjects with clinically significant weight gain (increase of ≥ 7 % in body weight) at any visit was 20.7 % and 0.4 % of the subjects discontinued due

to weight gain. In subjects who had a weight gain ≥ 7 % from baseline, weight increased over time, with mean weight gain up to 10.2 kg at week 52. The mean change in body weight overall for the brexpiprazole group in the long term, open label trial was 2.1 kg at week 52. See section 4.4.

Prolactin
The incidence of blood prolactin increased was 0.9 % in the 2 mg to 4 mg brexpiprazole group compared to 0.5 % in the placebo group in short-term, controlled trials. Higher frequencies of prolactin increased (1.5 % *versus* 0.60 %) were observed in females compared to males in short-term trials. In addition, the frequencies of prolactin elevations > 1 × ULN in the 2 mg to 4 mg brexpiprazole group was 13.7 % in females *versus* 6.4 % in the placebo group and 11.1 % in males *versus* 10.3 % in the placebo group. See section 4.4.

Neuroleptic malignant syndrome
A potentially fatal symptom complex referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with brexpiprazole (see section 4.4).

Nausea
For nausea, the incidence in the 2 mg to 4 mg brexpiprazole group was 2.3 % overall in short-term controlled trials, compared to 2.0 % in the placebo group. For vomiting, these incidences were 1.0 % in the brexpiprazole-treated group compared to 1.2 % in the placebo group.

In terms of gender differences, there were higher observed frequencies of nausea (4.8 % *versus* 2.8 %) and vomiting (4.6 % *versus* 1.4 %) in females compared to males among brexpiprazole-treated subjects in short-term trials. Concerning subjects receiving placebo, the frequency for nausea was 2.8 % for males *versus* 3.2 % for females, whereas the frequency for vomiting was 3.0 % for males *versus* 2.6 % for females (see section 5.2).

Paediatric population

Adolescents aged 13 years and older with schizophrenia
Frequency, type and severity of adverse reactions in adolescents are expected to be similar as in adults.

Extrapyramidal Symptoms (EPS)
In short-term trials, akathisia was the most frequently reported EPS related ADR in the brexpiprazole 1 mg/day to 4 mg/day group (3.6 %) compared to 2.9 % in placebo. The incidences of other EPS-related ADRs reported in short-term, controlled trials in paediatric patients were muscle rigidity (0.9 %), hypokinesia (0.9 %) and tremor (0.9 %).

Akathisia
The incidence of akathisia in the brexpiprazole-treated paediatric subjects in a short-term, randomized, double-blind trial was 3.6 % versus 2.9 % for placebo-treated subjects.
The incidence of akathisia in the ongoing-long-term, open label trial was 5.1 %. See section 4.4.

Suicidal behaviour
In a short-term, controlled trial, a TEAE of suicidal behaviour was reported in 1 subject (0.9 %, non-serious event) in the brexpiprazole treatment group and none in the placebo group. In a long-term, open-label trial, TEAEs of suicidal behaviour were reported in 8 subjects (2.7 %). See section 4.4.

QT prolongation
No TEAEs related to QT prolongation have been reported in the adolescent schizophrenia trials. The safety profile observed in the adolescent population is considered to be similar to that observed in the adult population (see section 4.4).

Weight gain
In a short-term, controlled trial the percentage of subjects with clinically significant weight gain (increase of ≥ 7 % from baseline in body weight) was 8.2 % in brexpiprazole treated group, compared with 4.9 % in placebo group The mean increase in weight from baseline to last visit was 0.8 kg in

brexpiprazole and 0.0 kg in placebo-treated subjects. To adjust for normal growth, z-scores were derived (measured in standard deviations [SD]), which normalize for natural growth of children and adolescents by comparisons to age- and gender- matched population standards. A z-score change <0.5 SD is considered not clinically significant. In this study, no change in mean z-score from baseline to last visit was observed in brexpiprazole and placebo-treated groups. 4.5 % of subjects in brexpiprazole and 3.9 % subjects in placebo had an increase in age-and-gender-adjusted body weight z-score of at least 0.5 SD from baseline. TEAEs of weight gain was reported in 1.7% of all patients in the brexpiprazole group compared to 3.4% in placebo group. See section 4.4.

In the long-term, open-label trial, the percentage of subjects with clinically significant weight gain (increase of ≥ 7 % from baseline in body weight) at any visit was 44.6% in brexpiprazole treated group. Mean change in z-score from baseline to last visit was 0.10 SD for body weight, while 20% of patients had an increase in age-and gender-adjusted body weight z-score of at least 0.5 SD from baseline. TEAEs related to weight increased were observed in 11.5 % of subjects, while other TEAEs related to weight increase, such as increased BMI and waist circumference, were each reported in one subject.

Prolactin
In the short-term trial, no treatment emergent adverse events associated with elevated prolactin were reported. The frequencies of prolactin elevations > 1 × ULN in the 2 mg to 4 mg brexpiprazole group was 26.8 % in females *versus* 6.3 % in the placebo group and 24.5 % in males *versus* 6 % in the placebo group. In the long-term trials, 1.7% of the subjects reported TEAEs of blood prolactin increased and 0.7% subjects reported TEAEs of hyperprolactinaemia. See section 4.4.

Neuroleptic malignant syndrome
No TEAEs related to NMS have been reported in the adolescent schizophrenia trials. The safety profile observed in the adolescent population is considered to be similar to that observed in the adult population (see section 4.4).

Nausea
TEAEs of Nausea have been reported in the adolescent schizophrenia trials. The safety profile observed in the adolescent population is considered to be similar to that observed in the adult population.

Somnolence including sedation and hypersomnia
In short-term trials, the incidence of somnolence-related TEAEs (sedation, somnolence, hypersomnia) was 7.3% in the brexpiprazole 2-4 mg group compared to 6.7% in the placebo group. In a long-term, open-label trial, the incidence of somnolence-related TEAEs (sedation, somnolence, hypersomnia) was 11.9%. These TEAEs were mild to moderate in severity.

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

Gastric lavage and treatment with an emetic may be useful immediately after overdose. An electrocardiogram should be obtained in case of overdose and if QT interval prolongation is present, cardiac monitoring should be instituted.

Otherwise, management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers.

Oral activated charcoal and sorbitol (50 g/240 mL), administered one hour after ingesting 2 mg oral dose of brexpiprazole, decreased brexpiprazole C_{max} and AUC by approximately 5 % to 23 % and 31 % to 39 % respectively. However, there is insufficient information available on the therapeutic potential of activated charcoal in treating an overdose with brexpiprazole.

Although there is no information on the effect of haemodialysis in treating an overdose with brexpiprazole, haemodialysis is unlikely to be useful in overdose management since brexpiprazole is highly bound to plasma proteins.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, other antipsychotics, ATC code N05AX16

Mechanism of action

Brexpiprazole is an atypical antipsychotic agent. The pharmacology of brexpiprazole is believed to be mediated by a modulatory activity at the serotonin and dopamine systems that combines partial agonist activity at serotonergic 5-HT_{1A} and at dopaminergic D_2 receptors with antagonist activity at serotonergic 5-HT_{2A} receptors, with similar high affinities at all of these receptors (Ki: 0.1 nM to 0.5 nM). Brexpiprazole also shows antagonist activity at noradrenergic $\alpha_{1B/2C}$ receptors with affinity in the same sub-nanomolar Ki range (Ki: 0.2 nM to 0.6 nM).

Pharmacodynamic effects

Influences of genetic variation on the pharmacodynamic responses to brexpiprazole have not been investigated.

Effects on QT
The effects of brexpiprazole on the QT interval were evaluated in patients with schizophrenia or schizoaffective disorder. In the overall analysis, brexpiprazole did not prolong the QT_c interval to a clinically relevant extent following therapeutic and supra-therapeutic doses (4 mg/day; n = 62 or 12 mg/day; n = 53) and no correlation has been observed between brexpiprazole concentrations and QT_c prolongation.

Subgroup analyses from the thorough QT_c trial suggested that the QT_c prolongation was larger in female subjects than in males. In the brexpiprazole 4 mg/day group, the maximum placebo-adjusted mean change from baseline in the QT_{cI} interval was 5.2 ms (90 % CI: 1.5, 8.9) in males (n = 48) and 15.0 ms (90 % CI: 7.7., 22.3) in females (n = 14) at 6 hours post-dosing. In the brexpiprazole 12 mg/day group, the maximum placebo-adjusted mean change from baseline in the QT_{cI} interval was 2.9 ms (90 % CI: −1.2, 6.9) in males (n = 40) at 12 hours post-dosing and 10.4 ms (90 % CI: 2.7, 18.2) in females (n = 13) at 24 hours post-dosing. The smaller number of female than male subjects enrolled in the study does not allow to draw definitive conclusions.

Clinical efficacy

Adults:
The efficacy and safety of brexpiprazole in the treatment of adults with schizophrenia was studied in two multi-national and one regional (Japan), 6-week, randomised, double-blind, placebo-controlled, fixed-dose clinical trials (trials 1 to 3), a multi-national, 6-week, randomised, double-blind, placebo-controlled, active reference (quetiapine), flexible-dose clinical trial (trial 4), and, one multi-national, placebo-controlled, 52-week maintenance trial (trial 5). The trials included 2 690 patients with the age of 18 years to 65 years.

In trials 1, 2 and 3, brexpiprazole was titrated as described in section 4.2 with 1 mg for 4 days, followed by 2 mg on days 5 to 7. On day 8, the dose was increased to 4 mg for some of the treatment arms.

Short-term trials
In the three fixed-dose, short-term trials (trials 1, 2 and 3), subjects were randomised to brexpiprazole 2 mg once daily, 4 mg once daily or placebo.

Trial 4 assessed the efficacy, safety, and tolerability of brexpiprazole in a flexible dose range of 2 mg/day to 4 mg/day and 400 mg to 800 mg quetiapine extended release (XR) for assay sensitivity. 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 multi-item inventory composed of five factors to evaluate positive symptoms, negative symptoms, disorganised thoughts, uncontrolled hostility/excitement, and anxiety/depression.

The key secondary endpoint in trials 1, 2 and 4 was the Clinical Global Impression of Severity (CGI-S) of schizophrenia, a 7-point clinician's assessment of the severity of disease. The CGI-S was also assessed in trials 3 and 5 as secondary endpoint.

The effects of brexpiprazole were also evaluated across a number of pre-specified secondary endpoints: the specific aspects of symptoms of schizophrenia (PANSS Positive Subscale score, PANSS Negative Subscale score, PANSS Excited Component [PEC] score, PANSS Marder factors positive, negative, disorganised thoughts, uncontrolled hostility/excitement and anxiety/depression), and analyses of response (defined as 30 % improvement in PANSS total score compared to baseline or a CGI-I score of 1 [very much improved] or 2 [much improved]).

Efficacy was demonstrated in trial 1 for both brexpiprazole 2 mg/day and 4 mg/day and replicated in trial 2 only for brexpiprazole 4 mg/day and in trial 3 only for brexpiprazole 2 mg/day.

In the flexible-dose trial 4, at week 6, subjects in the brexpiprazole treatment group had numerically greater improvements on PANSS total score than the subjects in the placebo group, although, the difference at week 6 did not reach statistical significance for the primary efficacy analysis (p = 0.0560; see table 2). In the same trial, the active reference, quetiapine XR added for assay sensitivity only, separated from placebo.

Table 2: Primary efficacy results for 6-week trials in schizophrenia

Trial	Treatment group	n	Primary efficacy measure: PANSS			
			Mean baseline score (SD)	LS mean change from baseline (SE)	LS mean difference[a, b] (95 % CI)	p-value
1	Brexpiprazole (2 mg/day)*	180	95.85 (13.75)	−20.73 (1.55)	−8.72 (−13.1, −4.37)	< 0.0001
	Brexpiprazole (4 mg/day)*	178	94.70 (12.06)	−19.65 (1.54)	−7.64 (−12.0, −3.30)	0.0006
	Placebo	178	95.69 (11.46)	−12.01 (1.60)	--	--
2	Brexpiprazole (2 mg/day)	179	96.30 (12.91)	−16.61 (1.49)	−3.08 (−7.23, 1.07)	0.1448
	Brexpiprazole (4 mg/day)*	181	94.99 (12.38)	−20.00 (1.48)	−6.47 (−10.6, −2.35)	0.0022
	Placebo	180	94.63 (12.84)	−13.53 (1.52)	--	--
3	Brexpiprazole (2 mg/day)*	113	96.55 (19.20)	−14.95 (2.00)	−7.32 (−13.04, −1.59)	0.0124
	Brexpiprazole (4 mg/day)	109	96.39 (15.73)	−11.49 (2.10)	−3.86 (−9.71, 2.00)	0.1959

Trial	Treatment group	n	Primary efficacy measure: PANSS			
			Mean baseline score (SD)	LS mean change from baseline (SE)	LS mean difference[a, b] (95 % CI)	p-value
	Placebo	113	97.19 (19.27)	−7.63 (2.11)	--	--
4	Brexpiprazole (2 mg/day to 4 mg/day)	150	97.82 (10.25)	−19.99 (1.51)	−4.1 (−8.2, 0.1)	0.0560
	Placebo	159	98.38 (10.30)	−15.93 (1.49)	--	--

SD Standard deviation
SE Standard error
LS Mean Least-squares mean.
CI Confidence interval
* Treatment statistically significantly superior to placebo
a Difference (brexpiprazole minus placebo) in least-squares mean change from baseline, at week 6
b The LS Mean, 95 % CI, and p-values for individual trials were derived from an MMRM (Mixed effect Model Repeat Measurement) analysis as follows: fixed effects of site, treatment, visit, and treatment-by-visit interaction, with baseline and baseline-by-visit interaction as covariates. Unstructured variance-covariance matrix structure was used.

The primary statistical analysis was performed using an MMRM model with MAR (Missing At Random) imputation. Results of a sensitivity analysis using placebo based multiple imputation (PMI) were consistent with the primary analysis.

Results for the (key) secondary outcome parameter and additional endpoints were supportive of the primary endpoint.

In trial 1, statistically significant greater improvement on the CGI-S, the key secondary efficacy measure, at week 6 was also shown for the 2 mg/day and 4 mg/day compared to the placebo dose groups. Due to the testing hierarchy the greater improvement shown for both 2 mg/day and 4 mg/day on the CGI-S can only be considered supportive for trials 2, 3 and 4 (see table 3).

Table 3: Key secondary efficacy results for 6-week trials in schizophrenia

Trial	Treatment group	n	Key secondary efficacy measure: CGI-S			
			Mean baseline score (SD)	LS mean change from baseline (SE)	LS mean difference[a] (95 % CI)	p-value
1	Brexpiprazole (2 mg/day)*	181	4.90 (0.64)	−1.15 (0.08)	−0.33 (−0.56, −0.10)	0.0056
	Brexpiprazole (4 mg/day)*	178	4.81 (0.64)	−1.20 (0.08)	−0.38 (−0.61, −0.15)	0.0012
	Placebo	181	4.84 (0.66)	−0.82 (0.09)	--	--
2	Brexpiprazole (2 mg/day)	180	4.96 (0.65)	−0.99 (0.09)	−0.19 (−0.42, 0.05)	0.1269
	Brexpiprazole (4 mg/day)*	183	4.85 (0.64)	−1.19 (0.08)	−0.38 (−0.62, −0.15)	0.0015
	Placebo	181	4.87 (0.61)	−0.81 (0.09)	--	--
3	Brexpiprazole (2 mg/day)*	113	4.80 (0.78)	−0.84 (0.11)	−0.35 (−0.67, −0.03)	0.0308
	Brexpiprazole (4 mg/day)	109	4.71 (0.75)	−0.64 (0.12)	−0.16 (−0.48, 0.17)	0.3461

Trial	Treatment group	n	Key secondary efficacy measure: CGI-S			
			Mean baseline score (SD)	LS mean change from baseline (SE)	LS mean difference[a] (95 % CI)	p-value
	Placebo	113	4.73 (0.71)	−0.48 (0.12)	--	--
4	Brexpiprazole* (2 mg/day to 4 mg/day)[b]	150	4.96 (0.59)	−1.21 (0.08)	−0.27 (−0.49, −0.06)	0.0142
	Placebo	159	4.94 (0.57)	−0.93 (0.08)	--	--

SD Standard deviation
SE Standard error
LS Mean Least-squares mean
CI Confidence interval
* Treatment statistically significantly superior to placebo
a Difference (brexpiprazole minus placebo) in least-squares mean change from baseline, at week 6
b Mean dose 3.5 mg/day

Maintenance of efficacy trial
In trial 5, a long-term trial designed to assess the maintenance of effect of brexpiprazole by assessing the delay in time to impending relapse of schizophrenia, patients with schizophrenia, who responded to treatment with brexpiprazole 1 mg/day to 4 mg/day, were stabilised over 12 weeks to 36 weeks, and then randomised in a double-blind manner to either continue treatment with the stabilisation dose of brexpiprazole (n = 96) or to receive placebo (n = 104) for 52 weeks or until relapse occurred.

In the primary analysis of time to impending relapse patients on brexpiprazole showed a significantly longer time to relapse compared with patients on placebo ($p < 0.0001$). At week 52 brexpiprazole (13.5 %) reduced the risk of impending relapse by 71 % compared with placebo (38.5 %). During the stabilisation, brexpiprazole improved clinical symptomology (as assessed by PANSS, CGI-S and CGI-I, [Analysis of Covariance - ANCOVA Last Observation Carried Forward - LOCF]) and functioning (as assessed by Global Assessment of Functioning (GAF) [ANCOVA LOCF]). These improvements were maintained during the 52-week double-blind maintenance phase in patients on brexpiprazole whereas patients randomised to placebo showed deterioration in PANSS, CGI-S and CGI-I, and GAF scores [ANCOVA LOCF]). Brexpiprazole maintained symptom control and functioning compared to placebo.

Paediatric population
The efficacy and safety of brexpiprazole in the treatment of paediatric patients with schizophrenia was studied in one 6-week, randomised, double-blind and placebo- controlled trial (trial 6) and an on-going long-term, 24-month open-label trial. The short-term trial included 110 patients randomized to

brexpiprazole, 101 patients to aripiprazole for assay sensitivity and 104 patients to placebo with a mean age of 15 years.
In the short-term trial (trial 6), patients received either brexpiprazole 2 to 4 mg/day, aripiprazole 10 to 20 mg/day or placebo.

The primary efficacy endpoint was defined as the mean change from baseline to week 6 in Positive and Negative Syndrome Scale (PANSS) total scores.

Brexpiprazole 2 to 4 mg/day and aripiprazole showed statistically significant improvements compared to placebo in the mean change from baseline in the PANSS Total Score.

Interim analyses from long-term trial with flexible doses of brexpiprazole 1 to 4 mg/day showed maintained improvement in symptoms from baseline through month 24 in PANSS Total Score.

Table 4: Primary efficacy results for 6-week trial in schizophrenia in Paediatric Patients

Trial	Treatment group	n	Primary efficacy measure: PANSS			
			Mean baseline score (SD)	LS mean change from baseline (SE)	LS mean difference[a] (95 % CI)	p-value
6	Brexpiprazole (2 mg/day to 4 mg/day)*	110	101.06 (14.87)	-22.75 (1.49)	-5.33 (-9.55, -1.10)	0.0136
	Aripiprazole (10 mg/day to 20 mg/day)	101	101.03 (13.08)	-23.95 (1.57)	-6.53 (-10.8, -2.21)	0.0032
	Placebo	103[b]	102.17 (16.30)	-17.42 (1.58)	--	--

SD Standard deviation
SE Standard error
LS Mean Least-squares mean
CI Confidence interval
* Treatment statistically significantly superior to placebo
a Difference (brexpiprazole minus placebo) in least-squares mean change from baseline, at week 6
b Efficacy sample includes treated subjects who have baseline and at least 1 post-baseline efficacy evaluation for the PANSS Total Score

Furthermore, a pharmacokinetic/pharmacodynamic analysis has been considered supportive for the comparison of clinical efficacy data between adolescents and adults with schizophrenia.

5.2 Pharmacokinetic properties

Absorption

Brexpiprazole is absorbed after administration of the tablet, with peak plasma concentrations occurring within 4.0 hours after single dose administrations; the absolute oral bioavailability of the tablet formulation is 95.1 %. Brexpiprazole steady-state concentrations are attained within 10 days to 12 days of dosing. Administration of a 4 mg brexpiprazole tablet with a standard high fat meal did not significantly affect the C_{max} or AUC of brexpiprazole. After single and multiple once daily dose administration, brexpiprazole exposure (C_{max} and AUC) increase in proportion to the dose administered. Based on *in vivo* studies, brexpiprazole is neither a substrate nor an inhibitor of efflux transporters, such as Multi Drug Resistance (MDR) 1 (P-gp) and BCRP.

Distribution

The volume of distribution of brexpiprazole following intravenous administration is high (1.56 L/kg ± 0.418 L/kg), indicating extravascular distribution. Brexpiprazole is highly protein bound in plasma (greater than 99 %) to serum albumin and α1-acid glycoprotein, and its protein binding is not affected by renal or hepatic impairment. Based on results of *in vitro* studies brexpiprazole protein binding is not affected by warfarin, diazepam, and digitoxin.

Biotransformation

Based on *in-vitro* metabolism studies using recombinant human cytochrome P450, the metabolism of brexpiprazole was shown to be mainly mediated by CYP3A4 and CYP2D6 leading to formation of oxidative metabolites. Based on *in vitro* data brexpiprazole showed little to no inhibition of other CYP450 isozymes. *In-vivo*, the metabolism of brexpiprazole is mainly mediated by CYP3A4 and CYP2D6 leading to formation of oxidative metabolites with only one metabolite, DM-3411, present in plasma with more than 10 % of plasma exposure.

At steady-state, DM-3411 represents 23.1 % to 47.7 % of brexpiprazole exposure (AUC) in plasma. It should be noted that *in-vivo* preclinical studies have shown that at clinically relevant plasma exposures of brexpiprazole, DM-3411 brain exposures were below the detection limit. Thus, DM-3411 is considered not to contribute to the therapeutic effects of brexpiprazole.

Elimination

Following a single oral dose of [^{14}C]-labelled brexpiprazole, approximately 24.6 % and 46 % of the administered radioactivity was recovered in the urine and faeces, respectively. Less than 1 % of unchanged brexpiprazole was excreted in the urine and approximately 14 % of the oral dose was recovered unchanged in the faeces. Apparent oral clearance of brexpiprazole tablet after once daily administration is 19.8 (± 11.4) mL/h/kg. After multiple once daily administration of brexpiprazole, the terminal elimination half-life of brexpiprazole and its major metabolite, DM-3411, is 91.4 hours and 85.7 hours, respectively.

Linearity/non-linearity

The pharmacokinetic of brexpiprazole is dose proportional and time-invariant after single-dose (0.2 mg to 8 mg) and multiple-dose (0.5 mg to 4 mg) using once-daily administration.

Pharmacokinetics in special populations

Age
After single dose administration of brexpiprazole (2 mg), elderly subjects (older than 65 years) exhibited similar brexpiprazole systemic exposure (C_{max} and AUC) in comparison with the adult subjects (18 years to 45 years old; see sections 4.2 and 4.4).

Gender
Population PK evaluation identified gender as statistically significant covariate. The exposure (AUC) of brexpiprazole in women was estimated to be 25 % higher than in men (see section 4.8).

Race
Although no specific pharmacokinetic study was conducted, population pharmacokinetic evaluation revealed no evidence of clinically significant race-related differences in the pharmacokinetics of brexpiprazole.

CYP2D6 genotype
Population pharmacokinetic evaluation shows that CYP2D6 poor metabolisers have 47 % higher exposure to brexpiprazole compared to extensive metabolisers (see section 4.2).

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

Renal impairment
In subjects (n = 10) with severe renal impairment (CL_{cr} < 30 mL/min), AUC of oral brexpiprazole (3 mg single dose) compared to matched healthy subjects was increased by 68 % while its C_{max} was

not changed. For patients with moderate to severe renal impairment (creatinine clearance CL_{cr} < 60 mL/minute), the maximum recommended dose is reduced to 3 mg once daily (see section 4.2).

Hepatic impairment
In subjects (n = 22) with varying degrees of hepatic impairment (Child-Pugh Classes A, B, and C), the AUC of oral brexpiprazole (2 mg single dose), compared to matched healthy subjects, increased 24 % in mild hepatic impairment, increased 60 % in moderate hepatic impairment, and did not change in severe hepatic impairment. For patients with moderate to severe hepatic impairment (Child-Pugh Classes B and C), the maximum recommended dose is reduced to 3 mg once daily (see section 4.2).

Paediatric population
A multiple dose PK study (0.5, 1, 2, 3 or 4 mg/day) has been conducted in 24 paediatric patients aged 13 years to 17 years old. Population PK analysis indicated systemic exposure (C_{max} and AUC) of brexpiprazole in paediatric patients (13 to 17 years of age) was comparable to that in adult patients across the dose range from 0.5 to 4 mg.

5.3 Preclinical safety data

Effects observed in repeated-dose toxicity studies in rats and monkeys were mainly related to the exaggerated pharmacological activity of brexpiprazole. No safety margins based on $AUC_{0\text{-}24\ h}$ at the Maximum Recommended Human Dose (MRHD) of 4 mg/day could be derived in both female and male rats and monkey.

Cardiovascular toxicity

Following oral administration, brexpiprazole decreased blood pressure and prolonged QT interval in safety pharmacology study in conscious male dog, in repeated-dose toxicity studies in male and female monkeys and in juvenile toxicity study in male and female dogs. The effect of brexpiprazole on blood pressure reduction is attributed to the expected blockade of α1-adrenoceptors in peripheral blood vessels.

Genotoxicity, carcinogenicity

Brexpiprazole did not show any genotoxic potential in both *in vitro* and *in vivo* studies using clinically relevant exposures. Brexpiprazole administered orally did not increase the incidence of tumours in a 2-year carcinogenicity study in both male and female rats and in male mice at exposures up to 4.4-fold and 3.1-fold the MRHD. In female mice, an increased incidence of mammary gland adenocarcinoma and adeno-squamous carcinoma, and pars distalis adenoma of the pituitary gland, was observed at similar or even lower clinically relevant exposures: these prolactin-mediated endocrine tumours were also observed in rodents with other antipsychotics and their clinical relevance is unknown.

Reproductive toxicity

Following oral administration, brexpiprazole did not affect male fertility in rats but prolonged diestrus and decreased fertility in female rats at similar or even lower exposure levels than those clinically achieved at MRHD. Significant increased pre-implantation losses were observed at 4.1-fold the clinical exposure at MRHD. In embryo-foetal developmental toxicity studies, brexpiprazole was not teratogen in orally treated rats up to exposure levels (based on data in non-pregnant rats) clinically achieved at MRHD. In rabbit, vertebral malformations were seen in 3 foetuses from 2 litters at maternally toxic brexpiprazole oral doses corresponding to exposure approximately 16.5-fold the clinical exposure at MRHD.

Delayed growth, physical development and impaired viability of the offspring were observed at maternally toxic brexpiprazole doses in a pre-/post-natal developmental toxicity study in orally administered rats.

Following oral administration in pregnant rats, foetus and milk transfer of brexpiprazole was demonstrated at concentrations that were generally comparable to levels seen in maternal blood.

Environmental risk assessment (ERA)

Brexpiprazole is very persistent and very bio-accumulative but not toxic, to the environment: possible enrichment of brexpiprazole in terrestrial food chains might pose a concern (see section 6.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate
Maize starch
Microcrystalline cellulose
Low-substituted hydroxypropylcellulose
Hydroxypropylcellulose
Magnesium stearate
Purified water

Tablet coat

Hypromellose (E 464)
Talc (E 553b)
Titanium dioxide (E 171)

RXULTI 0.25 mg film-coated tablets
Iron oxide (E 172) (yellow, red, black)

RXULTI 0.5 mg film-coated tablets
Iron oxide (E 172) (yellow, red)

RXULTI 1 mg film-coated tablets
Iron oxide (E 172) (yellow)

RXULTI 2 mg film-coated tablets
Iron oxide (E 172) (yellow, black)

RXULTI 3 mg film-coated tablets
Iron oxide (E 172) (red, black)

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

RXULTI 0.25 mg and 0.5 mg film-coated tablets

28 film-coated tablets in Aluminium/PVC blisters.

RXULTI 1 mg film-coated tablets

10, 28 or 56 film-coated tablets in Aluminium/PVC blisters.

RXULTI 2 mg, 3 mg and 4 mg film-coated tablets

28 or 56 film-coated tablets in Aluminium/PVC blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This medicinal product may pose a risk to the environment (see section 5.3).
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

RXULTI 0.25 mg film-coated tablets

EU/1/18/1294/001 (28 film-coated tablets)

RXULTI 0.5 mg film-coated tablets

EU/1/18/1294/002 (28 film-coated tablets)

RXULTI 1 mg film-coated tablets

EU/1/18/1294/003 (10 film-coated tablets)
EU/1/18/1294/004 (28 film-coated tablets)
EU/1/18/1294/008 (56 film-coated tablets)

RXULTI 2 mg film-coated tablets

EU/1/18/1294/005 (28 film-coated tablets)
EU/1/18/1294/009 (56 film-coated tablets)

RXULTI 3 mg film-coated tablets

EU/1/18/1294/006 (28 film-coated tablets)
EU/1/18/1294/010 (56 film-coated tablets)

RXULTI 4 mg film-coated tablets

EU/1/18/1294/007 (28 film-coated tablets)
EU/1/18/1294/011 (56 film-coated tablets)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 July 2018
Date of latest renewal: 26 May 2023

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(S) 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(S) RESPONSIBLE FOR BATCH RELEASE

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

Elaiapharm
2881 Route des Crêtes
Z.I. les Bouillides
Sophia Antipolis
06560 Valbonne
France

H. Lundbeck A/S
Ottiliavej 9
DK 2500 Valby
Denmark

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

RXULTI 0.25 mg film-coated tablets
brexpiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 0.25 mg brexpiprazole.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 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

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

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1294/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

RXULTI 0.25 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

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

RXULTI 0.25 mg film-coated tablets
brexpiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Otsuka

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

RXULTI 0.5 mg film-coated tablets
brexpiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 0.5 mg brexpiprazole.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 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

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

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1294/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

RXULTI 0.5 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

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

RXULTI 0.5 mg film-coated tablets
brexpiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Otsuka

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

RXULTI 1 mg film-coated tablets
brexpiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 1 mg brexpiprazole.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

10 film-coated tablets
28 film-coated tablets
56 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

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

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1294/003
EU/1/18/1294/004
EU/1/18/1294/008

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

RXULTI 1 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

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

RXULTI 1 mg film-coated tablets
brexpiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Otsuka

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

RXULTI 2 mg film-coated tablets
brexpiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 2 mg brexpiprazole.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 film-coated tablets
56 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

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

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1294/005
EU/1/18/1294/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

RXULTI 2 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

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

RXULTI 2 mg film-coated tablets
brexpiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Otsuka

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

RXULTI 3 mg film-coated tablets
brexpiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 3 mg brexpiprazole.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 film-coated tablets
56 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

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

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1294/006
EU/1/18/1294/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

RXULTI 3 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

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

RXULTI 3 mg film-coated tablets
brexpiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Otsuka

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

RXULTI 4 mg film-coated tablets
brexpiprazole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 4 mg brexpiprazole.

3. LIST OF EXCIPIENTS

Contains lactose.
See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet

28 film-coated tablets
56 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

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

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1294/007
EU/1/18/1294/011

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

RXULTI 4 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

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

RXULTI 4 mg film-coated tablets
brexpiprazole

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Otsuka

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

RXULTI 0.25 mg film-coated tablets
RXULTI 0.5 mg film-coated tablets
RXULTI 1 mg film-coated tablets
RXULTI 2 mg film-coated tablets
RXULTI 3 mg film-coated tablets
RXULTI 4 mg film-coated tablets
brexpiprazole

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 RXULTI is and what it is used for

RXULTI contains the active substance brexpiprazole, which belongs to a group of medicines called antipsychotics.

It is used to treat schizophrenia in adult and adolescent patients aged 13 years and older - a disease with symptoms such as hearing, seeing or sensing things - which are not there, suspiciousness, incoherent speech and behaviour and emotional flatness. People with this condition may also feel depressed, guilty, anxious or tense.

RXULTI can help to keep the symptoms under control and to prevent relapse as you continue treatment.

2. What you need to know before you take RXULTI

Do not take RXULTI
- if you are allergic to brexpiprazole or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Tell your doctor immediately if you
- experience a combination of fever, sweating, faster breathing, muscle stiffness and drowsiness or sleepiness (may be signs of neuroleptic malignant syndrome).
- are having any thoughts or feelings about hurting yourself or to commit suicide. Suicidal thoughts and behaviours are more likely at the beginning of the treatment.

- or your family/carer notices that you are developing urges or cravings to behave in ways that are unusual for you and you cannot resist the impulse, drive or temptation to carry out certain activities that could harm yourself or others. These are called impulse-control disorders and can include behaviours such as addictive gambling, excessive eating or spending, an abnormally high sex drive or preoccupation with an increase in sexual thoughts or feelings. Your doctor may need to adjust or stop your dose.
- have any difficulty in swallowing.
- have or had a low number of white blood cells in your blood and get a fever or any other sign of infection. This may for example be the case if other medicines lowered your white blood cells in the past. Your doctor will regularly measure the white blood cells in your blood to minimise the risk for diseases called leukopenia, neutropenia and agranulocytosis. It is important that you get your blood checked regularly, as this may be fatal. Your doctor will stop the treatment immediately if the white blood cells in your blood are too low.

Talk to your doctor or pharmacist before taking RXULTI, or during treatment if you have
- or had heart problems or a history of stroke, especially if you know that you have other risks factors for stroke.
- dementia (loss of memory and other mental abilities) especially if you are elderly.
- irregular heart beat or if someone else in your family has a history of irregular heart beat (including so called QT prolongation seen with ECG monitoring). Please inform your doctor if you take any other medicines that are known to prolong the QT interval.
- an electrolyte imbalance (problems with the amount of salts in your blood).
- or had low or high blood pressure.
- 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.
- or had dizziness on standing up due to a drop in your blood pressure, which may cause fainting.
- or had problems with your movements called extrapyramidal symptoms (EPS) in the past. These may include jerky movements, spasms, restlessness or slow movements.
- ever experienced or start to experience restlessness and inability to sit still. These symptoms may occur early during treatment. Tell your doctor if this happens.
- diabetes or risk factors for diabetes (e.g., obesity, or someone else in your family has diabetes). Your doctor will need to check your blood sugar regularly since it may be increased by this medicine. Signs of high blood sugar level are excessive thirst, passing of large amounts of urine, increase in appetite and feeling weak.
- a history of seizures (fits) or epilepsy.
- ever inhaled food, stomach acid, or saliva into your lungs causing a disease called aspiration pneumonia.
- increased levels of the hormone prolactin or have a tumour in your pituitary gland.

Weight gain
This medicine may cause significant weight gain, which may affect your health. Your doctor will therefore check your weight and your fats in the blood regularly.

Body temperature
While taking RXULTI you should avoid getting over-heated or dehydrated. Do not over-exercise and drink plenty of water.

Children and adolescents
This medicine must not be taken by children under 13 years of age. The safety and effectiveness in these patients were not evaluated.

Other medicines and RXULTI
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

RXULTI may increase the effect of medicines used to lower the blood pressure. Be sure to tell your doctor if you take a medicine to keep your blood pressure under control.

Receiving RXULTI with some medicines may mean the doctor will need to change your dose of RXULTI or the other medicines. It is especially important to mention the following medicines to your doctor:

- medicines to correct heart rhythm (such as quinidine),
- antidepressants or herbal remedies used to treat depression and anxiety (such as fluoxetine, paroxetine, St. John's Wort),
- antifungal medicines (such as ketoconazole, itraconazole),
- certain medicines to treat HIV infection (such as ritonavir),
- anticonvulsants used to treat epilepsy (such as carbamazepine, phenobarbital),
- antibiotics to treat bacterial infections (such as clarithromycin),
- certain antibiotics used to treat tuberculosis (such as rifampicin),
- medicines like moxifloxacin (an antibiotic) known to prolong your QT interval (an important measurement of your heart function in an electrocardiogram [ECG]),
- medicines changing the salt concentrations in your body (causing a so-called electrolyte imbalance), for example water tablets such as furosemide, bendroflumethiazide.
- medicines increasing an enzyme called creatine phosphokinase (CPK), for example medicines known as statins like simvastatin to reduce cholesterol levels in your blood,
- medicines having an effect on the central nervous system like codeine (a cough suppressant) or morphine (used to treat severe pain).

RXULTI with food and alcohol
RXULTI can be taken with or without food. Alcohol should be avoided as it can influence how this medicine works.

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.

It is not recommended to take RXULTI during your pregnancy. If you are of childbearing age, you should use effective contraception while taking RXULTI. Babies of mothers who take this medicine during the last three months of their pregnancy may show the following symptoms: shaking, muscle stiffness and/or muscle weakness, sleepiness, restlessness, breathing problems and difficulty in feeding. If your baby has any of these symptoms, you should contact your doctor.

Talk to your doctor about the best way to feed your baby if you are taking RXULTI. Your doctor will consider the benefit of the therapy for you and the benefit of breast-feeding for your baby.

Driving and using machines
There is a chance that the medicine could affect your ability to drive and use machines. Please check that you are not feeling dizzy or sleepy before you start driving or handling machines. Do not drive or use any tools or machines until you know that this medicine does not affect you in a negative way.

RXULTI contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take RXULTI

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 medicine will usually be given to you in increasing doses as follows:

For adults:
- for the first 4 days take one 1 mg film-coated tablet per day,
- from day 5 to day 7 take two 1 mg film-coated tablets per day,
- from day 8 onwards take one film-coated tablet of the strength prescribed by your doctor each day.

Paediatric patients:
- for the first 4 days take one 0.5 mg film-coated tablet per day,
- from day 5 to day 7 take one 1 mg film-coated tablet per day,
- from day 8 onwards take one film-coated tablet of the strength prescribed by your doctor each day.

However, your doctor may prescribe a lower or higher dose to a maximum of 4 mg once a day.

It does not matter whether you take your medicine with or without food.

If you were taking other medicine to treat schizophrenia before starting RXULTI, your doctor will decide whether to stop the other medicine gradually or immediately and how to adjust the dose of RXULTI. Your doctor will also inform you how to act if you switch from RXULTI to other medicine.

Patients with kidney problems
If you have kidney problems, your doctor may adjust your dose of this medicine.

Patients with liver problems
If you have liver problems, your doctor may adjust your dose of this medicine.

If you take more RXULTI than you should
If you have taken more RXULTI than your prescribed dose, contact your doctor or your local hospital immediately. Remember to take the medicine pack with you so that it is clear what you have taken.

If you forget to take RXULTI
If you forget to take a dose, take it as soon as you remember it. However, if it is almost time for your next dose, skip the missed dose and continue as usual. Do not take a double dose to make up for a forgotten dose. If you miss two or more doses, contact your doctor.

If you stop taking RXULTI
If you stop taking this medicine, you will lose the effects of the medicine. Even if you feel better, do not alter or stop your daily dose of RXULTI 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.

During treatment you may experience these serious side effects that require urgent medical attention. Tell your doctor **immediately** if you have:
- thoughts or feelings about hurting yourself or to commit suicide or a suicide attempt (*uncommon side effect* - may affect up to 1 in 100 people).
- combination of fever, sweating, muscle stiffness, and drowsiness or sleepiness. These can be the signs of the so-called neuroleptic malignant syndrome (it is not known how many people are affected).
- irregularities in heart rhythm that may be due to abnormal nerve impulses in the heart, abnormal readings during heart examination (ECG), QT prolongation - it is not known how many people are affected.

- symptoms related to 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 (*uncommon side effect* - may affect up to 1 in 100 people).

Other side effects

Very common side effects (may affect more than 1 in 10 people):
- during blood tests your doctor may find higher amounts of prolactin in your blood.

Common side effects (may affect up to 1 in 10 people):
- rash,
- weight gain,
- akathisia (an uncomfortable feeling of inner restlessness and a compelling need to move constantly),
- dizziness,
- shaking,
- feeling sleepy,
- diarrhoea,
- nausea,
- pain in the upper abdomen,
- back pain,
- pain in arms or legs or both,
- during blood tests your doctor may find higher amounts of creatine kinase (also called creatine phosphokinase) in your blood (enzyme important for muscle function).

Uncommon side effects (may affect up to 1 in 100 people):
- allergic reaction (e.g., swelling in the mouth, tongue, face and throat, itching, hives),
- parkinsonism - medical condition with many various symptoms which include decreased or slow movements, slowness of thought, jerks when bending the limbs (cogwheel rigidity), shuffling steps, shaking, little or no facial expression, muscle stiffness, drooling,
- dizziness on standing up due to a drop in your blood pressure, which may cause fainting,
- cough,
- tooth decay or cavities (dental caries),
- flatulence,
- muscle pain,
- higher blood pressure,
- during blood tests your doctor may find higher amounts of triglycerides in your blood,
- during blood tests your doctor may find increases in liver enzymes.

Other side effects (it is not known how many people are affected):
- seizure,
- muscle weakness, tenderness or pain and particularly, if at the same time, you feel unwell, have a high temperature or have dark urine. They may be caused by an abnormal muscle breakdown which can be life threatening and lead to kidney problems (a condition called rhabdomyolysis),
- withdrawal symptoms in new-born babies if the mother has taken this medicine during pregnancy.
- Inability to resist the impulse, drive or temptation to perform an action that could be harmful to you or others, which may include:
  - strong impulse to gamble excessively despite serious personal or family consequences
  - altered or increased sexual interest and behaviour of significant concern to you or to others, for example, an increased sexual drive
  - uncontrollable excessive shopping
  - binge eating (eating large amounts of food in a short time period) or compulsive eating (eating more food than normal and more than is needed to satisfy your hunger)

  Tell your doctor if you experience any of these behaviours; he/she will discuss ways of managing or reducing the symptoms.

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 RXULTI

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 and on the outer carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

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 RXULTI film-coated tablets contain
- The active substance is brexpiprazole.
  Each film-coated tablet contains 0.25 mg brexpiprazole.
  Each film-coated tablet contains 0.5 mg brexpiprazole.
  Each film-coated tablet contains 1 mg brexpiprazole.
  Each film-coated tablet contains 2 mg brexpiprazole.
  Each film-coated tablet contains 3 mg brexpiprazole.
  Each film-coated tablet contains 4 mg brexpiprazole.

- The other ingredients are:

  Tablet core:
  Lactose monohydrate (see section 2 “RXULTI contains lactose”), maize starch, microcrystalline cellulose, low-substituted hydroxypropylcellulose, hydroxypropylcellulose, magnesium stearate, purified water.

  Tablet coat:

  Hypromellose (E 464), talc (E 553b), titanium dioxide (E 171).

  RXULTI 0.25 mg film-coated tablets
  Iron oxide (E 172) (yellow, red, black)

  RXULTI 0.5 mg film-coated tablets
  Iron oxide (E 172) (yellow, red)

  RXULTI 1 mg film-coated tablets
  Iron oxide (E 172) (yellow)

  RXULTI 2 mg film-coated tablets
  Iron oxide (E 172) (yellow, black)

  RXULTI 3 mg film-coated tablets
  Iron oxide (E 172) (red, black)

What RXULTI film-coated tablets look like and contents of the pack

RXULTI 0.25 mg film-coated tablets

Light brown, round, 6 mm in diameter, shallow convex and bevel-edged, debossed with BRX and 0.25 on one side.

RXULTI 0.5 mg film-coated tablets

Light orange, round, 6 mm in diameter, shallow convex and bevel-edged, debossed with BRX and 0.5 on one side.

RXULTI 1 mg film-coated tablets

Light yellow, round, 6 mm in diameter, shallow convex and bevel-edged, debossed with BRX and 1 on one side.

RXULTI 2 mg film-coated tablets

Light green, round, 6 mm in diameter, shallow convex and bevel-edged, debossed with BRX and 2 on one side.

RXULTI 3 mg film-coated tablets

Light purple, round, 6 mm in diameter, shallow convex and bevel-edged, debossed with BRX and 3 on one side.

RXULTI 4 mg film-coated tablets

White, round, 6 mm in diameter, shallow convex and bevel-edged, debossed with BRX and 4 one side.

RXULTI film-coated tablets are supplied in Aluminium/PVC blisters containing 10, 28 or 56 film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Otsuka Pharmaceutical Netherlands B.V.
Herikerbergweg 292
1101 CT, Amsterdam
Netherlands

Manufacturer

Elaiapharm
2881 Route des Crêtes, Z.I. Les Bouillides-Sophia Antipolis,
06560 Valbonne
France

H. Lundbeck A/S
Ottiliavej 9
2500 Valby
Denmark

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Lundbeck S.A./N.V.
Tél/Tel: +32 2 535 79 79
Tél/Tel: +32 2 340 2828

Lietuva
H. Lundbeck A/S
Tel: +45 36301311

България
Lundbeck Export A/S Representative Office
Tel: +359 2 962 4696

Luxembourg/Luxemburg
Lundbeck S.A.
Tél: +32 2 535 79 79
Tél: +32 2 340 2828

Česká republika
Lundbeck Česká republika s.r.o.
Tel: +420 225 275 600

Magyarország
Lundbeck Hungaria Kft.
Tel: +36 1 4369980

Danmark
Otsuka Pharma Scandinavia AB
Tel: +46 8 54528660

Malta
H. Lundbeck A/S
Tel: +45 36301311

Deutschland
Otsuka Pharma GmbH
Tel: +49 69 1700860

Nederland
Lundbeck B.V.
Tel: +31 20 697 1901

Eesti
H. Lundbeck A/S
Tel: +45 36301311

Norge
Otsuka Pharma Scandinavia AB
Tel: +46 8 54528660

Ελλάδα
Lundbeck Hellas S.A.
Τηλ: +30 210 610 5036

Österreich
Lundbeck Austria GmbH
Tel: +43 1 253 621 6033

España
Otsuka Pharmaceutical S.A.
Tel: +34 93 208 10 20

Polska
Lundbeck Poland Sp. z o. o.
Tel.: +48 22 626 93 00

France
Otsuka Pharmaceutical France SAS
Tél: +33 (0)1 47 08 00 00

Portugal
Lundbeck Portugal – Produtos Farmacêuticos, Unipessoal Lda.
Tel: +351 21 00 45 900

Hrvatska
Lundbeck Croatia d.o.o.
Tel.: +385 1 644 82 63
Tel.: +385 1 3649 210

România
Lundbeck Romania SRL
Tel: +40 21319 88 26

Ireland
Lundbeck (Ireland) Limited
Tel: +353 1 468 9800

Slovenija
Lundbeck Pharma d.o.o.
Tel.: +386 2 229 4500

Ísland
Vistor hf.
Sími: +354 535 7000

Slovenská republika
Lundbeck Slovensko s.r.o.
Tel: +421 2 5341 42 18

Italia
Otsuka Pharmaceutical Italy S.r.l.
Tel: +39 02 00 63 27 10

Κύπρος
Lundbeck Hellas A.E
Τηλ.: +357 22490305

Latvija
H. Lundbeck A/S
Tel: +45 36301311

Suomi/Finland
Otsuka Pharma Scandinavia AB
Tel: +46 8 54528660

Sverige
Otsuka Pharma Scandinavia AB
Tel: +46 8 54528660

This leaflet was last revised in.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu/

Cariprazine

EMA

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Reagila 1.5 mg hard capsules
Reagila 3 mg hard capsules
Reagila 4.5 mg hard capsules
Reagila 6 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Reagila 1.5 mg hard capsules

Each hard capsule contains cariprazine hydrochloride corresponding to 1.5 mg cariprazine.

Reagila 3 mg hard capsules

Each hard capsule contains cariprazine hydrochloride corresponding to 3 mg cariprazine.

Excipient with known effect

Each hard capsule contains 0.0003 mg Allura red AC (E 129).

Reagila 4.5 mg hard capsules

Each hard capsule contains cariprazine hydrochloride corresponding to 4.5 mg cariprazine.

Excipient with known effect

Each hard capsule contains 0.0008 mg Allura red AC (E 129).

Reagila 6 mg hard capsules

Each hard capsule contains cariprazine hydrochloride corresponding to 6 mg cariprazine.

Excipient with known effect

Each hard capsule contains 0.0096 mg Allura red AC (E 129).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule

Reagila 1.5 mg hard capsules

‘Size 4’ (approximately 14.3 mm in length) hard gelatin capsule with white opaque cap and white opaque body imprinted with “GR 1.5” on the capsule body with black ink. The capsules are filled with white to yellowish white powder mixture.

Reagila 3 mg hard capsules

‘Size 4’ (approximately 14.3 mm in length) hard gelatin capsule with green opaque cap and white opaque body imprinted with “GR 3” on the capsule body with black ink. The capsules are filled with white to yellowish white powder mixture.

Reagila 4.5 mg hard capsules

'Size 4' (approximately 14.3 mm in length) hard gelatin capsule with green opaque cap and green opaque body imprinted with "GR 4.5" on the capsule body with white ink. The capsules are filled with white to yellowish white powder mixture.

Reagila 6 mg hard capsules

'Size 3' (approximately 15.9 mm in length) hard gelatin capsule with purple opaque cap and white opaque body imprinted with "GR 6" on the capsule body with black ink. The capsules are filled with white to yellowish white powder mixture.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reagila is indicated for the treatment of schizophrenia in adult patients.

4.2 Posology and method of administration

Posology

The recommended starting dose of cariprazine is 1.5 mg once daily. Thereafter the dose can be increased slowly in 1.5 mg increments to a maximum dose of 6 mg/day, if needed. The lowest effective dose should be maintained according to the clinical judgement of the treating physician. Because of the long half-life of cariprazine and its active metabolites, changes in dose will not be fully reflected in plasma for several weeks. Patients should be monitored for adverse reactions and treatment response for several weeks after starting cariprazine and after each dose change (see section 5.2).

Switching from other antipsychotics to cariprazine
When switching from another antipsychotic to cariprazine gradual cross-titration should be considered, with gradual discontinuation of the previous treatment while cariprazine treatment is initiated.

Switching to another antipsychotic from cariprazine
When switching to another antipsychotic from cariprazine, no gradual cross-titration is needed, the new antipsychotic should be initiated in its lowest dose while cariprazine is discontinued. It should be considered that plasma concentration of cariprazine and its active metabolites will decline by 50% in ~1 week (see section 5.2).

Missed dose
If the patient misses a dose, the patient should take the missed dose as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped and the next dose should be taken according to the regular schedule. It is not recommended to take a double dose to make up for the forgotten dose.

Special population

Renal impairment
No dose adjustment is required in patients with mild to moderate renal impairment (Creatinine & O H D U D Q F H 30 mL/min and < 89 mL/min). Safety and efficacy of cariprazine have not been evaluated in patients with severe renal impairment (CrCl < 30 mL/min). Use of cariprazine is not recommended in patients with severe renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is required in patients with mild to moderate hepatic impairment (Child-Pugh score between 5-9). Safety and efficacy of cariprazine have not been evaluated in patients with severe hepatic impairment (Child-Pugh score between 10 and 15). Use of cariprazine is not recommended in patients with severe hepatic impairment (see section 5.2).

Elderly
Available data in elderly patients aged 65 years treated with cariprazine are not sufficient to determine whether or not they respond differently from younger patients (see section 5.2). Dose selection for an elderly patient should be more cautious.

Paediatric population
The safety and efficacy of cariprazine in children and adolescents aged less than 18 years have not been established. No data are available.

Method of administration

Reagila is for oral use, to be taken once daily at the same time of the day with or without food.

Reagila orodispersible tablets may be used as an alternative to Reagila hard capsules for patients who have difficulty swallowing the hard capsules or for whom there is a preference for orodispersible tablets.

Alcohol should be avoided when taking cariprazine (see section 4.5).

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 (see section 4.5).
Concomitant administration of strong or moderate CYP3A4 inducers (see section 4.5).

4.4 Special warnings and precautions for use

Suicidal ideation and behaviour

The possibility of suicidality (suicidal ideation, suicide attempt and completed suicide) is inherent in psychotic illnesses and, generally, it is reported early after initiation or switch of antipsychotic therapy. Close supervision of high-risk patients should accompany antipsychotic therapy.

Akathisia, restlessness

Akathisia and restlessness are frequently occurring adverse reactions of antipsychotics. Akathisia is a movement disorder characterized by a feeling of inner restlessness and a compelling need to be in constant motion, as well as by actions such as rocking while standing or sitting, lifting the feet as if marching on the spot, and crossing and uncrossing the legs while sitting. As cariprazine causes akathisia and restlessness, it should be used cautiously in patients who are prone to or already exhibit symptoms of akathisia. Akathisia develops early in treatment. Therefore, close monitoring in the first phase of treatment is important. Prevention includes slow up-titration; treatment measures include slight down-titration of cariprazine or anti-extrapyramidal symptoms (EPS) medicinal product The dose can be modified based on individual response and tolerability (see section 4.8).

Tardive dyskinesia

Tardive dyskinesia is a syndrome consisting of potentially irreversible, rhythmical, involuntary movements, predominantly of the tongue and/or face that can develop in patients treated with antipsychotics. If signs and symptoms of tardive dyskinesia appear in a patient treated with

cariprazine, discontinuation should be considered.

Parkinson's disease

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

Ocular symptoms/cataract

In the preclinical studies of cariprazine lens opacity/cataract was detected in dogs (see sections 4.8 and 5.3). However, a causal relationship between lenticular changes / cataracts observed in human studies and cariprazine use has not been established. Nevertheless, patients who would develop symptoms potentially related to cataract should be advised to ophthalmologic examination and re-evaluated for treatment continuation.

Neuroleptic malignant syndrome (NMS)

A potentially fatal symptom complex referred to as NMS has been reported in association with antipsychotic treatment. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, elevated serum creatine phosphokinase levels, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include 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, cariprazine must be discontinued immediately.

Seizures and convulsions

Cariprazine should be used cautiously in patients with history of seizures or with conditions that potentially lower the seizure threshold.

Elderly patients with dementia

Cariprazine has not been studied in elderly patients with dementia and is not recommended to treat elderly patients with dementia due to increased risk of overall mortality.

Risk of cerebrovascular accidents (CVA)

An approximately 3-fold increased risk of CVA has been seen in randomised placebo-controlled clinical studies 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. Cariprazine should be used with caution in patients with risk factors for stroke.

Cardiovascular disorders

Blood pressure changes

Cariprazine can cause orthostatic hypotension as well as hypertension (see section 4.8). Cariprazine should be used with caution in patients with known cardiovascular disease predisposing to blood pressure changes. Blood pressure should be monitored.

Electrocardiogram (ECG) changes

QT prolongation can develop in patients treated with antipsychotics.
With cariprazine no QT interval prolongation was detected compared to placebo in a clinical study designed to assess QT prolongation (see section 5.1). In clinical studies, only a few, non-serious, QT-prolongations have been reported with cariprazine (see section 4.8). Therefore, cariprazine should be used cautiously in patients with known cardiovascular disease or in patients with a family history of QT prolongation and in patients treated with medicinal products that might cause QT prolongation

(see section 5.1).

Venous thromboembolism (VTE)

Cases of 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 cariprazine and preventive measures undertaken.

Hyperglycaemia and diabetes mellitus

Patients with an established diagnosis of diabetes mellitus or patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should be monitored for serum glucose levels. In clinical studies, glucose-related adverse reactions have been reported with cariprazine (see section 5.1).

Weight change

Significant weight gain has been observed with the use of cariprazine. Patients should have their weight monitored regularly (see section 4.8).

Concomitant treatment with moderate CYP3A4 inhibitors

Co-administration of cariprazine with moderate inhibitors of CYP3A4 may lead to increased total cariprazine exposure. Monitoring of the individual response and tolerability is recommended and, if needed, the cariprazine dose should be (temporarily) reduced to account for the potential increase in exposure (see section 4.5).

Excipients with known effect

Reagila 3 mg, 4.5 mg and 6 mg hard capsules contain Allura red AC (E 129), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicinal products to affect cariprazine

Metabolism of cariprazine and its major active metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), is mediated mainly by CYP3A4 with a minor contribution of CYP2D6.

CYP3A4 inhibitors

Ketoconazole, a strong CYP3A4 inhibitor, caused two-fold increase in plasma exposure for total cariprazine (sum of cariprazine and its active metabolites) during short-term (4 days) co-administration, either if unbound or unbound+bound moieties considered.
Due to the long half-life of the active moieties of cariprazine a further increase in plasma exposure of total cariprazine can be expected during longer co-administration. Therefore, co-administration of cariprazine with strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) is contraindicated (see section 4.3).

Erythromycin (500 mg twice daily), a moderate CYP3A4 inhibitor, caused on average a 1.4-fold (range 1.03-2.32-fold) increase in plasma exposure of total cariprazine after 3 weeks of co-administration. Therefore, during a period of co-administration of cariprazine with a moderate CYP3A4 inhibitor (e.g., erythromycin, fluconazole, diltiazem, verapamil), monitoring of the individual response and tolerability is recommended and, if needed, the cariprazine dose should be (temporarily) reduced to account for the potential increase in exposure. Because of the long half-life of cariprazine and its active metabolites, starting or stopping a treatment with a moderate CYP 3A4 inhibitor or changing the dose will not be fully reflected in plasma drug levels until after several

weeks. Patients should be monitored for adverse reactions and treatment response for several weeks after initiating or stopping an interacting drug or after each cariprazine dose change.

Consumption of grapefruit juice should be avoided.

CYP3A4 inducers
Co-administration of cariprazine with strong and moderate inducers of CYP3A4 may result in a significant decrease in total cariprazine exposure, therefore the co-administration of cariprazine and strong or moderate CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampicin, St. John's wort (*Hypericum perforatum*), bosentan, efavirenz, etravirine, modafinil, nafcillin) is contraindicated (see section 4.3).

CYP2D6 inhibitors
CYP2D6 mediated pathway plays a minor role in the metabolism of cariprazine, the major pathway is via CYP3A4 (see section 5.2). Therefore, CYP2D6 inhibitors are unlikely to have a clinically relevant effect on cariprazine metabolism.

Potential for cariprazine to affect other medicinal products

P-glycoprotein (Pgp) substrates
Cariprazine is a P-gp inhibitor *in vitro* at its theoretical maximum intestinal concentration. The clinical consequences of this effect is not fully understood, however the use of P-gp substrates with narrow therapeutic index such as dabigatran and digoxin could require extra monitoring and dose adjustment.

Hormonal contraceptives
In a drug interaction study, 28 days of treatment with cariprazine at 6 mg daily had no clinically relevant effect on the pharmacokinetics of oral contraceptives (ethinylestradiol and levonorgestrel).

Pharmacodynamic interactions

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Women of childbearing potential must be advised to avoid pregnancy while on Reagila. Female patients of child-bearing potential must use highly effective contraceptive methods during treatment and for at least 10 weeks following the last dose of Reagila.

Pregnancy

There are no or limited amount of data from the use of cariprazine in pregnant women.
Studies in animals have shown reproductive toxicity including developmental malformations in rats (see section 5.3).

Reagila is not recommended during pregnancy and in women of childbearing potential not using effective contraception. After discontinuation of cariprazine treatment contraception should be used for at least 10 weeks due to the slow elimination of active moieties.

Neonates exposed to antipsychotics (including cariprazine) 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. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases, neonates have required intensive care unit support and prolonged hospitalization. Consequently, newborns should be

monitored carefully.

Breast-feeding

It is unknown whether cariprazine or its major active metabolites are excreted in human milk. Cariprazine and its metabolites are excreted in milk of rats during lactation (see section 5.3). A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with cariprazine.

Fertility

The effect of cariprazine on human fertility has not been evaluated. In rat studies lower female fertility and conception indices were observed (see section 5.3).

4.7 Effects on ability to drive and use machines

Cariprazine has minor or moderate influence on the ability to drive and use machines. Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with Reagila does not affect them adversely.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse drug reactions (ADRs) with cariprazine in the dose range (1.5-6 mg) were akathisia (19%) and parkinsonism (17.5%). Most events were mild to moderate in severity.

Tabulated list of adverse reactions

ADRs based upon pooled data from cariprazine schizophrenia studies are shown by system organ class and by preferred term in Table 1.

Adverse reactions are ranked by MedDRA system organ class and by frequency, the most frequent ILUVW XVLQJ WKH IROORZLQJ FRQYHQWLRQ YHU\ FRPPRQ WR UDUH 000) very rare (<1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse drug reactions occurring in patients with schizophrenia

MedDRA System Organ Class	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)	Frequency not known
Blood and lymphatic system disorders			Anaemia Eosinophilia	Neutropenia	
Immune system disorders				Hypersensitivity	
Endocrine disorders			Blood thyroid stimulating hormone decreased	Hypothyroidism	
Metabolism and nutrition		Dyslipidaemia Weight increased	Blood sodium abnormal Diabetes		

disorders		Decreased appetite Increased appetite	mellitus Blood glucose increased		
Psychiatric disorders		Sleep disorders[1] Anxiety	Suicidal behaviour Delirium Depression Libido decreased Libido increased Erectile dysfunction		
Nervous system disorders	Akathisia[2] Parkinsonism[3]	Sedation Dizziness Dystonia[4] Other extrapyramidal diseases and abnormal movement disorders[5]	Tardive dyskinesia Dyskinesia[6] Dysaesthesia Lethargy	Seizures/ Convulsion Amnesia Aphasia	Neuroleptic malignant syndrome
Eye disorders		Vision blurred	Intraocular pressure increased Accommodation disorder Visual acuity reduced Eye irritation	Cataract Photophobia	
Ear and labyrinth disorders			Vertigo		
Cardiac disorders		Tachyarrhythmia	Cardiac conduction disorders Bradyarrhythmia Electrocardiogram QT prolonged Electrocardiogram T wave abnormal		
Vascular disorders		Hypertension	Hypotension		
Respiratory, thoracic and mediastinal disorders			Hiccups		
Gastrointestinal disorders		Vomiting Nausea Constipation	Gastrooesophageal reflux disease	Dysphagia	
Hepatobiliary disorders		Hepatic enzymes increased	Blood bilirubin increased		Toxic hepatitis

Skin and subcutaneous tissue disorders			Pruritus Rash		
Musculoskeletal and connective tissue disorders		Blood creatine phosphokinase increased		Rhabdomyolysis	
Renal and urinary disorders			Dysuria Pollakisuria		
Pregnancy, puerperium and perinatal conditions					Drug withdrawal syndrome neonatal (see section 4.6)
General disorders and administration site conditions		Fatigue	Thirst		

[1]Sleep disorders: Insomnia, Abnormal dreams/nightmare, Circadian rhythm sleep disorder, Dyssomnia, Hypersomnia, Initial insomnia, Middle insomnia, Nightmare, Sleep disorder, Somnambulism, Terminal insomnia
[2]Akathisia: Akathisia, Psychomotor hyperactivity, Restlessness
[3]Parkinsonism: Akinesia, Bradykinesia, Bradyphrenia, Cogwheel rigidity, Extrapyramidal disorder, Gait disturbance, Hypokinesia, Joint stiffness, Tremor, Masked facies, Muscle rigidity, Musculoskeletal stiffness, Nuchal rigidity, Parkinsonism
[4]Dystonia: Blepharospasm, Dystonia, Muscle tightness, Oromandibular dystonia, Torticollis, Trismus
[5]Other extrapyramidal diseases and abnormal movement disorders: Balance disorder, Bruxism, Drooling, Dysarthria, Gait deviation, Glabellar reflex abnormal, Hyporeflexia, Movement disorder, Restless legs syndrome, Salivary hypersecretion, Tongue movement disturbance
[6]Dyskinesia: Choreoathetosis, Dyskinesia, Grimacing, Oculogyric crisis, Protrusion tongue

Description of selected adverse reactions

Lens opacity/Cataract

Development of cataracts was observed in cariprazine non-clinical studies (see section 5.3). Therefore, cataract formation was closely monitored with slit lamp examinations in the clinical studies and patients with existing cataracts were excluded. During the schizophrenia clinical development program of cariprazine, few cataract cases were reported, characterized with minor lens opacities with no visual impairment (13/3 192; 0.4%). Some of these patients had confounding factors. The most commonly reported ocular adverse event was blurred vision (placebo: 1/683; 0.1%, cariprazine: 22/2 048; 1.1%).

Extrapyramidal symptoms (EPS)

In the short-term studies the incidence of EPS was observed in 27%; 11.5%; 30.7% and 15.1% in patients treated with cariprazine, placebo, risperidone and aripiprazole respectively. Akathisia was reported in 13.6%; 5.1%; 9.3% and 9.9% in patients treated with cariprazine, placebo, risperidone and aripiprazole respectively. Parkinsonism was experienced in 13.6%; 5.7%; 22.1% and 5.3% in patients treated with cariprazine, placebo, risperidone and aripiprazole respectively. Dystonia was observed in 1.8%; 0.2%; 3.6% and 0.7% in patients on cariprazine, placebo, risperidone and aripiprazole, respectively.

In the placebo-controlled part of the long-term maintenance of effect study EPS was 13.7% in the cariprazine group compared to 3.0% in the placebo treated patients. Akathisia was reported in 3.9% in

patients treated with cariprazine, versus 2.0% in the placebo group. Parkinsonism was experienced in 7.8% and 1.0% in cariprazine and placebo group respectively.

In the negative symptom study EPS was reported in 14.3% in the cariprazine group and 11.7% in the risperidone treated patients. Akathisia was reported in 10.0% in patients treated with cariprazine and 5.2% in the risperidone group. Parkinsonism was experienced in 5.2% and 7.4% in cariprazine and risperidone treated patients respectively. Most EPS cases were mild to moderate in intensity and could be handled with common anti-EPS medicinal products. The rate of discontinuation due to EPS related ADRs was low.

Venous thromboembolism (VTE)
Cases of VTE, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotics - Frequency unknown.

Elevated liver transaminases
Elevated liver transaminases (Alanine Aminotransferase [ALT], Aspartate Aminotransferase [AST]) are frequently observed with antipsychotic treatment. In the cariprazine clinical studies the incidence of ALT, AST elevation ADRs occurred in 2.2% of cariprazine-, 1.6% of risperidone- and 0.4% of placebo-treated patients. None of the cariprazine-treated patients had any liver damage.

Weight changes
In the short-term studies, there were slightly greater mean increases in body weight in the cariprazine group compared to the placebo group; 1 kg and 0.3 kg, respectively. In the long-term maintenance of effect study, there was no clinically relevant difference in change of body weight from baseline to end of treatment (1.1 kg for cariprazine and 0.9 kg for placebo). In the open-label phase of the study during 20 weeks cariprazine treatment 9.0% of patients developed potentially clinically significant (PCS) weight gain GHILQHG DV ≥7% while during the double-blind phase, 9.8 % of the patients who continued with cariprazine treatment had PCS weight gain versus 7.1% of the patients who were randomized to placebo after the 20 week open-label cariprazine treatment. In the negative symptom study, the mean change of body weight was -0.3 kg for cariprazine and +0.6 kg for risperidone and PCS weight gain was observed in 6% of the cariprazine group while 7.4% of the risperidone group.

QT- prolongation
With cariprazine no QT interval prolongation was detected compared to placebo in a clinical study designed to assess QT prolongation (see section 5.1). In other clinical studies, only a few, non-serious, QT-prolongations have been reported with cariprazine. During the long-term, open-label treatment period in, 3 patients (0.4%) had QTcB > 500 msec, one of whom also had QTcF > 500 msec. A > 60 msec increase from baseline was observed in 7 patients (1%) for QTcB and in 2 patients (0.3%) for QTcF. In the long-term, maintenance of effect study, during the open-label phase, > 60 msec increase of from baseline was observed in 12 patients (1.6%) for QTcB and in 4 patients (0.5%) for QTcF. During the double-blind treatment period, > 60 msec increases from baseline in QTcB were observed in 3 cariprazine-treated patients (3.1%) and 2 placebo-treated patients (2%).

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

Symptoms

Accidental acute overdose (48 mg/day) was reported in one patient. This patient experienced orthostasis and sedation. The patient fully recovered the same day.

Management of overdose

Management of overdose should concentrate on supportive therapy including maintenance of an adequate airway, oxygenation and ventilation and management of symptoms. Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. In case of severe extrapyramidal symptoms, anticholinergic medicinal products should be administered. Since cariprazine is highly bound to plasma proteins, haemodialysis is unlikely to be useful in the management of overdose. Close medical supervision and monitoring should continue until the patient recovers.

There is no specific antidote to cariprazine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, other antipsychotics, ATC code: N05AX15

Mechanism of action

The mechanism of action of cariprazine is not fully known. However the therapeutic effect of cariprazine may be mediated through a combination of partial agonist activity at dopamine D_3, D_2 (Ki values of 0.085-0.3 nM versus 0.49-0.71 nM respectively) and serotonin 5-HT_{1A} receptors (Ki values of 1.4-2.6 nM), and antagonist activity at serotonin 5-HT_{2B}, 5-HT_{2A} and histamine H_1 receptors (Ki values of 0.58-1.1 nM, 18.8 nM and 23.3 nM, respectively). Cariprazine has low affinity for serotonin 5-HT_{2C} DQG GRSDPLQH UHFHSWRUV (Ki values of 155 nM, respectively). Cariprazine has no appreciable affinity for cholinergic muscarinic receptors (IC_{50} > 1 000 nM). The two major active metabolites, desmethyl cariprazine and didesmethyl cariprazine have a similar *in vitro* receptor binding and functional activity profile as the parent active substance.

Pharmacodynamic effects

In vivo non-clinical studies demonstrated that cariprazine occupies D_3 receptors to a similar extent as D_2 receptors at pharmacologically effective doses. There was a dose-dependent occupancy of brain dopamine D_3 and D_2 receptors (with preferential occupancy in regions with higher D_3 expression) in patients with schizophrenia within the therapeutic dose range of cariprazine for 15 days.

The effects of cariprazine on the QT interval were evaluated in patients with schizophrenia or schizoaffective disorder. Holter monitor-derived electrocardiographic assessments were obtained in 129 patients over a twelve hour period at baseline and steady state. No QT interval prolongation was detected following supratherapeutic doses (9 mg/day or 18 mg/day). No patients treated with cariprazine experienced a QTcF interval increase from baseline of > 60 msec, nor did any patient experience a QTc of > 500 msec in the study.

Clinical efficacy and safety

Efficacy with short-term use

The efficacy of cariprazine for the treatment of acute schizophrenia was studied in three multi-center, multinational, randomized, double-blind, placebo-controlled 6-week studies including 1 754 patients with the age of 18 to 60 years. The primary endpoint was change from baseline to week 6 in the Positive and Negative Syndrome Scale (PANSS) total score and the secondary endpoint was change from baseline to week 6 in the Clinical Global Impressions-Severity (CGI-S) score in all acute schizophrenia studies. In a multinational placebo-controlled study using fixed doses of 1.5 mg, 3.0 mg and 4.5 mg cariprazine and 4.0 mg risperidone for assay sensitivity, all cariprazine doses and the active-control showed statistically significant improvement in both primary as well as secondary

endpoint compared to placebo. In another multinational placebo-controlled study using fixed doses of 3.0 mg, and 6.0 mg cariprazine and 10 mg aripiprazole for assay sensitivity, both cariprazine doses and the active-control showed statistically significant improvement in both primary as well as secondary endpoint compared to placebo. In a third multinational placebo-controlled study using fixed/flexible doses of 3.0-6.0 mg and 6.0-9.0 mg cariprazine, both cariprazine doses groups showed statistically significant improvement in both primary as well as secondary endpoint compared to placebo.
Results for the primary outcome parameter are summarized in Table 2 below. Results for the secondary outcome parameter (CGI) and additional endpoints were supportive of the primary endpoint.

Table 2. Change from baseline to week 6 in the PANSS total score in studies of acute exacerbations of schizophrenia—ITT population

	Baseline Mean ± SD	**Change LS mean (SE)**	**Treatment difference versus placebo (95% CI)**	**P-value**
PANSS total (MMRM)				
RGH-MD-16 (n=711)				
Placebo	97.3 ± 9.22	–13.29 (1.82)	—	—
Cariprazine 1.5 mg/day	97.1 ± 9.13	–21.27 (1.77)	–7.97 (–12.94, –3.01)	**0.0017**
Cariprazine 3 mg/day	97.2 ± 8.66	–21.45 (1.74)	–8.16 (–13.09, –3.22)	**0.0013**
Cariprazine 4.5 mg/day	96.7 ± 9.01	–23.77 (1.74)	–10.48 (–15.41, –5.55)	**< 0.0001**
Risperidone 4 mg/day	98.1 ± 9.50	–29.27 (1.74)	–15.98 (–20.91, –11.04)	< 0.0001*
RGH-MD-04 (n=604)				
Placebo	96.5 ± 9.1	–14.3 (1.5)	—	—
Cariprazine 3 mg/day	96.1 ± 8.7	–20.2 (1.5)	–6.0 (–10.1, –1.9)	**0.0044**
Cariprazine 6 mg/day	95.7 ± 9.4	–23.0 (1.5)	–8.8 (–12.9, –4.7)	**< 0.0001**
Aripiprazole 10 mg/day	95.6 ± 9.0	–21.2 (1.4)	–7.0 (–11.0, –2.9)	0.0008*
RGH-MD-05 (n=439)				
Placebo	96.6 ± 9.3	–16.0 (1.6)	—	—
Cariprazine 3 to 6 mg/day	96.3 ± 9.3	–22.8 (1.6)	–6.8 (–11.3, –2.4)	**0.0029**
Cariprazine 6 to 9 mg/day	96.3 ± 9.0	–25.9 (1.7)	–9.9 (–14.5, –5.3)	**< 0.0001**

CI = confidence interval; ITT = intent to treat; LS mean = least squares mean; PANSS = Positive and Negative Syndrome Scale.
*compared to placebo

Efficacy with long-term use

The efficacy of cariprazine for maintaining antipsychotic effect was investigated in a randomized-withdrawal, long-term clinical study. Totally, 751 patients with acute symptoms of schizophrenia received cariprazine 3-9 mg/day for 20 weeks, of whom 337 received cariprazine in the dose-range of 3 or 6 mg/day. Stabilized patients were then randomised to receive fixed doses of 3 or 6 mg cariprazine (n=51) or placebo (n=51) in a double-blind manner for up to 72 weeks. The primary outcome of the study was time to relapse. By the end of the study 49.0% of placebo-treated patients versus 21.6% of cariprazine-treated patients had a relapse of schizophrenic symptoms. Time to relapse (92 vs. 326 days-based on the 25th percentile) was therefore significantly longer in the cariprazine group than in the placebo group (p=0.009).

Efficacy in predominantly negative symptoms of schizophrenia

The efficacy of cariprazine for the treatment of predominantly negative symptoms of schizophrenia was investigated in a 26-week, multi-centre, double-blind, and active-controlled clinical study. Cariprazine (dose range 3-6 mg, target dose 4.5 mg) was investigated compared to risperidone (dose range 3-6 mg, target dose 4 mg) in patients with persistent, predominant negative symptoms of schizophrenia (n=461). 86% of patients were less than 55 years old, 54% of them were male.

Persistent predominant negative symptoms were defined as symptoms lasting for a period of at least 6 months with high level of negative symptoms and low level of positive symptoms [(PANSS factor VFRUH IRU QHJDWLYH V\PSWRPV 4 in a minimum 2 of the 3 PANSS items (N1: flat affect, N4: avolition, and N6: poverty of speech) and PANSS factor score for positive symptoms 19]. Patients with secondary negative symptoms, such as moderate to severe depressive symptoms and clinically relevant parkinsonism (EPS) were excluded.

Both cariprazine- and risperidone-treated patient groups have shown statistically significant improvement in the change from baseline for the primary efficacy parameter, PANSS factor score for negative symptoms (PANSS-FSNS) ($p < 0.001$). However, a statistically significant difference ($p=0.002$) in favour of cariprazine over risperidone was observed from Week 14 onward (Table 3). Both cariprazine- and risperidone-treated patient groups have shown statistically significant improvement in the change from baseline for the secondary efficacy parameter, Personal and Social Performance (PSP) total score ($p < 0.001$). However, a statistically significant difference ($p < 0.001$) in favour of cariprazine over risperidone was observed from Week 10 onward (Table 3). Differences on the Clinical Global Impression Severity ($p=0.005$) and Improvement ($p < 0.001$) scales, as well as PANSS-FSNS response rates (3$166)61 30% improvement at Week 26; $p=0.003$) were supportive of findings on the primary and secondary efficacy parameters.

Table 3 Summary of results in study RGH-188-005

Efficacy parameter	Cariprazine LS mean	Risperidone LS mean	Estimated treatment difference	95% CI	p-value
PANSS-FSNS at Baseline	27.8	27.5	-	-	-
PANSS-FSNS at Week 26	18.5	19.6	-	-	-
PANSS-FSNS CfB to Week 26	-8.9	-7.4	-1.5	-2,4; -0.5	0.002
Total PSP at Baseline	48.8	48.2	-	-	-
Total PSP at Week 26	64.0	59.7	-	-	-
Total PSP CfB to Week 26	14.3	9.7	4.6	2.7; 6.6	<0.001

CfB= change from baseline

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with cariprazine in one or more subsets of the paediatric population in the treatment of schizophrenia. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Cariprazine has two pharmacologically active metabolites with similar activities as cariprazine, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR). Total cariprazine (sum of cariprazine + DCAR and DDCAR) exposure approaches 50% of steady state exposure in ~1 week of daily dosing while 90% of steady state is achieved in 3 weeks. At steady state, exposure to DDCAR is approximately two to three-fold higher than to cariprazine, and exposure to DCAR is approximately 30% of cariprazine exposure.

Absorption

Absolute bioavailability of cariprazine is unknown. Cariprazine is well absorbed after oral administration. Following multiple-dose administration, peak plasma concentrations for cariprazine

and the major active metabolites generally occur at approximately 3-8 hours post dose. Administration of a single dose of 1.5 mg cariprazine with a high-fat meal (900 to 1 000 calories) did not significantly affect the C_{max} or AUC of cariprazine (AUC_{0-} increased by 12%, C_{max} decreased by < 5% under fed condition versus fasting). The effect of food on the exposure of the metabolites DCAR and DDCAR was also minimal.

Cariprazine can be administered with or without food.

Distribution

Based on a population pharmacokinetic analysis, the apparent volume of distribution (V/F) was 916 L for cariprazine, 475 L for DCAR and 1 568 L for DDCAR, indicating extensive distribution of cariprazine and its major active metabolites. Cariprazine and its major active metabolites are highly bound (96 to 97% for CAR, 94% to 97% for DCAR and 92% to 97% for DDCAR) to plasma proteins.

Biotransformation

The metabolism of cariprazine involves demethylation (DCAR and DDCAR), hydroxylation (hydroxy cariprazine, HCAR) and a combination of demethylation and hydroxylation (hydroxy desmethyl cariprazine, HDCAR and hydroxy didesmethyl cariprazine, HDDCAR). The metabolites of HCAR, HDCAR, and HDDCAR are subsequently biotransformed to their corresponding sulfate and glucuronide conjugates. An additional metabolite, desdichlorophenyl piperazine cariprazine (DDCPPCAR) acid, is produced by dealkylation and subsequent oxidation of cariprazine. Cariprazine is metabolized by CYP3A4 and, to a lesser extent, by CYP2D6, to DCAR and HCAR. DCAR is further metabolized by CYP3A4 and to a lesser extent by CYP2D6 into DDCAR and HDCAR. DDCAR is further metabolised to HDDCAR by CYP3A4.

Cariprazine and its major active metabolites are not substrates of P-glycoprotein (P-gp), the organic anion transporting polypeptide 1B1 and 1B3 (OATP1B1 and OATP1B3), and the breast cancer resistance protein (BCRP). This suggests that an interaction of cariprazine with inhibitors of P-gp, OATP1B1, OATP1B3 and BCRP is unlikely.

Elimination

Elimination of cariprazine and its major active metabolites is mainly through hepatic metabolism. Following administration of 12.5 mg/day cariprazine to patients with schizophrenia, 20.8% of the dose was excreted in urine as cariprazine and its metabolites.

Unchanged cariprazine is excreted by 1.2% of the dose in urine and 3.7% of the dose in faeces.

The mean terminal half-life (1 to 3 days for cariprazine and DCAR and 13 to 19 days for DDCAR) is not predictive of time to reach steady state or plasma concentration decline after treatment discontinuation. For the management of patients treated with cariprazine, the effective half-life is more relevant than the terminal half-life. The effective (functional) half-life is ~ 2 days for cariprazine and DCAR, 8 days for DDCAR and is ~1 week for total cariprazine. The plasma concentration of total cariprazine will gradually decline following dose discontinuation or interruption. The plasma concentration of total cariprazine decreases by 50% in ~1 week and greater than 90% decline in total cariprazine concentration occurs in ~3 weeks.

Linearity

After repeated administration plasma exposure of cariprazine and its two major active metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), increases proportionally over the therapeutic dose range of 1.5 to 6 mg.

Special populations

Renal impairment

Population pharmacokinetic modelling was performed using data from patients enrolled in the schizophrenia cariprazine clinical program with differing levels of renal function, including normal renal funct L R Q F U H D W L Q L Q H 90 mL/min), as well as mild (CrCl 60 to 89 mL/min) and moderate (CrCl 30 to 59 mL/min) renal impairment. No significant relationship was found between cariprazine plasma clearance and creatinine clearance.

Cariprazine has not been evaluated in patients with severe (CrCl < 30 mL/min) renal impairment (see section 4.2).

Hepatic impairment

A 2-part study (a single dose of 1 mg cariprazine [Part A] and a daily dose of 0.5 mg cariprazine for 14 days [Part B] was conducted in patients with varying degrees of impaired hepatic function (Child-Pugh Classes A and B). Compared to healthy subjects, patients with either mild or moderate hepatic impairment had up to approximately 25% higher exposure (C_{max} and AUC) for cariprazine and up to approximately 45% lower exposure for the major active metabolites, desmethyl cariprazine and didesmethyl cariprazine, following the single dose of 1 mg cariprazine or 0.5 mg cariprazine for 14 days.

The total active moiety (CAR+DCAR+DDCAR) exposure (AUC and C_{max}) decreased by 21-22% and 13-15% in mild or moderate hepatic impairment (HI), respectively, compared to healthy subjects if unbound + bound concentrations were considered, while for unbound total moiety a decrease of 12-13% and an increase of 20-25% were calculated in mild HI patients and in moderate HI patients, respectively, after multiple dosing of cariprazine.

Cariprazine has not been evaluated in patients with severe hepatic impairment (Child-Pugh Class C) (see section 4.2).

Age, gender and race

In the population PK analysis there were no clinically relevant differences in the PK parameters (AUC and C_{max} of the sum of cariprazine and its major active metabolites) based on age, gender and race. This analysis included 2 844 patients of different races, involving 536 patients between the ages of 50 and 65. Of the 2 844 patients 933 were female (see section 4.2). In elderly patients above 65 years of age data are limited.

Smoking status

Because cariprazine is not a substrate for CYP1A2, smoking is not expected to have an effect on the pharmacokinetics of cariprazine.

Potential for cariprazine to affect other medicinal products

Cariprazine and its major active metabolites did not induce CYP1A2, CYP2B6 and CYP3A4 enzymes and were not inhibitors of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP219, CYP2D6, CYP2E1 and CYP3A4 in vitro. Cariprazine and its major active metabolites are not inhibitors of transporters OATP1B1, OATP1B3, BCRP, organic cation transporter 2 (OCT2), and organic anion transporters 1 and 3 (OAT1 and OAT3) in vitro. DCAR and DDCAR were not inhibitors of transporter P-gp although cariprazine was a P-gp inhibitor in the intestine (see section 4.5).

5.3 Preclinical safety data

Cariprazine caused bilateral cataract and secondary retinal changes (retinal detachment and cystic degeneration) in the dog. The exposure (AUC of total cariprazine) at the no-observed-adverse-effect-level (NOAEL) for ocular toxicity is 4.2-fold the clinical AUC exposure at the maximal recommended human dose (MRHD) of 6 mg/day. Increased incidence of retinal degeneration/atrophy was observed

in albino rats in the 2-year study at clinically relevant exposures.

Phospholipidosis was observed in the lungs of rats, dogs, and mice (with or without inflammation) and in the adrenal gland cortex of dogs at clinically relevant exposures. Inflammation was observed in the lungs of dogs dosed for 1 year with a NOAEL at AUC exposures 2.7 (males) and 1.7 (females) times the clinical exposure at the MRHD. No inflammation was observed at the end of 2-month drug-free period at an exposure 4.2 times the clinical exposure at the MRHD; however, inflammation was still present at higher doses.

Hypertrophy of the adrenal gland cortex was observed at 4.1 times the clinical exposure at the MRHD in rats (females only) and at clinically relevant total cariprazine plasma concentrations in mice. In dogs, reversible hypertrophy/hyperplasia and vacuolation/vesiculation of the adrenal gland cortex were observed with a NOAEL 4.2 times the clinical exposure at the MRHD.

In female rats, lower fertility and conception indices were observed at clinically relevant exposures based on mg/m^2 body surface area. No effects on male fertility were noted at exposures up to 4.3 times the clinical exposure at the MRHD.

Administration of cariprazine to rats during the period of organogenesis caused malformations, lower pup survival, and developmental delays at drug exposures less than the human exposure at the MRHD of 6 mg/day. In rabbits, cariprazine caused maternal toxicity, but no foetal toxicity at exposures 5.8 times the clinical exposure at the MRHD.

Administration of cariprazine to pregnant rats during the period of organogenesis, throughout pregnancy and lactation at clinically relevant exposures decreased postnatal survival, birth weight, and post-weaning body weight of first-generation pups. In addition, pale, cold bodies and developmental delays (renal papillae not developed/underdeveloped and decreased auditory startle response in males) were observed in the absence of maternal toxicity. Reproductive performance of the first-generation pups was unaffected; however, second generation pups also had similar clinical signs and lower body weight.

Cariprazine and its metabolites were excreted in milk of rats during lactation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents

Pregelatinized (maize) starch
Magnesium stearate

Capsule shell (1.5 mg capsule)

Titanium dioxide (E 171)
Gelatin

Capsule shell (3 mg capsule)

Allura red AC (E 129)
Brilliant blue FCF (E 133)
Titanium dioxide (E 171)
Yellow iron oxide (E 172)
Gelatin

Capsule shell (4.5 mg capsule)

Allura red AC (E 129)
Brilliant blue FCF (E 133)
Titanium dioxide (E 171)
Yellow iron oxide (E 172)
Gelatin

Capsule shell (6 mg capsule)

Brilliant blue FCF (E 133)
Allura red AC (E 129)
Titanium dioxide (E 171)
Gelatin

Printing ink (black: 1.5 mg, 3 mg and 6 mg capsules)

Shellac
Black iron oxide (E 172)
Propylene glycol
Potassium hydroxide

Printing ink (white: 4.5 mg capsule)

Shellac
Titanium dioxide (E 171)
Propylene glycol
Simeticone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

Keep the blister in the outer carton in order to protect from light.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Transparent hard PVC/PE/PVDC blister heat-sealed with hard aluminium foil backing packed in folded carton box.

Reagila 1.5 mg and Reagila 3 mg hard capsules

Cartons contain 7, 14, 21, 28, 30, 49, 56, 60, 84, 90 or 98 hard capsules.

Reagila 4.5 mg and Reagila 6 mg hard capsules

Cartons contain 7, 21, 28, 30, 49, 56, 60, 84, 90 or 98 hard capsules.

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

Gedeon Richter Plc.
*\|PUL -2W -
1103 Budapest
Hungary

8. MARKETING AUTHORISATION NUMBERS

EU/1/17/1209/001-042

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 July 2017
Date of latest renewal: 04 April 2022

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.

1. NAME OF THE MEDICINAL PRODUCT

Reagila 1.5 mg orodispersible tablets
Reagila 3 mg orodispersible tablets
Reagila 4.5 mg orodispersible tablets
Reagila 6 mg orodispersible tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Reagila 1.5 mg orodispersible tablets

Each orodispersible tablet contains cariprazine hydrochloride corresponding to 1.5 mg cariprazine.

Reagila 3 mg orodispersible tablets

Each orodispersible tablet contains cariprazine hydrochloride corresponding to 3 mg cariprazine.

Reagila 4.5 mg orodispersible tablets

Each orodispersible tablet contains cariprazine hydrochloride corresponding to 4.5 mg cariprazine.

Reagila 6 mg orodispersible tablets

Each orodispersible tablet contains cariprazine hydrochloride corresponding to 6 mg cariprazine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablet

Reagila 1.5 mg orodispersible tablets

White or almost white, triangle, biconvex tablet. The diameter of the tablet is approx. 8 mm and thickness is approx. 3-4 mm.
Engraving on one side is “C2”, the other side is without engraving.

Reagila 3 mg orodispersible tablets

White or almost white, round, biconvex tablet. The diameter of the tablet is 7 mm and thickness is approx. 3-4 mm.
Engraving on one side is “C3”, the other side is without engraving.

Reagila 4.5 mg orodispersible tablets

White or almost white, square, biconvex tablet. The diameter of the tablet is approx. 7 mm and thickness is approx. 3-4 mm.
Engraving on one side is “C4”, the other side is without engraving.

Reagila 6 mg orodispersible tablets

White or almost white, oval, biconvex tablet. The width of the tablet is 5 mm, length is 8.5 mm and thickness is approx. 3-4 mm.
Engraving on one side is “CI”, the other side is without engraving.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Reagila is indicated for the treatment of schizophrenia in adult patients.

4.2 Posology and method of administration

Posology

The recommended starting dose of cariprazine is 1.5 mg once daily. Thereafter the dose can be increased slowly in 1.5 mg increments to a maximum dose of 6 mg/day, if needed. The lowest effective dose should be maintained according to the clinical judgement of the treating physician. Because of the long half-life of cariprazine and its active metabolites, changes in dose will not be fully reflected in plasma for several weeks. Patients should be monitored for adverse reactions and treatment response for several weeks after starting cariprazine and after each dose change (see section 5.2).

Switching from other antipsychotics to cariprazine
When switching from another antipsychotic to cariprazine gradual cross-titration should be considered, with gradual discontinuation of the previous treatment while cariprazine treatment is initiated.

Switching to another antipsychotic from cariprazine
When switching to another antipsychotic from cariprazine, no gradual cross-titration is needed, the new antipsychotic should be initiated in its lowest dose while cariprazine is discontinued. It should be considered that plasma concentration of cariprazine and its active metabolites will decline by 50% in ~1 week (see section 5.2).

Missed dose
If the patient misses a dose, the patient should take the missed dose as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped and the next dose should be taken according to the regular schedule. It is not recommended to take a double dose to make up for the forgotten dose.

Special population

Renal impairment
No dose adjustment is required in patients with mild to moderate renal impairment (Creatinine &OHDUDQFH 30 mL/min and < 89 mL/min). Safety and efficacy of cariprazine have not been evaluated in patients with severe renal impairment (CrCl < 30 mL/min). Use of cariprazine is not recommended in patients with severe renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is required in patients with mild to moderate hepatic impairment (Child-Pugh score between 5-9). Safety and efficacy of cariprazine have not been evaluated in patients with severe hepatic impairment (Child-Pugh score between 10 and 15). Use of cariprazine is not recommended in patients with severe hepatic impairment (see section 5.2).

Elderly
$YDLODEOH GDWD LQ 65 years treated with cariprazine are not sufficient to determine whether or not they respond differently from younger patients (see section 5.2). Dose selection for an elderly patient should be more cautious.

Paediatric population
The safety and efficacy of cariprazine in children and adolescents aged less than 18 years have not

been established. No data are available.

Method of administration

Reagila is for oral use, to be taken once daily at the same time of the day with or without food.
Reagila orodispersible tablets may be used as an alternative to Reagila hard capsules for patients who have difficulty swallowing the hard capsules or for whom there is a preference for orodispersible tablets.
The orodispersible tablet should carefully be removed from the blister with dry hands and immediately placed on the tongue, where it will dissolve and can be swallowed with or without water.
Alternatively, disperse the tablet in water and drink the resulting suspension. In this case, the contents of the glass should be thoroughly stirred to avoid settling down of the undissolved residues.

Alcohol should be avoided when taking cariprazine (see section 4.5).

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 (see section 4.5).
Concomitant administration of strong or moderate CYP3A4 inducers (see section 4.5).

4.4 Special warnings and precautions for use

Suicidal ideation and behaviour

The possibility of suicidality (suicidal ideation, suicide attempt and completed suicide) is inherent in psychotic illnesses and, generally, it is reported early after initiation or switch of antipsychotic therapy. Close supervision of high-risk patients should accompany antipsychotic therapy.

Akathisia, restlessness

Akathisia and restlessness are frequently occurring adverse reactions of antipsychotics. Akathisia is a movement disorder characterized by a feeling of inner restlessness and a compelling need to be in constant motion, as well as by actions such as rocking while standing or sitting, lifting the feet as if marching on the spot, and crossing and uncrossing the legs while sitting. As cariprazine causes akathisia and restlessness, it should be used cautiously in patients who are prone to or already exhibit symptoms of akathisia. Akathisia develops early in treatment. Therefore, close monitoring in the first phase of treatment is important. Prevention includes slow up-titration; treatment measures include slight down-titration of cariprazine or anti-extrapyramidal symptoms (EPS) medicinal product The dose can be modified based on individual response and tolerability (see section 4.8).

Tardive dyskinesia

Tardive dyskinesia is a syndrome consisting of potentially irreversible, rhythmical, involuntary movements, predominantly of the tongue and/or face that can develop in patients treated with antipsychotics. If signs and symptoms of tardive dyskinesia appear in a patient treated with cariprazine, discontinuation should be considered.

Parkinson's disease

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

Ocular symptoms/cataract

In the preclinical studies of cariprazine lens opacity/cataract was detected in dogs (see sections 4.8 and

5.3). However, a causal relationship between lenticular changes / cataracts observed in human studies and cariprazine use has not been established. Nevertheless, patients who would develop symptoms potentially related to cataract should be advised to ophthalmologic examination and re-evaluated for treatment continuation.

Neuroleptic malignant syndrome (NMS)

A potentially fatal symptom complex referred to as NMS has been reported in association with antipsychotic treatment. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, elevated serum creatine phosphokinase levels, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include 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, cariprazine must be discontinued immediately.

Seizures and convulsions

Cariprazine should be used cautiously in patients with history of seizures or with conditions that potentially lower the seizure threshold.

Elderly patients with dementia

Cariprazine has not been studied in elderly patients with dementia and is not recommended to treat elderly patients with dementia due to increased risk of overall mortality.

Risk of cerebrovascular accidents (CVA)

An approximately 3-fold increased risk of CVA has been seen in randomised placebo-controlled clinical studies 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. Cariprazine should be used with caution in patients with risk factors for stroke.

Cardiovascular disorders

Blood pressure changes

Cariprazine can cause orthostatic hypotension as well as hypertension (see section 4.8). Cariprazine should be used with caution in patients with known cardiovascular disease predisposing to blood pressure changes. Blood pressure should be monitored.

Electrocardiogram (ECG) changes

QT prolongation can develop in patients treated with antipsychotics.
With cariprazine no QT interval prolongation was detected compared to placebo in a clinical study designed to assess QT prolongation (see section 5.1). In clinical studies, only a few, non-serious, QT-prolongations have been reported with cariprazine (see section 4.8). Therefore, cariprazine should be used cautiously in patients with known cardiovascular disease or in patients with a family history of QT prolongation and in patients treated with medicinal products that might cause QT prolongation (see section 5.1).

Venous thromboembolism (VTE)

Cases of 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 cariprazine and preventive measures undertaken.

Hyperglycaemia and diabetes mellitus

Patients with an established diagnosis of diabetes mellitus or patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical

antipsychotics should be monitored for serum glucose levels. In clinical studies, glucose-related adverse reactions have been reported with cariprazine (see section 5.1).

Weight change

Significant weight gain has been observed with the use of cariprazine. Patients should have their weight monitored regularly (see section 4.8).

Concomitant treatment with moderate CYP3A4 inhibitors

Co-administration of cariprazine with moderate inhibitors of CYP3A4 may lead to increased total cariprazine exposure. Monitoring of the individual response and tolerability is recommended and, if needed, the cariprazine dose should be (temporarily) reduced to account for the potential increase in exposure (see section 4.5).

Excipients with known effect

This medicinal product contains sodium starch glycolate type A and sodium stearyl fumarate. This medicinal product contains less than 1 mmol sodium (23 mg) per orodispersible tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicinal products to affect cariprazine

Metabolism of cariprazine and its major active metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), is mediated mainly by CYP3A4 with a minor contribution of CYP2D6.

CYP3A4 inhibitors

Ketoconazole, a strong CYP3A4 inhibitor, caused two-fold increase in plasma exposure for total cariprazine (sum of cariprazine and its active metabolites) during short-term (4 days) co-administration, either if unbound or unbound+bound moieties considered.
Due to the long half-life of the active moieties of cariprazine a further increase in plasma exposure of total cariprazine can be expected during longer co-administration. Therefore, co-administration of cariprazine with strong CYP3A4 inhibitors (e.g., boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) is contraindicated (see section 4.3).

Erythromycin (500 mg twice daily), a moderate CYP3A4 inhibitor, caused on average a 1.4-fold (range 1.03-2.32-fold) increase in plasma exposure of total cariprazine after 3 weeks of co-administration. Therefore, during a period of co-administration of cariprazine with a moderate CYP3A4 inhibitor (e.g., erythromycin, fluconazole, diltiazem, verapamil), monitoring of the individual response and tolerability is recommended and, if needed, the cariprazine dose should be (temporarily) reduced to account for the potential increase in exposure. Because of the long half-life of cariprazine and its active metabolites, starting or stopping a treatment with a moderate CYP 3A4 inhibitor or changing the dose will not be fully reflected in plasma drug levels until after several weeks. Patients should be monitored for adverse reactions and treatment response for several weeks after initiating or stopping an interacting drug or after each cariprazine dose change.

Consumption of grapefruit juice should be avoided.

CYP3A4 inducers

Co-administration of cariprazine with strong and moderate inducers of CYP3A4 may result in a significant decrease in total cariprazine exposure, therefore the co-administration of cariprazine and strong or moderate CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampicin, St. John's wort (Hypericum perforatum), bosentan, efavirenz, etravirine, modafinil, nafcillin) is

contraindicated (see section 4.3).

CYP2D6 inhibitors

CYP2D6 mediated pathway plays a minor role in the metabolism of cariprazine, the major pathway is via CYP3A4 (see section 5.2). Therefore, CYP2D6 inhibitors are unlikely to have a clinically relevant effect on cariprazine metabolism.

Potential for cariprazine to affect other medicinal products

P-glycoprotein (Pgp) substrates

Cariprazine is a P-gp inhibitor in vitro at its theoretical maximum intestinal concentration. The clinical consequences of this effect is not fully understood, however the use of P-gp substrates with narrow therapeutic index such as dabigatran and digoxin could require extra monitoring and dose adjustment.

Hormonal contraceptives

In a drug interaction study, 28 days of treatment with cariprazine at 6 mg daily had no clinically relevant effect on the pharmacokinetics of oral contraceptives (ethinylestradiol and levonorgestrel).

Pharmacodynamic interactions

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Women of childbearing potential must be advised to avoid pregnancy while on Reagila. Female patients of child-bearing potential must use highly effective contraceptive methods during treatment and for at least 10 weeks following the last dose of Reagila.

Pregnancy

There are no or limited amount of data from the use of cariprazine in pregnant women.
Studies in animals have shown reproductive toxicity including developmental malformations in rats (see section 5.3).

Reagila is not recommended during pregnancy and in women of childbearing potential not using effective contraception. After discontinuation of cariprazine treatment contraception should be used for at least 10 weeks due to the slow elimination of active moieties.

Neonates exposed to antipsychotics (including cariprazine) 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. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases, neonates have required intensive care unit support and prolonged hospitalization. Consequently, newborns should be monitored carefully.

Breast-feeding

It is unknown whether cariprazine or its major active metabolites are excreted in human milk. Cariprazine and its metabolites are excreted in milk of rats during lactation (see section 5.3). A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with cariprazine.

Fertility

The effect of cariprazine on human fertility has not been evaluated. In rat studies lower female fertility and conception indices were observed (see section 5.3).

4.7 Effects on ability to drive and use machines

Cariprazine has minor or moderate influence on the ability to drive and use machines. Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with Reagila does not affect them adversely.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse drug reactions (ADRs) with cariprazine in the dose range (1.5-6 mg) were akathisia (19%) and parkinsonism (17.5%). Most events were mild to moderate in severity.

Tabulated list of adverse reactions

ADRs based upon pooled data from cariprazine schizophrenia studies are shown by system organ class and by preferred term in Table 1.

Adverse reactions are ranked by MedDRA system organ class and by frequency, the most frequent ILUVW XVLQJ WKH IROORZLQJ FRQYHQWLRQ YHU\ FRPPRQ WR UDUH 000) very rare (<1/10 000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse drug reactions occurring in patients with schizophrenia

MedDRA System Organ Class	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)	Frequency not known
Blood and lymphatic system disorders			Anaemia Eosinophilia	Neutropenia	
Immune system disorders				Hypersensitivity	
Endocrine disorders			Blood thyroid stimulating hormone decreased	Hypothyroidism	
Metabolism and nutrition disorders		Dyslipidaemia Weight increased Decreased appetite Increased appetite	Blood sodium abnormal Diabetes mellitus Blood glucose increased		
Psychiatric disorders		Sleep disorders[1] Anxiety	Suicidal behaviour Delirium Depression Libido decreased		

			Libido increased Erectile dysfunction		
Nervous system disorders	Akathisia[2] Parkinsonism[3]	Sedation Dizziness Dystonia[4] Other extrapyramidal diseases and abnormal movement disorders[5]	Tardive dyskinesia Dyskinesia[6] Dysaesthesia Lethargy	Seizures/ Convulsion Amnesia Aphasia	Neuroleptic malignant syndrome
Eye disorders		Vision blurred	Intraocular pressure increased Accommodation disorder Visual acuity reduced Eye irritation	Cataract Photophobia	
Ear and labyrinth disorders			Vertigo		
Cardiac disorders		Tachyarrhythmia	Cardiac conduction disorders Bradyarrhythmia Electrocardiogram QT prolonged Electrocardiogram T wave abnormal		
Vascular disorders		Hypertension	Hypotension		
Respiratory, thoracic and mediastinal disorders			Hiccups		
Gastrointestinal disorders		Vomiting Nausea Constipation	Gastrooesophageal reflux disease	Dysphagia	
Hepatobiliary disorders		Hepatic enzymes increased	Blood bilirubin increased		Toxic hepatitis
Skin and subcutaneous tissue disorders			Pruritus Rash		
Musculoskeletal and connective tissue disorders		Blood creatine phosphokinase increased		Rhabdomyolysis	

Renal and urinary disorders			Dysuria Pollakisuria		
Pregnancy, puerperium and perinatal conditions					Drug withdrawal syndrome neonatal (see section 4.6)
General disorders and administration site conditions		Fatigue	Thirst		

[1]Sleep disorders: Insomnia, Abnormal dreams/nightmare, Circadian rhythm sleep disorder, Dyssomnia, Hypersomnia, Initial insomnia, Middle insomnia, Nightmare, Sleep disorder, Somnambulism, Terminal insomnia
[2]Akathisia: Akathisia, Psychomotor hyperactivity, Restlessness
[3]Parkinsonism: Akinesia, Bradykinesia, Bradyphrenia, Cogwheel rigidity, Extrapyramidal disorder, Gait disturbance, Hypokinesia, Joint stiffness, Tremor, Masked facies, Muscle rigidity, Musculoskeletal stiffness, Nuchal rigidity, Parkinsonism
[4]Dystonia: Blepharospasm, Dystonia, Muscle tightness, Oromandibular dystonia, Torticollis, Trismus
[5]Other extrapyramidal diseases and abnormal movement disorders: Balance disorder, Bruxism, Drooling, Dysarthria, Gait deviation, Glabellar reflex abnormal, Hyporeflexia, Movement disorder, Restless legs syndrome, Salivary hypersecretion, Tongue movement disturbance
[6]Dyskinesia: Choreoathetosis, Dyskinesia, Grimacing, Oculogyric crisis, Protrusion tongue

Description of selected adverse reactions

Lens opacity/Cataract

Development of cataracts was observed in cariprazine non-clinical studies (see section 5.3). Therefore, cataract formation was closely monitored with slit lamp examinations in the clinical studies and patients with existing cataracts were excluded. During the schizophrenia clinical development program of cariprazine, few cataract cases were reported, characterized with minor lens opacities with no visual impairment (13/3 192; 0.4%). Some of these patients had confounding factors. The most commonly reported ocular adverse event was blurred vision (placebo: 1/683; 0.1%, cariprazine: 22/2 048; 1.1%).

Extrapyramidal symptoms (EPS)

In the short-term studies the incidence of EPS was observed in 27%; 11.5%; 30.7% and 15.1% in patients treated with cariprazine, placebo, risperidone and aripiprazole respectively. Akathisia was reported in 13.6%; 5.1%; 9.3% and 9.9% in patients treated with cariprazine, placebo, risperidone and aripiprazole respectively. Parkinsonism was experienced in 13.6%; 5.7%; 22.1% and 5.3% in patients treated with cariprazine, placebo, risperidone and aripiprazole respectively. Dystonia was observed in 1.8%; 0.2%; 3.6% and 0.7% in patients on cariprazine, placebo, risperidone and aripiprazole, respectively.

In the placebo-controlled part of the long-term maintenance of effect study EPS was 13.7% in the cariprazine group compared to 3.0% in the placebo treated patients. Akathisia was reported in 3.9% in patients treated with cariprazine, versus 2.0% in the placebo group. Parkinsonism was experienced in 7.8% and 1.0% in cariprazine and placebo group respectively.

In the negative symptom study EPS was reported in 14.3% in the cariprazine group and 11.7% in the risperidone treated patients. Akathisia was reported in 10.0% in patients treated with cariprazine and 5.2% in the risperidone group. Parkinsonism was experienced in 5.2% and 7.4% in cariprazine and risperidone treated patients respectively. Most EPS cases were mild to moderate in intensity and could be handled with common anti-EPS medicinal products. The rate of discontinuation due to EPS related ADRs was low.

Venous thromboembolism (VTE)
Cases of VTE, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotics - Frequency unknown.

Elevated liver transaminases
Elevated liver transaminases (Alanine Aminotransferase [ALT], Aspartate Aminotransferase [AST]) are frequently observed with antipsychotic treatment. In the cariprazine clinical studies the incidence of ALT, AST elevation ADRs occurred in 2.2% of cariprazine-, 1.6% of risperidone- and 0.4% of placebo-treated patients. None of the cariprazine-treated patients had any liver damage.

Weight changes
In the short-term studies, there were slightly greater mean increases in body weight in the cariprazine group compared to the placebo group; 1 kg and 0.3 kg, respectively. In the long-term maintenance of effect study, there was no clinically relevant difference in change of body weight from baseline to end of treatment (1.1 kg for cariprazine and 0.9 kg for placebo). In the open-label phase of the study during 20 weeks cariprazine treatment 9.0% of patients developed potentially clinically significant (PCS) weight gain, while during the double-blind phase, 9.8 % of the patients who continued with cariprazine treatment had PCS weight gain versus 7.1% of the patients who were randomized to placebo after the 20 week open-label cariprazine treatment. In the negative symptom study, the mean change of body weight was -0.3 kg for cariprazine and +0.6 kg for risperidone and PCS weight gain was observed in 6% of the cariprazine group while 7.4% of the risperidone group.

QT- prolongation
With cariprazine no QT interval prolongation was detected compared to placebo in a clinical study designed to assess QT prolongation (see section 5.1). In other clinical studies, only a few, non-serious, QT-prolongations have been reported with cariprazine. During the long-term, open-label treatment period in, 3 patients (0.4%) had QTcB > 500 msec, one of whom also had QTcF > 500 msec. A > 60 msec increase from baseline was observed in 7 patients (1%) for QTcB and in 2 patients (0.3%) for QTcF. In the long-term, maintenance of effect study, during the open-label phase, > 60 msec increase of from baseline was observed in 12 patients (1.6%) for QTcB and in 4 patients (0.5%) for QTcF. During the double-blind treatment period, > 60 msec increases from baseline in QTcB were observed in 3 cariprazine-treated patients (3.1%) and 2 placebo-treated patients (2%).

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

Symptoms

Accidental acute overdose (48 mg/day) was reported in one patient. This patient experienced orthostasis and sedation. The patient fully recovered the same day.

Management of overdose

Management of overdose should concentrate on supportive therapy including maintenance of an adequate airway, oxygenation and ventilation and management of symptoms. Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. In case of severe extrapyramidal symptoms, anticholinergic medicinal products should be administered. Since cariprazine is highly bound to plasma proteins, haemodialysis is unlikely to be useful in the management of overdose. Close medical supervision and monitoring should continue until the patient recovers.

There is no specific antidote to cariprazine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, other antipsychotics, ATC code: N05AX15

Mechanism of action

The mechanism of action of cariprazine is not fully known. However, the therapeutic effect of cariprazine may be mediated through a combination of partial agonist activity at dopamine D_3, D_2 (Ki values of 0.085-0.3 nM versus 0.49-0.71 nM respectively) and serotonin 5-HT_{1A} receptors (Ki values of 1.4-2.6 nM), and antagonist activity at serotonin 5-HT_{2B}, 5-HT_{2A} and histamine H_1 receptors (Ki values of 0.58-1.1 nM, 18.8 nM and 23.3 nM, respectively). Cariprazine has low affinity for serotonin 5-HT_{2C} and adrenergic α1 receptors (Ki values of [illegible] nM and 155 nM, respectively). Cariprazine has no appreciable affinity for cholinergic muscarinic receptors (IC_{50} > 1 000 nM). The two major active metabolites, desmethyl cariprazine and didesmethyl cariprazine have a similar *in vitro* receptor binding and functional activity profile as the parent active substance.

Pharmacodynamic effects

In vivo non-clinical studies demonstrated that cariprazine occupies D_3 receptors to a similar extent as D_2 receptors at pharmacologically effective doses. There was a dose-dependent occupancy of brain dopamine D_3 and D_2 receptors (with preferential occupancy in regions with higher D_3 expression) in patients with schizophrenia within the therapeutic dose range of cariprazine for 15 days.

The effects of cariprazine on the QT interval were evaluated in patients with schizophrenia or schizoaffective disorder. Holter monitor-derived electrocardiographic assessments were obtained in 129 patients over a twelve hour period at baseline and steady state. No QT interval prolongation was detected following supratherapeutic doses (9 mg/day or 18 mg/day). No patients treated with cariprazine experienced QTc increases ≥ 60 msec from baseline, nor did any patient experience a QTc of > 500 msec in the study.

Clinical efficacy and safety

Efficacy with short-term use

The efficacy of cariprazine for the treatment of acute schizophrenia was studied in three multi-center, multinational, randomized, double-blind, placebo-controlled 6-week studies including 1 754 patients with the age of 18 to 60 years. The primary endpoint was change from baseline to week 6 in the Positive and Negative Syndrome Scale (PANSS) total score and the secondary endpoint was change from baseline to week 6 in the Clinical Global Impressions-Severity (CGI-S) score in all acute schizophrenia studies. In a multinational placebo-controlled study using fixed doses of 1.5 mg, 3.0 mg and 4.5 mg cariprazine and 4.0 mg risperidone for assay sensitivity, all cariprazine doses and the active-control showed statistically significant improvement in both primary as well as secondary endpoint compared to placebo. In another multinational placebo-controlled study using fixed doses of 3.0 mg, and 6.0 mg cariprazine and 10 mg aripiprazole for assay sensitivity, both cariprazine doses and the active-control showed statistically significant improvement in both primary as well as secondary endpoint compared to placebo. In a third multinational placebo-controlled study using fixed/flexible doses of 3.0-6.0 mg and 6.0-9.0 mg cariprazine, both cariprazine doses groups showed statistically significant improvement in both primary as well as secondary endpoint compared to placebo.
Results for the primary outcome parameter are summarized in Table 2 below. Results for the secondary outcome parameter (CGI) and additional endpoints were supportive of the primary endpoint.

Table 2. Change from baseline to week 6 in the PANSS total score in studies of acute exacerbations of schizophrenia—ITT population

	Baseline Mean ± SD	**Change LS mean (SE)**	**Treatment difference versus placebo (95% CI)**	**P-value**
PANSS total (MMRM)				
RGH-MD-16 (n=711)				
Placebo	97.3 ± 9.22	–13.29 (1.82)	—	—
Cariprazine 1.5 mg/day	97.1 ± 9.13	–21.27 (1.77)	–7.97 (–12.94, –3.01)	**0.0017**
Cariprazine 3 mg/day	97.2 ± 8.66	–21.45 (1.74)	–8.16 (–13.09, –3.22)	**0.0013**
Cariprazine 4.5 mg/day	96.7 ± 9.01	–23.77 (1.74)	–10.48 (–15.41, –5.55)	**< 0.0001**
Risperidone 4 mg/day	98.1 ± 9.50	–29.27 (1.74)	–15.98 (–20.91, –11.04)	< 0.0001*
RGH-MD-04 (n=604)				
Placebo	96.5 ± 9.1	–14.3 (1.5)	—	—
Cariprazine 3 mg/day	96.1 ± 8.7	–20.2 (1.5)	–6.0 (–10.1, –1.9)	**0.0044**
Cariprazine 6 mg/day	95.7 ± 9.4	–23.0 (1.5)	–8.8 (–12.9, –4.7)	**< 0.0001**
Aripiprazole 10 mg/day	95.6 ± 9.0	–21.2 (1.4)	–7.0 (–11.0, –2.9)	0.0008*
RGH-MD-05 (n=439)				
Placebo	96.6 ± 9.3	–16.0 (1.6)	—	—
Cariprazine 3 to 6 mg/day	96.3 ± 9.3	–22.8 (1.6)	–6.8 (–11.3, –2.4)	**0.0029**
Cariprazine 6 to 9 mg/day	96.3 ± 9.0	–25.9 (1.7)	–9.9 (–14.5, –5.3)	**< 0.0001**

CI = confidence interval; ITT = intent to treat; LS mean = least squares mean; PANSS = Positive and Negative Syndrome Scale.
*compared to placebo

Efficacy with long-term use

The efficacy of cariprazine for maintaining antipsychotic effect was investigated in a randomized-withdrawal, long-term clinical study. Totally, 751 patients with acute symptoms of schizophrenia received cariprazine 3-9 mg/day for 20 weeks, of whom 337 received cariprazine in the dose-range of 3 or 6 mg/day. Stabilized patients were then randomised to receive fixed doses of 3 or 6 mg cariprazine (n=51) or placebo (n=51) in a double-blind manner for up to 72 weeks. The primary outcome of the study was time to relapse. By the end of the study 49.0% of placebo-treated patients versus 21.6% of cariprazine-treated patients had a relapse of schizophrenic symptoms. Time to relapse (92 vs. 326 days-based on the 25th percentile) was therefore significantly longer in the cariprazine group than in the placebo group (p=0.009).

Efficacy in predominantly negative symptoms of schizophrenia

The efficacy of cariprazine for the treatment of predominantly negative symptoms of schizophrenia was investigated in a 26-week, multi-centre, double-blind, and active-controlled clinical study. Cariprazine (dose range 3-6 mg, target dose 4.5 mg) was investigated compared to risperidone (dose range 3-6 mg, target dose 4 mg) in patients with persistent, predominant negative symptoms of schizophrenia (n=461). 86% of patients were less than 55 years old, 54% of them were male.

Persistent predominant negative symptoms were defined as symptoms lasting for a period of at least 6 months with high level of negative symptoms and low level of positive symptoms [(PANSS factor VFRUH IRU QHJDWLYH V\PSWRPV 4 in a minimum 2 of the 3 PANSS items (N1: flat affect, N4: avolition, and N6: poverty of speech) and PANSS factor score for positive symptoms 19]. Patients with secondary negative symptoms, such as moderate to severe depressive symptoms and clinically relevant parkinsonism (EPS) were excluded.

Both cariprazine- and risperidone-treated patient groups have shown statistically significant

improvement in the change from baseline for the primary efficacy parameter, PANSS factor score for negative symptoms (PANSS-FSNS) ($p < 0.001$). However, a statistically significant difference ($p=0.002$) in favour of cariprazine over risperidone was observed from Week 14 onward (Table 3). Both cariprazine- and risperidone-treated patient groups have shown statistically significant improvement in the change from baseline for the secondary efficacy parameter, Personal and Social Performance (PSP) total score ($p < 0.001$). However, a statistically significant difference ($p < 0.001$) in favour of cariprazine over risperidone was observed from Week 10 onward (Table 3). Differences on the Clinical Global Impression Severity ($p=0.005$) and Improvement ($p < 0.001$) scales, as well as PANSS-FSNS response rates (3 $ 1 6 6) 6 136% improvement at Week 26; $p=0.003$) were supportive of findings on the primary and secondary efficacy parameters.

Table 3 Summary of results in study RGH-188-005

Efficacy parameter	Cariprazine LS mean	Risperidone LS mean	Estimated treatment difference	95% CI	p-value
PANSS-FSNS at Baseline	27.8	27.5	-	-	-
PANSS-FSNS at Week 26	18.5	19.6	-	-	-
PANSS-FSNS CfB to Week 26	-8.9	-7.4	-1.5	-2,4; -0.5	0.002
Total PSP at Baseline	48.8	48.2	-	-	-
Total PSP at Week 26	64.0	59.7	-	-	-
Total PSP CfB to Week 26	14.3	9.7	4.6	2.7; 6.6	<0.001

CfB= change from baseline

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with cariprazine in one or more subsets of the paediatric population in the treatment of schizophrenia. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Cariprazine has two pharmacologically active metabolites with similar activities as cariprazine, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR). Total cariprazine (sum of cariprazine + DCAR and DDCAR) exposure approaches 50% of steady state exposure in ~1 week of daily dosing while 90% of steady state is achieved in 3 weeks. At steady state, exposure to DDCAR is approximately two to three-fold higher than to cariprazine, and exposure to DCAR is approximately 30% of cariprazine exposure.

Absorption

Absolute bioavailability of cariprazine is unknown. Cariprazine is well absorbed after oral administration. Following multiple-dose administration, peak plasma concentrations for cariprazine and the major active metabolites generally occur at approximately 3-8 hours post dose. Administration of a single dose of 1.5 mg cariprazine with a high-fat meal (900 to 1 000 calories) did not significantly affect the C_{max} or AUC of cariprazine (AUC_{0-} increased by 12%, C_{max} decreased by < 5% under fed condition versus fasting). The effect of food on the exposure of the metabolites DCAR and DDCAR was also minimal. The orodispersible tablets can be considered bioequivalent with the hard capsule formulation.

Cariprazine can be administered with or without food.

Distribution

Based on a population pharmacokinetic analysis, the apparent volume of distribution (V/F) was 916 L for cariprazine, 475 L for DCAR and 1 568 L for DDCAR, indicating extensive distribution of cariprazine and its major active metabolites. Cariprazine and its major active metabolites are highly bound (96 to 97% for CAR, 94% to 97% for DCAR and 92% to 97% for DDCAR) to plasma proteins.

Biotransformation

The metabolism of cariprazine involves demethylation (DCAR and DDCAR), hydroxylation (hydroxy cariprazine, HCAR) and a combination of demethylation and hydroxylation (hydroxy desmethyl cariprazine, HDCAR and hydroxy didesmethyl cariprazine, HDDCAR). The metabolites of HCAR, HDCAR, and HDDCAR are subsequently biotransformed to their corresponding sulfate and glucuronide conjugates. An additional metabolite, desdichlorophenyl piperazine cariprazine (DDCPPCAR) acid, is produced by dealkylation and subsequent oxidation of cariprazine. Cariprazine is metabolized by CYP3A4 and, to a lesser extent, by CYP2D6, to DCAR and HCAR. DCAR is further metabolized by CYP3A4 and to a lesser extent by CYP2D6 into DDCAR and HDCAR. DDCAR is further metabolised to HDDCAR by CYP3A4.

Cariprazine and its major active metabolites are not substrates of P-glycoprotein (P-gp), the organic anion transporting polypeptide 1B1 and 1B3 (OATP1B1 and OATP1B3), and the breast cancer resistance protein (BCRP). This suggests that an interaction of cariprazine with inhibitors of P-gp, OATP1B1, OATP1B3 and BCRP is unlikely.

Elimination

Elimination of cariprazine and its major active metabolites is mainly through hepatic metabolism. Following administration of 12.5 mg/day cariprazine to patients with schizophrenia, 20.8% of the dose was excreted in urine as cariprazine and its metabolites.

Unchanged cariprazine is excreted by 1.2% of the dose in urine and 3.7% of the dose in faeces.

The mean terminal half-life (1 to 3 days for cariprazine and DCAR and 13 to 19 days for DDCAR) is not predictive of time to reach steady state or plasma concentration decline after treatment discontinuation. For the management of patients treated with cariprazine, the effective half-life is more relevant than the terminal half-life. The effective (functional) half-life is ~ 2 days for cariprazine and DCAR, 8 days for DDCAR and is ~1 week for total cariprazine. The plasma concentration of total cariprazine will gradually decline following dose discontinuation or interruption. The plasma concentration of total cariprazine decreases by 50% in ~1 week and greater than 90% decline in total cariprazine concentration occurs in ~3 weeks.

Linearity

After repeated administration plasma exposure of cariprazine and its two major active metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), increases proportionally over the therapeutic dose range of 1.5 to 6 mg.

Special populations

Renal impairment

Population pharmacokinetic modelling was performed using data from patients enrolled in the schizophrenia cariprazine clinical program with differing levels of renal function, including normal UHQDO IXQFWLRQ FUHDWLQLQH FOHDUDQFH &U&O PO PLQ DV ZHOO DV PLOG &U&O WR PO PLQ DQG moderate (CrCl 30 to 59 mL/min) renal impairment. No significant relationship was found between cariprazine plasma clearance and creatinine clearance.

Cariprazine has not been evaluated in patients with severe (CrCl < 30 mL/min) renal impairment (see section 4.2).

Hepatic impairment

A 2-part study (a single dose of 1 mg cariprazine [Part A] and a daily dose of 0.5 mg cariprazine for 14 days [Part B] was conducted in patients with varying degrees of impaired hepatic function (Child-Pugh Classes A and B). Compared to healthy subjects, patients with either mild or moderate hepatic impairment had up to approximately 25% higher exposure (C_{max} and AUC) for cariprazine and up to approximately 45% lower exposure for the major active metabolites, desmethyl cariprazine and didesmethyl cariprazine, following the single dose of 1 mg cariprazine or 0.5 mg cariprazine for 14 days.

The total active moiety (CAR+DCAR+DDCAR) exposure (AUC and C_{max}) decreased by 21-22% and 13-15% in mild or moderate hepatic impairment (HI), respectively, compared to healthy subjects if unbound + bound concentrations were considered, while for unbound total moiety a decrease of 12-13% and an increase of 20-25% were calculated in mild HI patients and in moderate HI patients, respectively, after multiple dosing of cariprazine.

Cariprazine has not been evaluated in patients with severe hepatic impairment (Child-Pugh Class C) (see section 4.2).

Age, gender and race

In the population PK analysis there were no clinically relevant differences in the PK parameters (AUC and C_{max} of the sum of cariprazine and its major active metabolites) based on age, gender and race. This analysis included 2 844 patients of different races, involving 536 patients between the ages of 50 and 65. Of the 2 844 patients 933 were female (see section 4.2). In elderly patients above 65 years of age data are limited.

Smoking status

Because cariprazine is not a substrate for CYP1A2, smoking is not expected to have an effect on the pharmacokinetics of cariprazine.

Potential for cariprazine to affect other medicinal products

Cariprazine and its major active metabolites did not induce CYP1A2, CYP2B6 and CYP3A4 enzymes and were not inhibitors of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP219, CYP2D6, CYP2E1 and CYP3A4 *in vitro*. Cariprazine and its major active metabolites are not inhibitors of transporters OATP1B1, OATP1B3, BCRP, organic cation transporter 2 (OCT2), and organic anion transporters 1 and 3 (OAT1 and OAT3) *in vitro*. DCAR and DDCAR were not inhibitors of transporter P-gp although cariprazine was a P-gp inhibitor in the intestine (see section 4.5).

5.3 Preclinical safety data

Cariprazine caused bilateral cataract and secondary retinal changes (retinal detachment and cystic degeneration) in the dog. The exposure (AUC of total cariprazine) at the no-observed-adverse-effect-level (NOAEL) for ocular toxicity is 4.2-fold the clinical AUC exposure at the maximal recommended human dose (MRHD) of 6 mg/day. Increased incidence of retinal degeneration/atrophy was observed in albino rats in the 2-year study at clinically relevant exposures.

Phospholipidosis was observed in the lungs of rats, dogs, and mice (with or without inflammation) and in the adrenal gland cortex of dogs at clinically relevant exposures. Inflammation was observed in the lungs of dogs dosed for 1 year with a NOAEL at AUC exposures 2.7 (males) and 1.7 (females) times the clinical exposure at the MRHD. No inflammation was observed at the end of 2-month drug-free period at an exposure 4.2 times the clinical exposure at the MRHD; however, inflammation was still present at higher doses.

Hypertrophy of the adrenal gland cortex was observed at 4.1 times the clinical exposure at the MRHD in rats (females only) and at clinically relevant total cariprazine plasma concentrations in mice. In dogs, reversible hypertrophy/hyperplasia and vacuolation/vesiculation of the adrenal gland cortex were observed with a NOAEL 4.2 times the clinical exposure at the MRHD.

In female rats, lower fertility and conception indices were observed at clinically relevant exposures based on mg/m^2 body surface area. No effects on male fertility were noted at exposures up to 4.3 times the clinical exposure at the MRHD.

Administration of cariprazine to rats during the period of organogenesis caused malformations, lower pup survival, and developmental delays at drug exposures less than the human exposure at the MRHD of 6 mg/day. In rabbits, cariprazine caused maternal toxicity, but no foetal toxicity at exposures 5.8 times the clinical exposure at the MRHD.

Administration of cariprazine to pregnant rats during the period of organogenesis, throughout pregnancy and lactation at clinically relevant exposures decreased postnatal survival, birth weight, and post-weaning body weight of first-generation pups. In addition, pale, cold bodies and developmental delays (renal papillae not developed/underdeveloped and decreased auditory startle response in males) were observed in the absence of maternal toxicity. Reproductive performance of the first-generation pups was unaffected; however, second generation pups also had similar clinical signs and lower body weight.

Cariprazine and its metabolites were excreted in milk of rats during lactation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E 421)
Maize starch
Sodium starch glycolate type A
Malic acid (E 296)
Sodium stearyl fumarate (E 485)
Silicon dioxide (E 551)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Keep the tablets in the original packaging in order to protect from moisture.
This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Blisters made of PA/Al/PVC foil (forming foil) and Paper/PET/Al blister lidding foil with peelable functionality (sealing foil) and are packed in folded carton box.

<u>Reagila 1.5 mg, 3 mg, 4.5 mg and 6 mg orodispersible tablets</u>

Cartons contain 28 or 30 orodispersible tablets.

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

Gedeon Richter Plc.
*\|PU L -2W -
1103 Budapest
Hungary

8. MARKETING AUTHORISATION NUMBERS

EU/1/17/1209/043-050

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13 July 2017
Date of latest renewal: 04 April 2022

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

Gedeon Richter Plc.
*\|PU L -21W -
1103 Budapest
HUNGARY

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

folded carton

1. NAME OF THE MEDICINAL PRODUCT

Reagila 1.5 mg hard capsules
cariprazine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains cariprazine hydrochloride corresponding to 1.5 mg cariprazine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

7 hard capsules
14 hard capsules
21 hard capsules
28 hard capsules
30 hard capsules
49 hard capsules
56 hard capsules
60 hard capsules
84 hard capsules
90 hard capsules
98 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

QR code to be included
www.reagila.com

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

Keep the blister in the outer carton 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

Gedeon Richter Plc.
*\|PUL-2W -
1103 Budapest, Hungary

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1209/001-010 {7×,14×,28×,30×,49×,56×,60×,84×,90×,98×}
EU/1/17/1209/037 {21×}

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

reagila 1.5 mg hard capsules

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

blisterfoil

1. NAME OF THE MEDICINAL PRODUCT

Reagila 1.5 mg hard capsules
cariprazine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

folded carton

1. NAME OF THE MEDICINAL PRODUCT

Reagila 3 mg hard capsules
cariprazine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains cariprazine hydrochloride corresponding to 3 mg cariprazine.

3. LIST OF EXCIPIENTS

Also contains Allura red AC (E 129). See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

7 hard capsules
14 hard capsules
21 hard capsules
28 hard capsules
30 hard capsules
49 hard capsules
56 hard capsules
60 hard capsules
84 hard capsules
90 hard capsules
98 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

QR code to be included
www.reagila.com

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

Keep the blister in the outer carton 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

Gedeon Richter Plc.
*\|PUL-2W-
1103 Budapest, Hungary

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1209/011-020 {7×,14×,28×,30×,49×,56×,60×,84×,90×,98×}
EU/1/17/1209/038 {21×}

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

reagila 3 mg hard capsules

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

blisterfoil

1. NAME OF THE MEDICINAL PRODUCT

Reagila 3 mg hard capsules
cariprazine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

folded carton

1. NAME OF THE MEDICINAL PRODUCT

Reagila 4.5 mg hard capsules
cariprazine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains cariprazine hydrochloride corresponding to 4.5 mg cariprazine.

3. LIST OF EXCIPIENTS

Also contains Allura red AC (E 129). See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

7 hard capsules
21 hard capsules
28 hard capsules
30 hard capsules
49 hard capsules
56 hard capsules
60 hard capsules
84 hard capsules
90 hard capsules
98 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

QR code to be included
www.reagila.com

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

Keep the blister in the outer carton 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

Gedeon Richter Plc.
*\|PU L -2W -
1103 Budapest, Hungary

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1209/021-028	{28×,30×,49×,56×,60×,84×,90×,98×}
EU/1/17/1209/039	{21×}
EU/1/17/1209/041	{7×}

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

reagila 4.5 mg hard capsules

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

blisterfoil

1. NAME OF THE MEDICINAL PRODUCT

Reagila 4.5 mg hard capsules
cariprazine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

folded carton

1. NAME OF THE MEDICINAL PRODUCT

Reagila 6 mg hard capsules
cariprazine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains cariprazine hydrochloride corresponding to 6 mg cariprazine.

3. LIST OF EXCIPIENTS

Also contains Allura red AC (E 129). See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule

7 hard capsules
21 hard capsules
28 hard capsules
30 hard capsules
49 hard capsules
56 hard capsules
60 hard capsules
84 hard capsules
90 hard capsules
98 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

QR code to be included
www.reagila.com

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

Keep the blister in the outer carton 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

Gedeon Richter Plc.
*\|PU L -2W -
1103 Budapest, Hungary

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1209/029-036	{28×,30×,49×,56×,60×,84×,90×,98×}
EU/1/17/1209/040	{21×}
EU/1/17/1209/042	{7×}

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

reagila 6 mg hard capsules

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

blisterfoil

1. NAME OF THE MEDICINAL PRODUCT

Reagila 6 mg hard capsules
cariprazine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

folded carton

1. NAME OF THE MEDICINAL PRODUCT

Reagila 1.5 mg orodispersible tablets
cariprazine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each orodispersible tablet contains cariprazine hydrochloride corresponding to 1.5 mg cariprazine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Orodispersible tablet

28 orodispersible tablets
30 orodispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

QR code to be included
www.reagila.com

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

Keep the tablets in the original packaging 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

Gedeon Richter Plc.
*\|PU L -2W -
1103 Budapest, Hungary

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1209/043-044 {28×,30×}

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

reagila 1.5 mg orodispersible tablets

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

blisterfoil

1. NAME OF THE MEDICINAL PRODUCT

Reagila 1.5 mg orodispersible tablets
cariprazine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

folded carton

1. NAME OF THE MEDICINAL PRODUCT

Reagila 3 mg orodispersible tablets
cariprazine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each orodispersible tablet contains cariprazine hydrochloride corresponding to 3 mg cariprazine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Orodispersible tablet

28 orodispersible tablets
30 orodispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

QR code to be included
www.reagila.com

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

Keep the tablets in the original packaging 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

Gedeon Richter Plc.
*\|PU L -2W -
1103 Budapest, Hungary

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1209/045-046 {28×,30×}

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

reagila 3 mg orodispersible tablets

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

blisterfoil

1. NAME OF THE MEDICINAL PRODUCT

Reagila 3 mg orodispersible tablets
cariprazine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

folded carton

1. NAME OF THE MEDICINAL PRODUCT

Reagila 4.5 mg orodispersible tablets
cariprazine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each orodispersible tablet contains cariprazine hydrochloride corresponding to 4.5 mg cariprazine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Orodispersible tablet

28 orodispersible tablets
30 orodispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

QR code to be included
www.reagila.com

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

Keep the tablets in the original packaging 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

Gedeon Richter Plc.
*\|PU L -2W -
1103 Budapest, Hungary

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1209/047-048 {28×,30×}

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

reagila 4.5 mg orodispersible tablets

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

blisterfoil

1. NAME OF THE MEDICINAL PRODUCT

Reagila 4.5 mg orodispersible tablets
cariprazine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

folded carton

1. NAME OF THE MEDICINAL PRODUCT

Reagila 6 mg orodispersible tablets
cariprazine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each orodispersible tablet contains cariprazine hydrochloride corresponding to 6 mg cariprazine.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Orodispersible tablet

28 orodispersible tablets
30 orodispersible tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use.

QR code to be included
www.reagila.com

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

Keep the tablets in the original packaging 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

Gedeon Richter Plc.
*\|PU L -2W -
1103 Budapest, Hungary

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1209/049-050 {28×,30×}

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

reagila 6 mg orodispersible tablets

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

blisterfoil

1. NAME OF THE MEDICINAL PRODUCT

Reagila 6 mg orodispersible tablets
cariprazine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Reagila 1.5 mg hard capsules
Reagila 3 mg hard capsules
Reagila 4.5 mg hard capsules
Reagila 6 mg hard capsules
cariprazine

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. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Reagila is and what it is used for

Reagila contains the active substance cariprazine and belongs to a group of medicines called antipsychotics. It is used to treat adults with schizophrenia.

Schizophrenia is a disease characterised by symptoms such as hearing, seeing or sensing things which are not there (hallucination), suspiciousness, mistaken beliefs, incoherent speech and behaviour and emotional flatness. People with this condition may also feel depressed, guilty, anxious, tense, or not being able to start or keep up planned activities, unwillingness to speak, lack of emotional response to a situation that would normally stimulate feelings in others.

2. What you need to know before you take Reagila

Do not take Reagila
- if you are allergic to cariprazine or any of the other ingredients of this medicine (listed in section 6).
- if you are taking medicines used to treat:
  - hepatitis caused by the hepatitis C virus (medicines containing boceprevir and telaprevir)
  - bacterial infections (medicines containing clarithromycin, telithromycin and nafcillin)
  - tuberculosis (medicines containing rifampicin)
  - HIV infections (medicines containing cobicistat, indinavir, nelfinavir, ritonavir, saquinavir, efavirenz and etravirine)
  - fungal infections (medicines containing itraconazole, posaconazole and voriconazole)
  - Cushing's syndrome - when the body produces an excess of cortisol (medicines containing ketoconazole)
  - depression (herbal therapy containing St. John's wort (Hypericum perforatum) and medicines containing nefazodone)
  - epilepsy and seizures (medicines containing carbamazepine, phenobarbital and

phenytoin)
- sleepiness (medicines containing modafinil)
- high blood pressure in the lungs (medicines containing bosentan).

Warnings and precautions
Tell your doctor immediately:
- if you are having any thoughts or feelings about harming yourself or to commit suicide. Suicidal thoughts and behaviours are more likely at the beginning of the treatment.
- if you experience a combination of fever, sweating, faster breathing, muscle stiffness and drowsiness or sleepiness (may be signs of neuroleptic malignant syndrome).

Talk to your doctor or pharmacist before taking Reagila, or during treatment if you have:
- ever experienced or start to experience restlessness and inability to sit still. These symptoms may occur early during treatment with Reagila. Tell your doctor if this happens.
- ever experienced or start to experience abnormal, involuntary movements, most commonly of the tongue or face. Tell your doctor if this happens.
- visual impairment. Your doctor will advise you to visit an ophthalmologist.
- irregular heartbeat or if someone else in your family has a history of irregular heartbeat (including so called QT prolongation seen with electrocardiogram (ECG) monitoring), and tell your doctor if you are taking other medicines, because they might cause or worsen this ECG change.
- high or low blood pressure, cardiovascular disease. Your doctor will need to check your blood pressure regularly.
- dizziness on standing up due to a drop in your blood pressure, which may cause fainting
- 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.
- a history of stroke, especially if you are elderly or know that you have other risk factors for stroke. Tell your doctor immediately if you notice any signs of a stroke.
- dementia (loss of memory and other mental abilities) especially if you are elderly.
- Parkinson's disease.
- if you have diabetes or risk factors for diabetes (e.g. obesity, or someone else in your family has diabetes). Your doctor will need to check your blood sugar regularly since it may be increased by Reagila. Signs of high blood sugar level are excessive thirst, passing of large amounts of urine, increase in appetite and feeling weak.
- a history of seizures (fits) or epilepsy.

<u>Weight increase</u>
Reagila may cause significant weight increase which may affect your health. Your doctor will therefore check your weight regularly.

Children and adolescents
This medicine is not recommended for children and adolescents under 18 years due to the lack of data in these patients.

Other medicines and Reagila
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. You cannot take certain medicines together with Reagila (see section "Do not take Reagila").

Taking Reagila together with some medicines may require a dose adjustment of Reagila or the other medicine. These include medicines used for the treatment of:
- heart diseases (e.g., digoxin, verapamil, diltiazem),
- blood clotting (anticoagulants (medicines that prevents the blood from clotting), e.g., dabigatran),
- bacterial infections (e.g., erythromycin),
- fungal infections (e.g., fluconazole).

Reagila should be used with caution in combination with other medicines affecting your mental functions.

Reagila with food, drink and alcohol
You should not drink grapefruit juice during treatment with Reagila.
Alcohol should be avoided when taking Reagila.

Pregnancy and breast-feeding

Women of childbearing potential/Contraception
Women of childbearing potential must use effective contraception during Reagila treatment. Even after treatment is stopped, contraception must be used for at least 10 weeks after your last dose of Reagila. This is because the medicine will stay in your body for some time after the last dose was taken.

Pregnancy
Do not take this medicine during pregnancy unless your doctor has told you to do so.

If your doctor decides that you should take this medicine during pregnancy, your doctor will monitor your baby closely after birth. This is because the following symptoms may occur in newborn babies of mothers who have used this medicine 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.

Breast-feeding
Do not breast-feed if you are taking Reagila because a risk for the baby cannot be excluded. Contact your doctor for advice.

Driving and using machines
There is a minor or moderate risk that the medicine could affect the ability to drive and use machines. Drowsiness, dizziness and vision problems may occur during treatment with this medicine (see section 4). Do not drive or use any tools or machines until you know that this medicine does not affect you in a negative way.

Reagila 3 mg, 4.5 mg, 6 mg hard capsules contain Allura red AC (E 129).
Allura red AC is a coloring agent, which may cause allergic reactions.

3. How to take Reagila

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended starting dose is 1.5 mg once a day by mouth. Thereafter, the dose may be slowly adjusted by your doctor, in steps of 1.5 mg, depending on how the treatment works for you.
The maximum dose should not exceed 6 mg once a day.

Take Reagila at the same time each day with or without food.

If you were taking another medicine to treat schizophrenia before starting Reagila, your doctor will decide whether to stop the other medicine gradually or immediately and how to adjust the dose of Reagila. Your doctor will also inform you how to act if you switch from Reagila to another medicine.

Patients with kidney or liver problems
If you have serious kidney or liver problems Reagila may not be appropriate for you. Talk to your doctor.

Elderly patients
Your doctor will carefully select the appropriate dose for your needs.
Reagila should not be used by elderly patients with dementia (loss of memory).

If you take more Reagila than you should
If you have taken more Reagila than your doctor has recommended or if, for example, a child has taken it by mistake, contact your doctor or go to the nearest hospital right away and take the pack of the medicine with you. You may experience dizziness from low blood pressure, or have abnormal heartbeats, you may feel sleepy, tired, or have abnormal body movements and find it difficult to stand or walk.

If you forget to take Reagila
If you forget to take a dose, take it as soon as you remember it. However, if it is almost time for your next dose, skip the missed dose and continue as usual.
Do not take a double dose to make up for a forgotten dose.
If you miss two or more doses, contact your doctor.

If you stop taking Reagila
If you stop taking this medicine you will lose the effects of the medicine. Even if you feel better, do not alter or stop your daily dose of Reagila 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.

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:
- 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. (Rare side effect)
- combination of fever, sweating, muscle stiffness, and drowsiness or sleepiness. These can be the signs of the so-called neuroleptic malignant syndrome. (Side effect with frequency not known)
- inexplicable muscle pains, muscle cramps or muscle weakness. These may be signs of muscle damage which can cause very serious kidney problems. (Rare side effect)
- symptoms related to 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. (Side effect with frequency not known)
- thoughts or feelings about harming yourself or to commit suicide, suicide attempt. (Uncommon side effect)

Other side effects
Very common side effects (may affect more than 1 in 10 people)

- feeling of restlessness and inability to sit still
- Parkinsonism - a medical condition with many various symptoms which include decreased or slow movements, slowness of thought, jerks when bending the limbs (cogwheel rigidity), shuffling, steps, shaking, little or no facial expression, muscle stiffness, drooling

Common side effects (may affect up to 1 in 10 people)

- anxiety
- sleepiness, difficulty in sleeping, abnormal dreams, nightmare, sleepwalking
- dizziness
- involuntary twisting movements and strange postures

- excessive teeth grinding or jaw clenching, drooling, persistent blinking in response to tapping of the forehead (an abnormal reflex), movement problems, tongue movement disturbance (these are called extrapyramidal symptoms)
- blurred vision
- high blood pressure
- fast, irregular heartbeat
- decreased or increased appetite
- nausea, vomiting, constipation
- weight increased
- tiredness
- the following can be seen in laboratory tests:
    - increases in liver enzymes
    - increases in the level of creatine phosphokinase in the blood
    - abnormal amount of lipids (e.g., cholesterol and/or fat) in the blood

Uncommon side effects (may affect up to 1 in 100 people)

- depression
- sudden and severe confusion
- spinning sensation
- unpleasant, abnormal sense of touch
- drowsiness, lack of energy or a lack of interest in doing things
- involuntary movements, most commonly of the tongue or face. This can appear after short or long-term use.
- decreased or increased sexual desire, erectile problems
- eye irritation, high pressure in the eye, poor vision
- focusing problems seeing at a distance to or seeing close-to
- low blood pressure
- abnormal ECG reading, abnormal nerve impulses in the heart
- slow, irregular heart rate
- hiccups
- heartburn
- thirst
- pain when passing urine
- abnormally frequent and large urinations
- itching, rash
- diabetes
- the following can be seen in laboratory tests:
    - abnormal sodium level in the blood
    - increased blood glucose (blood sugar), increased bile pigment (bilirubin) in the blood
    - anaemia (reduced levels of red blood cells)
    - increase in a type of white blood cells
    - decreased level of thyroid stimulating hormone (TSH) in the blood

Rare side effects (may affect up to 1 in 1 000 people)

- seizure
- loss of memory, loss of speech
- eye discomfort in bright light
- clouding of the lens in the eye leading to a decrease in vision (cataract)
- difficulty in swallowing
- reduced levels of a type of white blood cells, this can make you more susceptible to infections
- underactive thyroid gland

Side effects with unknown frequency (frequency cannot be estimated from the available data)

- inflammation of the liver (pain in the upper right abdomen, yellowing of the eye and skin,

weakness, fever)

Reporting of side effects
If you get any side effects, talk to your doctor. 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 Reagila

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 the blister after EXP. The expiry date refers to the last day of that month.

Keep the blister in the outer carton in order to protect from light.
This medicine does not require any special temperature storage conditions.

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 Reagila contains

- The active substance is cariprazine.
  Reagila 1.5 mg: Each hard capsule contains cariprazine hydrochloride corresponding to 1.5 mg cariprazine.
  Reagila 3 mg: Each hard capsule contains cariprazine hydrochloride corresponding to 3 mg cariprazine.
  Reagila 4.5 mg: Each hard capsule contains cariprazine hydrochloride corresponding to 4.5 mg cariprazine.
  Reagila 6 mg: Each hard capsule contains cariprazine hydrochloride corresponding to 6 mg cariprazine.

- The other ingredients are:
  Reagila 1.5 mg hard capsules: pregelatinized (maize) starch, magnesium stearate, titanium dioxide (E 171), gelatin, black ink (shellac, black iron oxide (E 172), propylene glycol, potassium hydroxide).

  Reagila 3 mg hard capsules: pregelatinized (maize) starch, magnesium stearate, allura red AC (E 129), brilliant blue FCF (E 133), titanium dioxide (E 171), yellow iron oxide (E 172), gelatin, black ink (shellac, black iron oxide (E 172), propylene glycol, potassium hydroxide) (See also section 2 - Reagila 3 mg, 4.5 mg, 6 mg hard capsules contain Allura red AC (E 129)).

  Reagila 4.5 mg hard capsules: pregelatinized (maize) starch, magnesium stearate, allura red AC (E 129), brilliant blue FCF (E 133), titanium dioxide (E 171), yellow iron oxide (E 172), gelatin, white ink (shellac, titanium dioxide (E 171), propylene glycol, simeticone) (See also section 2 - Reagila 3 mg, 4.5 mg, 6 mg hard capsules contain Allura red AC (E 129)).

  Reagila 6 mg hard capsules: pregelatinized (maize) starch, magnesium stearate, brilliant blue FCF (E 133), allura red AC (E 129), titanium dioxide (E 171), gelatin, black ink (shellac, black iron oxide (E 172), propylene glycol, potassium hydroxide) (See also section 2 - Reagila 3 mg, 4.5 mg, 6 mg hard capsules contain Allura red AC (E 129)).

What Reagila looks like and contents of the pack

- Reagila 1.5 mg hard capsules: ‘Size 4’ (approximately 14.3 mm in length) hard gelatin capsule with white opaque cap and white opaque body imprinted with “GR 1.5” on the capsule body with black ink. The capsules are filled with white to yellowish white powder.

- Reagila 3 mg hard capsules: ‘Size 4’ (approximately 14.3 mm in length) hard gelatin capsule with green opaque cap and white opaque body imprinted with “GR 3” on the capsule body with black ink. The capsules are filled with white to yellowish white powder.

- Reagila 4.5 mg hard capsules: ‘Size 4’ (approximately 14.3 mm in length) hard gelatin capsule with green opaque cap and green opaque body imprinted with “GR 4.5” on the capsule body with white ink. The capsules are filled with white to yellowish white powder.

- Reagila 6 mg hard capsules: ‘Size 3’ (approximately 15.9 mm in length) hard gelatin capsule with purple opaque cap and white opaque body imprinted with “GR 6” on the capsule body with black ink. The capsules are filled with white to yellowish white powder.

Reagila 1.5 mg and Reagila 3 mg hard capsules are available in pack sizes containing 7, 14, 21, 28, 30, 49, 56, 60, 84, 90 or 98 hard capsules.

Reagila 4.5 mg and Reagila 6 mg hard capsules are available in pack sizes containing 7, 21, 28, 30, 49, 56, 60, 84, 90 or 98 hard capsules.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Gedeon Richter Plc.
*\|PU L -21W -
1103 Budapest
Hungary

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Recordati BV
Tél/Tel: +32 2 461 01 36

;te]Zjby
LI ~=_^_hg Jbol_j :>·
7He 359 2 8129063

ýHVNi UHSXEOLND
*HGHRQ 5LFKWHU 0DUNHWLQJ
Tel: +420 261 141 200

Danmark
Recordati AB
Tlf: +46 8 545 80 230 (Sverige)

Deutschland
Recordati Pharma GMBH
Tel: + 49 731 70470

Eesti

Lietuva
*HGHRQ 5LFKWHU 3OF DWVWRYVEi
Tel: +370 5 261 01 54

Luxembourg/Luxemburg
Recordati BV
Tél/Tel: + 32 2 461 01 36 (Belgique/Belgien)

Magyarország
Richter Gedeon Nyrt.
Tel.: +36 1 505 7032

Malta
Recordati Ireland Limited
Tel: + 353 21 4379400 (Ireland)

Nederland
Recordati BV
Tel: + 32 2 461 01 36 (België)

Norge

Richter Gedeon Eesti filiaal
Tel: +372 608 5301

ü / .
Recordati Hellas Pharmaceuticals S.A.
6773822

España
Casen Recordati S.L.
Tel: + 34 91 659 15 50

France
Bouchara-Recordati S.A.S.
Tél: + 33 1 45 19 10 00

Hrvatska
Gedeon Richter Croatia d.o.o.
Tel: + 385 1 5625 712

Ireland
Recordati Ireland Limited
Tel: + 353 21 4379400

Ísland
Recordati AB
Sími: +46 8 545 80 230 (Svíþjóð)

Italia
RECORDATI S.p.A.
Tel: + 39 02 487871

* ! "
C.G. PAPALOISOU LTD.
357 22 490305

Latvija
*HGHRQ 5LFKWHU 3OF S UVV YQLHFLED/DW.YLM
Tel: +371 67845338

Recordati AB
Tlf: + 46 8 545 80 230 (Sverige)

Österreich
Recordati Austria GmbH
Tel: + 43 676 353 0 262

Polska
GEDEON RICHTER POLSKA Sp. z o.o.
Tel.: + 48 (22)755 96 48

Portugal
Jaba Recordati S.A.
Tel: + 351 21 432 95 00

România
Gedeon Richter România S.A.
Tel: +40-265-257 011

Slovenija
Gedeon Richter d.o.o.
Tel: + +386 8 205 68 70

Slovenská republika
Gedeon Richter Slovakia, s.r.o.
Tel: +421 2 5020 5801

Suomi/Finland
Recordati AB
Puh/Tel: +46 8 545 80 230 (Ruotsi/Sverige)

Sverige
Recordati AB
Tel: +46 8 545 80 230

United Kingdom (Northern Ireland)
Recordati Pharmaceuticals Ltd.
Tel: + 44 1491 576336

This leaflet was last revised in

Other sources of information
Detailed and updated information on this medicine is available by scanning the QR code below and the outer carton with a smartphone.
The same information is also available on the following URL: www.reagila.com

'QR code to be included' + www.reagila.com

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

Reagila 1.5 mg orodispersible tablets
Reagila 3 mg orodispersible tablets
Reagila 4.5 mg orodispersible tablets
Reagila 6 mg orodispersible tablets
cariprazine

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. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Reagila is and what it is used for

Reagila contains the active substance cariprazine and belongs to a group of medicines called antipsychotics. It is used to treat adults with schizophrenia.

Schizophrenia is a disease characterised by symptoms such as hearing, seeing or sensing things which are not there (hallucination), suspiciousness, mistaken beliefs, incoherent speech and behaviour and emotional flatness. People with this condition may also feel depressed, guilty, anxious, tense, or not being able to start or keep up planned activities, unwillingness to speak, lack of emotional response to a situation that would normally stimulate feelings in others.

2. What you need to know before you take Reagila

Do not take Reagila
- if you are allergic to cariprazine or any of the other ingredients of this medicine (listed in section 6).
- if you are taking medicines used to treat:
- hepatitis caused by the hepatitis C virus (medicines containing boceprevir and telaprevir)
- bacterial infections (medicines containing clarithromycin, telithromycin and nafcillin)
- tuberculosis (medicines containing rifampicin)
- HIV infections (medicines containing cobicistat, indinavir, nelfinavir, ritonavir, saquinavir, efavirenz and etravirine)
- fungal infections (medicines containing itraconazole, posaconazole and voriconazole)
- Cushing’s syndrome - when the body produces an excess of cortisol (medicines containing ketoconazole)
- depression (herbal therapy containing St. John's wort (Hypericum perforatum) and medicines containing nefazodone)
- epilepsy and seizures (medicines containing carbamazepine, phenobarbital and phenytoin)

-
- sleepiness (medicines containing modafinil)
- high blood pressure in the lungs (medicines containing bosentan).

Warnings and precautions
Tell your doctor immediately:
- if you are having any thoughts or feelings about harming yourself or to commit suicide. Suicidal thoughts and behaviours are more likely at the beginning of the treatment.
- if you experience a combination of fever, sweating, faster breathing, muscle stiffness and drowsiness or sleepiness (may be signs of neuroleptic malignant syndrome).

Talk to your doctor or pharmacist before taking Reagila, or during treatment if you have:
- ever experienced or start to experience restlessness and inability to sit still. These symptoms may occur early during treatment with Reagila. Tell your doctor if this happens.
- ever experienced or start to experience abnormal, involuntary movements, most commonly of the tongue or face. Tell your doctor if this happens.
- visual impairment. Your doctor will advise you to visit an ophthalmologist.
- irregular heartbeat or if someone else in your family has a history of irregular heartbeat (including so called QT prolongation seen with electrocardiogram (ECG) monitoring), and tell your doctor if you are taking other medicines, because they might cause or worsen this ECG change.
- high or low blood pressure, cardiovascular disease. Your doctor will need to check your blood pressure regularly.
- dizziness on standing up due to a drop in your blood pressure, which may cause fainting
- 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.
- a history of stroke, especially if you are elderly or know that you have other risk factors for stroke. Tell your doctor immediately if you notice any signs of a stroke.
- dementia (loss of memory and other mental abilities) especially if you are elderly.
- Parkinson's disease.
- if you have diabetes or risk factors for diabetes (e.g. obesity, or someone else in your family has diabetes). Your doctor will need to check your blood sugar regularly since it may be increased by Reagila. Signs of high blood sugar level are excessive thirst, passing of large amounts of urine, increase in appetite and feeling weak.
- a history of seizures (fits) or epilepsy.

<u>Weight increase</u>
Reagila may cause significant weight increase which may affect your health. Your doctor will therefore check your weight regularly.

Children and adolescents
This medicine is not recommended for children and adolescents under 18 years due to the lack of data in these patients.

Other medicines and Reagila
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. You cannot take certain medicines together with Reagila (see section "Do not take Reagila").

Taking Reagila together with some medicines may require a dose adjustment of Reagila or the other medicine. These include medicines used for the treatment of:
- heart diseases (e.g., digoxin, verapamil, diltiazem),
- blood clotting (anticoagulants (medicines that prevents the blood from clotting), e.g., dabigatran),
- bacterial infections (e.g., erythromycin),
- fungal infections (e.g., fluconazole).

Reagila should be used with caution in combination with other medicines affecting your mental functions.

Reagila with food, drink and alcohol
You should not drink grapefruit juice during treatment with Reagila.
Alcohol should be avoided when taking Reagila.

Pregnancy and breast-feeding

Women of childbearing potential/Contraception
Women of childbearing potential must use effective contraception during Reagila treatment. Even after treatment is stopped, contraception must be used for at least 10 weeks after your last dose of Reagila. This is because the medicine will stay in your body for some time after the last dose was taken.

Pregnancy
Do not take this medicine during pregnancy unless your doctor has told you to do so.

If your doctor decides that you should take this medicine during pregnancy, your doctor will monitor your baby closely after birth. This is because the following symptoms may occur in newborn babies of mothers who have used this medicine 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.

Breast-feeding
Do not breast-feed if you are taking Reagila because a risk for the baby cannot be excluded. Contact your doctor for advice.

Driving and using machines
There is a minor or moderate risk that the medicine could affect the ability to drive and use machines. Drowsiness, dizziness and vision problems may occur during treatment with this medicine (see section 4). Do not drive or use any tools or machines until you know that this medicine does not affect you in a negative way.

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

3. How to take Reagila

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended starting dose is 1.5 mg once a day by mouth. Thereafter, the dose may be slowly adjusted by your doctor, in steps of 1.5 mg, depending on how the treatment works for you.
The maximum dose should not exceed 6 mg once a day.

Take Reagila at the same time each day with or without food.
Do not open the blister until ready to administer. Tear off one individual blister from the blister card along the perforated line and peel back the foil on the blister to expose the tablet. Do not push the tablet through the foil because this could damage the tablet.

Immediately upon opening the blister, using dry hands, remove the tablet and place the entire orodispersible tablet on the tongue. Tablet disintegration occurs rapidly in saliva. Do not chew or swallow the tablet whole, wait until it dissolves in your mouth.
Alternatively, disperse the tablet in water and drink the resulting suspension. In this case, the contents of the glass should be thoroughly stirred to avoid settling down of the undissolved residues.

If you were taking another medicine to treat schizophrenia before starting Reagila, your doctor will decide whether to stop the other medicine gradually or immediately and how to adjust the dose of Reagila. Your doctor will also inform you how to act if you switch from Reagila to another medicine.

Patients with kidney or liver problems
If you have serious kidney or liver problems Reagila may not be appropriate for you. Talk to your doctor.

Elderly patients
Your doctor will carefully select the appropriate dose for your needs.
Reagila should not be used by elderly patients with dementia (loss of memory).

If you take more Reagila than you should
If you have taken more Reagila than your doctor has recommended or if, for example, a child has taken it by mistake, contact your doctor or go to the nearest hospital right away and take the pack of the medicine with you. You may experience dizziness from low blood pressure, or have abnormal heartbeats, you may feel sleepy, tired, or have abnormal body movements and find it difficult to stand or walk.

If you forget to take Reagila
If you forget to take a dose, take it as soon as you remember it. However, if it is almost time for your next dose, skip the missed dose and continue as usual.
Do not take a double dose to make up for a forgotten dose.
If you miss two or more doses, contact your doctor.

If you stop taking Reagila
If you stop taking this medicine you will lose the effects of the medicine. Even if you feel better, do not alter or stop your daily dose of Reagila 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.

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:
- 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. (Rare side effect)
- combination of fever, sweating, muscle stiffness, and drowsiness or sleepiness. These can be the signs of the so-called neuroleptic malignant syndrome. (Side effect with frequency not known)
- inexplicable muscle pains, muscle cramps or muscle weakness. These may be signs of muscle

damage which can cause very serious kidney problems. (Rare side effect)
- symptoms related to 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. (Side effect with frequency not known)
- thoughts or feelings about harming yourself or to commit suicide, suicide attempt. (Uncommon side effect)

Other side effects

Very common side effects (may affect more than 1 in 10 people)

- feeling of restlessness and inability to sit still
- Parkinsonism - a medical condition with many various symptoms which include decreased or slow movements, slowness of thought, jerks when bending the limbs (cogwheel rigidity), shuffling, steps, shaking, little or no facial expression, muscle stiffness, drooling

Common side effects (may affect up to 1 in 10 people)

- anxiety
- sleepiness, difficulty in sleeping, abnormal dreams, nightmare, sleepwalking
- dizziness
- involuntary twisting movements and strange postures
- excessive teeth grinding or jaw clenching, drooling, persistent blinking in response to tapping of the forehead (an abnormal reflex), movement problems, tongue movement disturbance (these are called extrapyramidal symptoms)
- blurred vision
- high blood pressure
- fast, irregular heartbeat
- decreased or increased appetite
- nausea, vomiting, constipation
- weight increased
- tiredness
- the following can be seen in laboratory tests:
- increases in liver enzymes
- increases in the level of creatine phosphokinase in the blood
- abnormal amount of lipids (e.g., cholesterol and/or fat) in the blood

Uncommon side effects (may affect up to 1 in 100 people)

- depression
- sudden and severe confusion
- spinning sensation
- unpleasant, abnormal sense of touch
- drowsiness, lack of energy or a lack of interest in doing things
- involuntary movements, most commonly of the tongue or face. This can appear after short or long-term use.
- decreased or increased sexual desire, erectile problems
- eye irritation, high pressure in the eye, poor vision
- focusing problems seeing at a distance to or seeing close-to
- low blood pressure
- abnormal ECG reading, abnormal nerve impulses in the heart
- slow, irregular heart rate
- hiccups
- heartburn
- thirst
- pain when passing urine
- abnormally frequent and large urinations
- itching, rash

- diabetes
- the following can be seen in laboratory tests:
- abnormal sodium level in the blood
- increased blood glucose (blood sugar), increased bile pigment (bilirubin) in the blood
- anaemia (reduced levels of red blood cells)
- increase in a type of white blood cells
- decreased level of thyroid stimulating hormone (TSH) in the blood

Rare side effects (may affect up to 1 in 1 000 people)

- seizure
- loss of memory, loss of speech
- eye discomfort in bright light
- clouding of the lens in the eye leading to a decrease in vision (cataract)
- difficulty in swallowing
- reduced levels of a type of white blood cells, this can make you more susceptible to infections
- underactive thyroid gland

Side effects with not known frequency (frequency cannot be estimated from the available data)
- inflammation of the liver (pain in the upper right abdomen, yellowing of the eye and skin, weakness, fever)

Reporting of side effects
If you get any side effects, talk to your doctor. 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 Reagila

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 the blister after EXP. The expiry date refers to the last day of that month.

Keep the tablets in the original packaging in order to protect from moisture.
This medicinal product does not require any special temperature storage conditions.

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 Reagila contains

- The active substance is cariprazine.
  Reagila 1.5 mg: Each orodispersible tablet contains cariprazine hydrochloride corresponding to 1.5 mg cariprazine.
  Reagila 3 mg: Each orodispersible tablet contains cariprazine hydrochloride corresponding to 3 mg cariprazine.
  Reagila 4.5 mg: Each orodispersible tablet contains cariprazine hydrochloride corresponding to 4.5 mg cariprazine.
  Reagila 6 mg: Each orodispersible tablet contains cariprazine hydrochloride corresponding to 6 mg cariprazine.

- The other ingredients are:

Mannitol (E 421), maize starch, sodium starch glycolate type A, malic acid (E 296), sodium stearyl fumarate (E 485), silicon dioxide (E 551) (See also section 2 - Reagila orodispersible tablets contain sodium).

What Reagila looks like and contents of the pack

- Reagila 1.5 mg orodispersible tablets: White or almost white, triangle, biconvex tablet. The diameter of the tablet is approx.. 8 mm and thickness is approx. 3-4 mm. Engraving on one side is “C2”, the other side is without engraving.

- Reagila 3 mg orodispersible tablets: White or almost white, round, biconvex tablet. The diameter of the tablet is 7 mm and thickness is approx. 3-4 mm. Engraving on one side is “C3”, the other side is without engraving.

- Reagila 4.5 mg orodispersible tablets: White or almost white, square, biconvex tablet. The diameter of the tablet is approx.. 7 mm and thickness is approx. 3-4 mm. Engraving on one side is “C4”, the other side is without engraving.

- Reagila 6 mg orodispersible tablets: White or almost white, oval, biconvex tablet. The width of the tablet is 5 mm, length is 8.5 mm and thickness is approx. 3-4 mm. Engraving on one side is “CI”, the other side is without engraving.

Reagila 1.5 mg, 3 mg, 4.5 mg and 6 mg orodispersible tablets are available in pack sizes containing 28 or 30 orodispersible tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Gedeon Richter Plc.
* \ | P U L ~2W -
1103 Budapest
Hungary

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien/Danmark/Deutschland / ü / ./España/France/Ireland/Ísland/Italia/ * ! "/Luxembourg/Luxemburg/ Magyarország/Malta/Nederland/Norge/ Österreich/Portugal/Suomi/Finland/Sverige/ United Kingdom (Northern Ireland)
Richter Gedeon Nyrt.
Tél/Tel/Tlf/ /Sími/Puh: +36 1 505 7032

; t e] Z j b y
L I ~ = _ ^ _ h g J b o l _ j : > ·
7 H e

ýH V N i U H S X E O L N D
* H G H R Q 5 L F K W H U 0 D U N H W L Q J ý5 Y U R
Tel: +420 261 141 200

Eesti
Richter Gedeon Eesti filiaal
Tel: +372 608 5301

Lietuva
* H G H R Q 5 L F K W H U 3 O F D W V W R Y \ E ¡
Tel: +370 5 261 01 54

Polska
GEDEON RICHTER POLSKA Sp. z o.o.
Tel.: + 48 (22)755 96 48

România
Gedeon Richter România S.A.
Tel: +40-265-257 011

Slovenija
Gedeon Richter d.o.o.
Tel: + +386 8 205 68 70

Hrvatska
Gedeon Richter Croatia d.o.o.
Tel: + 385 1 5625 712

Slovenská republika
Gedeon Richter Slovakia, s.r.o.
Tel: +421 2 5020 5801

Latvija
*HGHRQ 5LFKWHU 3OF S UVW YQLHFflED /DWYLM
Tel: +371 67845338

This leaflet was last revised in

Other sources of information
Detailed and updated information on this medicine is available by scanning the QR code below and the outer carton with a smartphone.
The same information is also available on the following URL: www.reagila.com

'QR code to be included' + www.reagila.com

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Chlorpromazine

EMC

Chlorpromazine 100mg Tablets

Summary of Product Characteristics Updated 17-Oct-2024 | Dr. Reddy's Laboratories (UK) Ltd

1. Name of the medicinal product

Chlorpromazine 100mg Tablets

2. Qualitative and quantitative composition

Each tablet contains 100 mg Chlorpromazine as Hydrochloride salt

Excipient(s) with known effect

Each tablet contains 267.90 mg of lactose.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet

Round, white, film-coated tablet market 'CPZ 100'with diameter 11.20 mm ± 0.3.

4. Clinical particulars

4.1 Therapeutic indications

Schizophrenia and other psychoses (especially where paranoia is a predominant symptom), mania and hypomania. In anxiety, psychomotor agitation, excitement, violent or dangerously impulsive behaviour. Chlorpromazine may be used as an adjunct in the short-term management of these conditions.

Intractable hiccup.

Nausea and vomiting in terminal illness (where other drugs have failed or are not available).

Induction of hypothermia is facilitated by Chlorpromazine Tablets which prevents shivering and causes vasodilatation.

Childhood schizophrenia and autism.

4.2 Posology and method of administration

Posology

Dosages should be low to begin with and gradually increased under close supervision until the optimum dosage for the individual is reached. Individuals vary considerably and the optimum dose may be affected by the formulation used.

Dosage of chlorpromazine in schizophrenia, other psychoses, anxiety and agitation etc.

Adult:

Initially 25 mg t.d.s. or 75 mg at bedtime increasing by daily amounts of 25 mg to an effective maintenance dose. This is usually in the range 75 to 300 mg daily but some patients may require up to 1 g daily.

Children under 1 year:

Do not use unlessthe risk-benefit ratio has been assessed.

Children 1-5 years:

0.5 mg/kg body weight every 4-6 hours to a maximum recommended dose of 40 mg daily.

Children 6-12 years:

$^{1}/_{3}$-½ adult dose to a maximum recommended dose of 75 mg daily.

Elderly or debilitated patients:

Start with $^{1}/_{3}$-½ usual adult dose with a more gradual increase in dosage.

Hiccups

Adult:

25-50 mg t.d.s. or q.d.s.

Children under 1 year:

No information available.

Children 1-5 years:

No information available.

Children 6-12 years:

No information available.

Elderly or debilitated patients:

As for adults.

Nausea and vomiting of terminal illness:

Adults:

10-25 mg every 4-6 hours.

Children under 1 year:

Do not use unlessthe risk-benefit ratio has been assessed..

Children 1-5 years:

0.5 mg/kg every 4-6 hours. Maximum daily dosage should not exceed 40 mg.

Children 6-12 years:

0.5 mg/kg every 4-6 hours. Maximum daily dosage should not exceed 75 mg.

Elderly or debilitated patients:

Initially $^{1}/_{3}$-½ adult dose. The physician should then use his clinical judgment to obtain control.

Method of administration: Oral

4.3 Contraindications

• Hypersensitivity to chlorpromazine or to any of the excipients listed in section 6.1

• Hypothyroidism

• Bone marrow depression

• Phaeochromocytoma

• Myasthenia gravis

• Risk of angle-closure glaucoma

• Risk of urinary retention related to urethroprostatic disorders

• History of agranulocytosis

• Dopaminergic antiparkinsonism agents (see Section 4.5)

• Nursing mothers (see Section 4.6)

• Citalopram, escitalopram.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use

Blood Dyscrasias: All patients must be advised that, if they experience fever, sore throat or any other infection, they should inform their physician immediately and undergo a complete blood count. Treatment will be discontinued if any marked changes (hyperleucocytosis, granulocytopenia) are observed in the latter.

As agranulocytosis has been reported, regular monitoring of the complete blood count is recommended. The occurrence of unexplained infections or fever may be evidence of blood dyscrasia (see Section 4.8) and requires immediate haematological investigation.

Neuroleptic malignant syndrome: treatment must be interrupted in the event of unexplained hyperpyrexia since this can be one of the signs of neuroleptic malignant syndrome (pallor, hyperthermia, disorders of autonomic function, altered consciousness, muscle rigidity). Signs of autonomic instability, such as hyperhydrosis and irregular blood pressure, can precede the onset of hyperthermia and as such constitute premonitory signs of the syndrome. While this neuroleptic-related effect can be of idiosyncratic origin, certain risk factors such as dehydration and brain damage would seem to indicate a predisposition.

Chlorpromazine should be avoided in patients with hypothyroidism, phaeochromocytoma, myasthenia gravis and prostate hypertrophy. It should be avoided in patients known to be hypersensitive to phenothiazines or with a history of narrow angle glaucoma or agranulocytosis.

Acute withdrawal symptoms, including nausea, vomiting and insomnia, have very rarely have been reported following the abrupt cessation of high doses of neuroleptics. Relapse may also occur, and the emergence of extrapyramidal

reactions has been reported. Therefore, gradual withdrawal is advisable.

In schizophrenia, the response to neuroleptic treatment may be delayed. If treatment is withdrawn, the recurrence of symptoms may not become apparent for some time.

Neuroleptic phenothiazines may potentiate QT interval prolongation which increases the risk of onset of serious ventricular arrhythmias of the torsade de pointes type, which is potentially fatal (sudden death). QT prolongation is exacerbated, in particular, in the presence of bradycardia, hypokalaemia, and congenital or acquired (i.e. drug induced) QT prolongation. If the clinical situation permits, medical and laboratory evaluations should be performed to rule out possible risk factors before initiating treatment with a neuroleptic agent and as deemed necessary during treatment (see Section 4.8).

Where clinically possible, the absence of any factors favouring the onset of ventricular arrhythmias should be ensured before administration:

• bradycardia less than 55 beats per minute;

• hypokalaemia;

• hypocalcaemia;

• hypomagnesaemia;

• starvation;

• alcohol abuse;

• concomitant therapy with other drugs to prolong QT interval;

• congenital long QT interval;

• ongoing treatment with any drug which could induce marked bradycardia (<55 beats per minute), hypokalaemia, intracardiac conduction depression or QT prolongation (see Section 4.5).

With the exception of emergencies, it is recommended that the initial work up of patients receiving a neuroleptic should include an ECG.

Except under exceptional circumstances, this drug must not be administered to patients with Parkinson's disease.

The concomitant use of chlorpromazine with lithium, other QT prolongation agents, and dopaminergic antiparkinsonism agents is not recommended (see Section 4.5).

The onset of paralytic ileus, potentially indicated by abdominal bloating and pain, must be treated as an emergency (see section 4.8).

Cases of venous thromboembolism (VTE) sometimes fatal, have been reported with antipsychotic drugs. Since patients treated with anti-psychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with Chlorpromazine and preventive measures undertaken.

Stroke: In randomised clinical trials versus placebo performed in a population of elderly patients with dementia and treated with certain atypical antipsychotic drugs, a 3-fold increase of the risk of cerebrovascular events has been observed. The mechanism of such risk increase is not known. An increase in the risk with other antipsychotic drugs or other populations of patient cannot be excluded. Chlorpromazine should be used with caution in patients with stroke risk factors.

Elderly Patients with Dementia: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-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 trial, the rate of death in drug-treated patients was about 4.5% compared to a rate of about 2.6% in the placebo group. Although the cause of death in clinical trials with atypical antipsychotics 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, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. 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 patient is not clear.

As with all anti-psychotic drugs, Chlorpromazine should not be used alone where depression is predominant. However, it may be combined with antidepressant therapy to treat those conditions in which depression and psychosis coexist.

Chlorpromazine Tablets are not licensed for the treatment of dementia-related behavioural disturbances.

Because of the risk of photosensitisation, patients should be advised to avoid exposure to direct sunlight (see Section 4.8). In those frequently handling preparations of phenothiazines, the greatest care must be taken to avoid contact of the drug with the skin.

Hyperglycaemia or intolerance to glucose has been reported in patients treated with Chlorpromazine Tablets. Patients with an established diagnosis of diabetes mellitus or with risk factors for the development of diabetes who are started on Chlorpromazine Tablets should get appropriate glycaemic monitoring during treatment (see Section 4.8).

• The following populations must be closely monitored after administration of chlorpromazine.

o epileptics, since chlorpromazine may lower the seizure threshold. Treatment must be discontinued if seizures occur.

o elderly patients presenting with heightened susceptibility to orthostatic hypotension, sedation and extrapyramidal effects; chronic constipation (risk of paralytic ileus), and potentially prostatic hypertrophy. It should be used with caution particularly during very hot or cold weather (risk of hyper-, hypothermia).

o patients presenting with certain forms of cardiovascular disease, since this class of drug has quinidine-like effects and can induce tachycardia and hypotension.

o patients with severe liver and/or renal failure because of the risk of accumulation.

• Patients on long-term treatment should receive regular ophthalmological and haematological examinations.

• Patients are strongly advised not to consume alcohol and alcohol-containing drugs throughout treatment (see Section 4.5).

Treatment should be discontinued immediately and another anti-psychotic drug should be considered as an alternative in the following situation:

• Severe liver toxicity

o Severe liver toxicity, resulting sometimes in death, has been reported with chlorpromazine use. Patients or caregivers should immediately report signs and symptoms such as asthenia, anorexia, nausea, vomiting, abdominal pain or icterus to a physician. Investigations including clinical examination and biological assessment of liver function should be undertaken immediately (see section 4.8).

• Eosinophilia

o The presence of eosinophilia may indicate an allergic reaction to chlorpromazine. A thorough clinical examination and a repeat complete blood count (CBC) with differential count to confirm the presence of eosinophilia should be performed (see section 4.8).

• Drug reaction with eosinophilia and systemic symptoms

o Drug reaction with eosinophilia and systemic symptoms (DRESS) which can be life threatening or fatal, have been reported in association with chlorpromazine treatment.

o At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, chlorpromazine should be withdrawn immediately and not be restarted.

Chlorpromazine tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium content

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially, 'sodium free'

Paediatric population

Since there is a potential to impact on cognitive function, children should undergo a yearly clinical examination to evaluate learning capacity. The dosage should be adjusted regularly as a function of the clinical status of the child.

4.5 Interaction with other medicinal products and other forms of interaction

Adrenaline must not be used in patients overdosed with Chlorpromazine.

Antichlolinergic drugs may reduce the antipsychotic effect of Chlorpromazine and the mild anticholinergic effect of Chlorpromazine may be enhanced by other anticholinergic drugs possibly leading to constipation, heat stroke etc.

The action of some drugs may be opposed by Chlorpromazine; these include amphetamine, levodopa, clonidine, guanethidine and adrenaline.

Increases or decreases in the plasma concentrations of a number of drugs e.g. propranolol Phenobarbital have been observed but were not of clinical significance.

Simultaneous administration of deferoxamine and prochlorperazine has been observed to induce a transient metabolic encephalopathy characterised by loss of consciousness for 48-72 hours. It is possible this may occur with Chlorpromazine since it shares many of the pharmacological properties of prochlorperazine.

There is an increased risk of agranulocytosis when neuroleptics are used concurrently with drugs with myelosuppressive potential, such as carbamazepine or certain antibiotics and cytotoxics.

Combinations contraindicated

Dopaminergics (quinagolide, cabergoline), not including dopaminergic antiparkinsonism agents, are contraindicated (see Section 4.3): reciprocal antagonism of the dopaminergic agent and neuroleptic. Citalopram and escitalopram are contraindicated.

Combinations not recommended

Dopaminergic antiparkinsonism agents (amantadine, bromocriptine, cabergoline, levodopa, lisuride, pergolide, piribedil, ropinirole) are not recommended: reciprocal antagonism of the antiparkinsonism agent and neuroleptic (see Section 4.4). Neuroleptic-induced extrapyramidal syndrome should be treated with an anticholinergic rather than a dopaminergic antiparkinsonism agent (dopaminergic receptors blocked by neuroleptics).

Levodopa: reciprocal antagonism of levodopa and the neuroleptic. In Parkinson's patients, it is recommended to use the minimal doses of each drug.

QT prolonging drugs: there is an increased risk of arrhythmias when chlorpromazine is used with concomitant QT prolonging drugs (including certain antiarrhythmics and other antipsychotics including sultopride) and drugs causing electrolyte imbalance (see Section 4.4).

Alcohol: alcohol potentiates the sedative effect of neuroleptics. Changes in alertness can make it dangerous to drive or operate machinery. Alcoholic beverages and medication containing alcohol should be avoided (see Section 4.4).

Lithium (high doses of neuroleptics): concomitant use can cause confusional syndrome, hypertonia and hyperreflexivity, occasionally with a rapid increase in serum concentrations of lithium (see Section 4.4). There have been rare cases of neurotoxicity Lithium can interfere with the absorption of neuroleptic agents.

Combinations requiring precautions

Antidiabetic agents: concomitant administration of high chlorpromazine doses (100 mg/day), and antidiabetic agents can lead to an increase in blood sugar levels (decreased insulin release). Forewarn the patient and advise increased self-monitoring of blood and urine levels. If necessary, adjust the antidiabetic dosage during and after discontinuing neuroleptic treatment.

Topical gastrointestinal agents (magnesium, aluminium and calcium salts, oxides and hydroxides): decreased GI absorption of phenothiazine neuroleptics. Do not administer phenothiazine neuroleptics simultaneously with topical GI agents (administer more than 2 hours apart if possible).

CYP1A2 inhibitors

Administration of chlorpromazine with CYP1A2 inhibitors, in particular strong or moderate inhibitors may lead to an increase of chlorpromazine plasma concentrations. Therefore, patients may experience a chlorpromazine dose-dependent adverse drug reaction.

There is a possible pharmacokinetic interaction between inhibitors of CYP2D6, such as phenothiazines and CYP2D6 substrates.

Combinations to be taken into consideration

Antihypertensive agents: potentiation of the antihypertensive effect and risk of orthostatic hypotension (additive effects). Guanethidine has adverse clinically significant interactions documented.

Atropine and other atropine derivatives: imipramine antidepressants, histamine H1-receptor antagonists, anticholinergic, antiparkinsonism agents, atropinic antispasmodics, disopyramide: build up of atropine-associated adverse effects such as urinary retention, constipation dry mouth and heat stroke etc.

Other CNS depressants: morphine derivatives (analgesics, antitussives and substitution treatments), barbiturates, benzodiazepines, anxiolytics other than benzodiazepines, hypnotics, sedative anti-depressants, histamine H1 receptor antagonists, central antihypertensive agents increased central depression. Changes in alertness can make it dangerous to drive or operate machinery.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is inadequate evidence of the safety of chlorpromazine in human pregnancy. There is evidence of harmful effects in animals, so like other drugs, it should be avoided in pregnancy unless the physician considers it essential. It may occasionally prolong labour and at such a time should be withheld until the cervix is dilated 3-4cm. Possible adverse effects on the foetus include lethargy or paradoxical hyperexcitability, tremor and low Apgar score.

A large amount of exposure to chlorpromazine during pregnancy did not reveal any teratogenic effect.

It is advised to keep an adequate maternal psychic balance during pregnancy in order to avoid decompensation. If a treatment is necessary to ensure this balance, the treatment should be started or continued at effective dose all through the pregnancy.

Neonates exposed to antipsychotics (including chlorpromazine) 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, bradycardia, tachycardia, feeding disorder, meconium ileus, delayed meconium passage, abdominal bloating. Consequently, newborns should be monitored carefully in order to plan appropriate treatment.

Breast-feeding

Chlorpromazine being excreted in milk, breast-feeding is not recommended during treatment.

Fertility

A decrease in fertility was observed in female animals treated with chlorpromazine. In male animals data are insufficient to assess fertility.

In humans, because of the interaction with dopamine receptors, chlorpromazine may cause hyperprolactinaemia which can be associated with impaired fertility in women (see Section 4.8). In men, data on consequences of hyperprolactinaemia are insufficient with regard to fertility.

4.7 Effects on ability to drive and use machines

The attention of patients, particularly drivers and machine operators, should be drawn to the risk of drowsiness with this medication especially at the start of treatment.

4.8 Undesirable effects

The following undesired events, listed by body system, have been reported with the following frequencies: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1000 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).

System organ class	Very common (≥ 1/10)	Common (≥ 1/100 to <1/10)	Not known (cannot be estimated from available data)
Blood and lymphatic system disorders			Agranulocytosis Leukopenia Eosinophilia Thrombocytopenia
Immune system disorders			Systemic lupus erythematosus Antinuclear antibody positive[1] Bronchospasm Anaphylactic reactions
Endocrine disorders		Hyperprolactinaemia Amenorrhoea	Galactorrhoea Gynaecomastia Erectile dysfunction Impotence Female sexual arousal disorder
Metabolism and nutrition disorders	Weight increased	Glucose tolerance impaired (see Section 4.4)	Hyperglycaemia (see Section 4.4) Hypertriglyceridaemia Hyponatraemia Inappropriate antidiuretic hormone secretion
Psychiatric disorders		Anxiety	Lethargy Mood altered
Nervous system disorders	Sedation[2] Somnolence[2] Dyskinesia (Acute dystonias or dyskenias, usually transitory are more common in children and young adults and usually occur within the first 4 days of treatment or after dosage increases) Tardive dyskinesia[3]	Hypertonia Convulsion	Torticollis Oculogyric crisis Trismus Akinesia Hyperkinesia Neuroleptic malignant syndrome (hyperthermia, rigidity, autonomic dysfunction and altered consciousness) (see Section 4.4.)

	Extrapyramidal disorder Akathisia often after large initial dose		Parkinsonism (more common in adults and the elderly. It usually develops after weeks or months of treatment) to include tremor, rigidity or other features of Parkinsonism
Eye disorders			Accommodation disorder[4] Deposit eye[5] Ocular changes[7]
Cardiac disorders		ECG changes include Electrocardiogram QT Prolonged (as with other neuroleptics) (see Section 4.4) , ST depression, U-Wave and T-Wave changes	Cardiac arrhythmias including Ventricular arrhythmia, a-v block, Ventricular fibrillation Ventricular tachycardia Torsade de pointes Cardiac arrest has been reported during neuroleptic phenothiazine therapy, possibly related to dosage. Pre-existing cardiac disease, old afe, hypokalaemia and concurrent tricyclic antidepressants may predispose. Sudden death/sudden cardiac death (with possible causes of cardiac origin as well as cases of unexplained sudden death, in patients receiving neuroleptic phenothiazines) (see Section 4.4)
Vascular disorders	Orthostatic hypotension (Elderly or volume depleted subjects are particularly susceptible: it is more likely to occur after intramuscular administration).		Embolism venous Pulmonary embolism (sometimes fatal) Deep vein thrombosis (see Section 4.4)
Respiratory, thoracic and mediastinal disorders			Respiratory depression Nasal stuffiness
Gastrointestinal disorders	Dry mouth Constipation (see Section 4.4)		Colitis ischaemic Ileus paralytic (see Section 4.4) Intestinal perforation (sometimes fatal) Gastrointestinal necrosis (sometimes fatal) Necrotising colitis (sometimes fatal) Intestinal obstruction
Hepatobiliary disorders			Jaundice cholestatic[6] Hepatocellular Liver injury[6] Cholestatic liver injury[6] Mixed liver injury

Skin and subcutaneous tissue disorders			Dermatitis allergic Angioedema Contact skin sensitisation may occur rarely in those frequently handling preparation of chlorpromazine (see section 4.4) Skin rashes Urticaria Photosensitivity reaction
Renal and urinary disorders			Urinary retention[4]
Pregnancy, puerperium and perinatal conditions			Drug withdrawal syndrome neonatal (see Section 4.6)
Reproductive system and breast disorders			Priapism
General disorders and administration site conditions			Temperature regulation disorder Insomnia Agitation

[1] may be seen without evidence of clinical disease.

[2] particularly at the start of treatment

[3] particularly during long term treatment; may occur after the neuroleptic is withdrawn and resolve after reintroduction of treatment or if the dose is increased.

[4] linked to anticholinergic effects.

[5] in the anterior segment of the eye caused by accumulation of the drug but generally without any impact on sight.

[6] A premonitory sign may be a sudden onset of fever after one to three weeks of treatment followed by the development of jaundice. Chlorpromazine jaundice has the biochemical and other characteristics of obstructive (cholestatic) jaundice and is associated with obstructions of the canaliculi by bile thrombi; the frequent presence of an accompanying eosinophilia indicates the allergic nature of this phenomenon. Liver injury, sometimes fatal, has been reported rarely in patients treated with chlorpromazine. Treatment should be withheld on the development of jaundice (see section 4.4). Cases of hepatocellular, cholestatic and mixed Liver injury, sometimes fatal, has been reported rarely in patients treated with chlorpromazine.

[7] The development of a metallic greyish-mauve coloration of exposed skin has been noted in some individuals, mainly females, who have received chlorpromazine continuously for long periods (four to eight years).

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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Toxicity and treatment of overdosage: Symptoms of chlorpromazine overdosage include drowsiness or loss of consciousness, hypotension, tachycardia, E.C.G. changes, ventricular arrhythmias and hypothermia, Parkinsonism, convulsions and coma. Severe extra-pyramidal dyskinesias may occur.

Treatment should be symptomatic with continuous respiratory and cardiac monitoring (risk of prolonged QT interval) until the patient's condition resolves.

If the patient is seen sufficiently soon (up to 6 hours) after ingestion of a toxic dose, gastric lavage may be attempted. Pharmacological induction of emesis is unlikely to be of any use. Activated charcoal should be given. There is no specific antidote. Treatment is supportive.

Generalised vasodilatation may result in circulatory collapse; raising the patient's legs may be sufficient in mild hypotension but, in severe cases, volume expansion by intravenous fluids may be needed; infusion fluids should be warmed before administration in order not to aggravate hypothermia.

Positive inotropic agents such as dopamine may be tried if fluid replacement is insufficient to correct the circulatory collapse. Peripheral vasoconstriction agents are not generally recommended; avoid use of adrenaline.

Ventricular or supraventricular tachy-arrhythmias usually respond to restoration of normal body temperature and correction of circulatory or metabolic disturbances. If persistent or life threatening, appropriate antiarrhythmic therapy may be considered. Avoid lidocaine and, as far as possible, long acting antiarrhythmic drugs.

Pronounced central nervous system depression requires airway maintenance or, in extreme circumstances, assisted respiration. Severe dystonic reactions usually respond to procyclidine (5-10 mg) or orphenedrine (20-40 mg) administered intramuscularly or intravenously. Convulsions should be treated with intravenous diazepam.

Neuroleptic malignant syndrome should be treated with cooling. Dantrolene sodium may be tried.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antipsychotics, ATC Code: N05AA01. Chlorpromazine is a phenothiazine neuroleptic.

Chlorpromazine has depressant actions on the Central Nervous System, with alpha-adrenergic blocking and anticholinergic activities. It inhibits Dopamine and Prolactin release-inhibitory factor, thus stimulating the release of Prolactin. It increases the turnover of Dopamine in the brain.

It has anti-emetic, anti-pruritic, serotonin-blocking and weak anti-histamine properties and slight ganglion blocking activity. It inhibits the heat regulating centre in the brain, and is analgesic and can relax skeletal muscle.

Due to its action on the autonomic system, it produces vasodilatation, hypotension and tachycardia.

Salivary and gastric secretions are reduced.

5.2 Pharmacokinetic properties

Chlorpromazine is rapidly absorbed and widely distributed in the body. It is metabolised in the liver and excreted in the urine and bile. Whilst plasma concentration of chlorpromazine itself rapidly declines excretion of chlorpromazine metabolites is very slow. The drug is highly bound to plasma protein. It readily diffuses across the placenta. Small quantities have been detected in milk from treated women. Children require smaller dosages per kg than adults.

5.3 Preclinical safety data

Not applicable.

6. Pharmaceutical particulars

6.1 List of excipients

Core:

Lactose

Maize Starch

Povidone

Sodium starch glycollate

Colloidal anhydrous silica

Magnesium stearate

In coating:

Hypromellose

Eththylcellulose 10 cps

Diethylphthalate

Titanium dioxide

6.2 Incompatibilities

Chlorpromazine can increase the central nervous system depression produced by other CNS-depressant drugs including alcohol, hypnotics, sedatives or strong analgesics.

It antagonises the action of adrenaline and other sympathomimetic agents and reverses the blood pressure lowering effects of adrenergic blocking agents such as guanethidine and clonidine. It may impair the metabolism of tricyclic antidepressants, the anti-Parkinson effects of levodopa and the effects of anticonvulsants; it may possibly affect the control of diabetes, or the action of anticoagulants. Antacids can impair absorption. Tea and coffee may prevent absorption by causing insoluble precipitates.

Undesirable anticholinergic effects can be enhanced by anti-Parkinson or other anticholinergic drugs. It may enhance the cardiac-depressant effects of quinidine, the absorption of corticosteroids and digoxin, the effect of diazoxide and of neuromuscular blocking agents. Interactions with propanolol have been reported. The possibility of interaction with lithium should be bone in mind.

Further information: Chlorpromazine is a phenothiazine with an aliphatic side-chain. Its pharmacological profile of activity includes pronounced sedative and hypotensive properties, with fairly marked anticholinergic and anti-emetic activity and a moderate tendency to cause extrapyramidal reactions.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25° C. Store in the original package.

6.5 Nature and contents of container

High density polystyrene with polythene lids and/or polypropylene containers with polypropylene or polythene lids and polyurethane/polythene wads.

250 micron PVC glass-clear/green rigid PVC (pharmaceutical grade). 20 micron hard-tempered aluminium foil coated on the dull side with 6-7 gsm heat seal lacquer and printed on the bright side.

Packs of 28, 30, 50, 56, 60, 84, 100, 250, 500 & 1000 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. Marketing authorisation holder

Dr. Reddy's Laboratories (UK) Ltd,

410 Cambridge Science Park,

Milton Road,

Cambridge,

CB4 0PE,

United Kingdom

8. Marketing authorisation number(s)

PL 08553/0076

9. Date of first authorisation/renewal of the authorisation

Date of first authorization: 17 Oct 2005

10. Date of revision of the text

10/2024

Company Contact Details

Dr. Reddy's Laboratories (UK) Ltd

Address

Dr. Reddy's Laboratories (UK) Limited, 410 Cambridge Science Park, Milton Road, Cambridge, CB4 0PE, UK

Medical Information Direct Line

+44 (0)1748 828 873

Customer Care direct line

+44 (0)1223 651 475

E-mail

customerserviceuk@drreddys.com

Telephone

+44 (0)1223 728 010

Medical Information e-mail

drreddysgb@eu.propharmagroup.com

WWW

http://www.drreddys.com/united-kingdom

Clozapine

EMC

Clozaril 100 mg Tablets

Summary of Product Characteristics Updated 13-Feb-2024 | Mylan

1. Name of the medicinal product

Clozaril® 100 mg Tablets.

Clozapine Mylan 100 mg Tablets

UK Clozaril® Official Recommendations

As a consequence of a recent European regulatory initiative, the Clozaril Summary of Product Characteristics (SmPC) has been harmonised across Europe. The SmPC states that blood monitoring should be carried out in accordance with national-specific official recommendations. These are reproduced below.

The UK Clozaril Patient Monitoring Service (CPMS) was developed in order to manage the risk of agranulocytosis associated with clozapine. It is available 24 hours a day. When a monitoring service is not used, evidence suggests a mortality rate from agranulocytosis of 0.3% [1]. This is compared to a mortality rate when Clozaril is used in conjunction with the Clozaril Patient Monitoring Service, of 0.01%[2].

The Clozaril Patient Monitoring Service provides for the centralised monitoring of leucocyte and neutrophil counts which is a mandatory requirement for all patients in the UK who are treated with Clozaril. The use of Clozaril is restricted to patients who are registered with the Clozaril Patient Monitoring Service. In addition to registering their patients, prescribing physicians must register themselves and a nominated pharmacist with the Clozaril Patient Monitoring Service. All Clozaril-treated patients must be under the supervision of an appropriate specialist and supply of Clozaril is restricted to hospital and retail pharmacies registered with the Clozaril Patient Monitoring Service. Clozaril is not sold to, or distributed through wholesalers.

In the UK, a white cell count with a differential count must be monitored:

• At least weekly for the first 18 weeks of treatment

• At least at 2 week intervals between weeks 18 and 52

• After 1 year of treatment with stable neutrophil counts, patients may be monitored at least at 4 week intervals

• Monitoring must continue throughout treatment and for at least 4 weeks after discontinuation

The Clozaril Patient Monitoring Service maintains a database which includes all patients who have developed abnormal leucocyte or neutrophil findings and who should not be re-exposed to Clozaril.

Prescribers and pharmacists should adhere to brand prescribing and dispensing of clozapine in order to prevent the disruption to effective monitoring that may be caused if patients switch brands.

Furthermore, in order to protect patient safety, at any one time patients should only be prescribed one brand of clozapine and only registered with the monitoring service connected to that brand.

Advice on monitoring clozapine blood levels

Blood clozapine level monitoring is advised in certain clinical situations such as when a patient ceases smoking or switches to e-cigarettes, when concomitant medicines may interact to increase clozapine blood levels, where poor clozapine metabolism is suspected, when a patient has pneumonia or other serious infection and in the event of onset of symptoms suggestive of toxicity (see section 4.4).

For further information regarding Clozaril and the Clozaril Patient Monitoring Service please call 08457 698269.

[1] De la Chapelle A, et al. *Clozapine-induced agranulocytosis: a genetic and epidemiologic study.* Hum Genet, 1977. 37: p. 183-194.

[2] Clozaril Patient Monitoring Service, data on file.

Clozaril can cause agranulocytosis. Its use should be limited to patients:

- with schizophrenia who are non-responsive to or intolerant of antipsychotic medication, or with psychosis in Parkinson's disease when other treatment strategies have failed (see section 4.1),

- who have initially normal leukocyte findings (white blood cell count ≥ 3500/mm^3(≥ 3.5x10^9/l), and ANC ≥ 2000/mm^3 (≥ 2.0x10^9/l)), and

- in whom regular white blood cell (WBC) counts and absolute neutrophil counts (ANC) can be performed as follows: weekly during the first 18 weeks of treatment, and at least every 4 weeks thereafter throughout

treatment. Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of Clozaril (see section 4.4.).

Prescribing physicians must comply fully with the required safety measures. At each consultation, a patient receiving Clozaril must be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention must be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia (see section 4.4).

Clozaril must be dispensed under strict medical supervision in accordance with official recommendations (see section 4.4).

Myocarditis

Clozapine is associated with an increased risk of myocarditis which has, in rare cases, been fatal. The increased risk of myocarditis is greatest in the first 2 months of treatment. Fatal cases of cardiomyopathy have also been reported rarely (see section 4.4).

Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first 2 months of treatment, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (e.g. unexplained fatigue, dyspnoea, tachypnoea) or symptoms that mimic myocardial infarction (see section 4.4).

If myocarditis or cardiomyopathy are suspected, Clozaril treatment should be promptly stopped and the patient immediately referred to a cardiologist (see section 4.4).

Patients who develop clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine (see section 4.3 and 4.4).

2. Qualitative and quantitative composition

Each tablet contains 100 mg clozapine.

Excipient(s) with known effect: also includes lactose monohydrate 192.0 mg per tablet.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Tablets.

Yellow, circular, flat tablet with bevelled edges. Coded “ Z/A” with an angle score on one side and “ CLOZ” on the reverse.

The tablet can be divided into equal halves.

4. Clinical particulars

4.1 Therapeutic indications

Treatment-resistant schizophrenia

Clozaril is indicated in treatment-resistant schizophrenic patients and in schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics.

Treatment resistance is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two different antipsychotic agents, including an atypical antipsychotic agent, prescribed for adequate duration.

Psychosis during the course of Parkinson's disease

Clozaril is also indicated in psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed.

4.2 Posology and method of administration

Posology

The dosage must be adjusted individually. For each patient the lowest effective dose should be used. For doses not realisable/practicable with one strength, other strengths of this medicinal product are available. Cautious titration and a divided dosage schedule are necessary to minimise the risks of hypotension, seizure and sedation.

Initiation of Clozaril treatment must be restricted to those patients with a WBC count ≥ 3500/mm^3 ($3.5x10^9$/l) and an ANC ≥ 2000/mm^3 ($2.0x10^9$/l) within standardised normal limits.

Dose adjustment is indicated in patients who are also receiving medicinal products that have pharmacodynamic and pharmacokinetic interactions with Clozaril, such as benzodiazepines or selective serotonin re-uptake inhibitors (see section 4.5).

Switching from a previous antipsychotic therapy to Clozaril

It is generally recommended that Clozaril should not be used in combination with other antipsychotics. When Clozaril therapy is to be initiated in a patient undergoing oral antipsychotic therapy, it is recommended that the other antipsychotic should first be discontinued by tapering the dosage downwards.

The following dosages are recommended:

Treatment-resistant schizophrenic patients

Starting therapy

12.5 mg once or twice on the first day, followed by 25 mg once or twice on the second day. If well tolerated, the daily dose may then be increased slowly in increments of 25 to 50 mg in order to achieve a dose level of up to 300 mg/day within 2 to 3 weeks. Thereafter, if required, the daily dose may be further increased in increments of 50 to 100 mg at half-weekly or, preferably, weekly intervals.

Therapeutic dose range

In most patients, antipsychotic efficacy can be expected with 200 to 450 mg/day given in divided doses. The total daily dose may be divided unevenly, with the larger portion at bedtime.

Maximum dose

To obtain full therapeutic benefit, a few patients may require larger doses, in which case judicious increments (not exceeding 100 mg) are permissible up to 900 mg/day. However, the possibility of increased adverse reactions (in particular seizures) occurring at doses over 450 mg/day must be borne in mind.

Maintenance dose

After achieving maximum therapeutic benefit, many patients can be maintained effectively on lower doses. Careful downward titration is therefore recommended. Treatment should be maintained for at least 6 months. If the daily dose does not exceed 200 mg, once daily administration in the evening may be appropriate.

Ending therapy

In the event of planned termination of Clozaril therapy, a gradual reduction in dose over a 1 to 2-week period is recommended. If abrupt discontinuation is necessary, the patient should be carefully observed for the occurrence of withdrawal reactions (see section 4.4).

Re-starting therapy

In patients in whom the interval since the last dose of Clozaril exceeds 2 days, treatment should be re-initiated with 12.5 mg given once or twice on the first day. If this dose is well tolerated, it may be feasible to titrate the dose to the therapeutic level more quickly than is recommended for initial treatment. However, in any patient who has previously experienced respiratory or cardiac arrest with initial dosing (see section 4.4), but was then able to be successfully titrated to a therapeutic dose, re-titration should be carried out with extreme caution.

Psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed

Starting therapy

The starting dose must not exceed 12.5 mg/day, taken in the evening. Subsequent dose increases must be by 12.5 mg increments, with a maximum of two increments a week up to a maximum of 50 mg, a dose that cannot be reached until the end of the second week. The total daily amount should preferably be given as a single dose in the evening.

Therapeutic dose range

The mean effective dose is usually between 25 and 37.5 mg/day. In the event that treatment for at least one week with a dose of 50 mg fails to provide a satisfactory therapeutic response, dosage may be cautiously increased by increments of 12.5 mg/week.

Maximum dose

The dose of 50 mg/day should only be exceeded in exceptional cases, and the maximum dose of 100 mg/day must never be exceeded.

Dose increases should be limited or deferred if orthostatic hypotension, excessive sedation or confusion occurs. Blood

pressure should be monitored during the first weeks of treatment.

Maintenance dose

When there has been complete remission of psychotic symptoms for at least 2 weeks, an increase in anti-parkinsonian medication is possible if indicated on the basis of motor status. If this approach results in the recurrence of psychotic symptoms, Clozaril dosage may be increased by increments of 12.5 mg/week up to a maximum of 100 mg/day, taken in one or two divided doses (see above).

Ending therapy

A gradual reduction in dose by steps of 12.5 mg over a period of at least one week (preferably two) is recommended.

Treatment must be discontinued immediately in the event of neutropenia or agranulocytosis (see section 4.4). In this situation, careful psychiatric monitoring of the patient is essential since symptoms may recur quickly.

Special populations

Hepatic impairment

Patients with hepatic impairment should receive Clozaril with caution along with regular monitoring of liver function tests (see section 4.4).

Paediatric population

No paediatric studies have been performed. The safety and efficacy of Clozaril in children and adolescents under the age of 16 years have not yet been established. It should not be used in this group until further data become available.

Patients 60 years of age and older

Initiation of treatment is recommended at a particularly low dose (12.5 mg given once on the first day), with subsequent dose increments restricted to 25 mg/day.

Method of administration

Clozaril is administered orally.

4.3 Contraindications

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

• Patients unable to undergo regular blood tests.

• History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/ agranulocytosis from previous chemotherapy).

• History of Clozaril-induced agranulocytosis.

• Clozaril treatment must not be started concurrently with substances known to have a substantial potential for causing agranulocytosis; concomitant use of depot antipsychotics is to be discouraged

• Impaired bone marrow function.

• Uncontrolled epilepsy.

• Alcoholic and other toxic psychoses, drug intoxication, comatose conditions.

• Circulatory collapse and/or CNS depression of any cause.

• Severe renal or cardiac disorders (e.g. myocarditis).

• Active liver disease associated with nausea, anorexia or jaundice; progressive liver disease, hepatic failure.

• Paralytic ileus.

4.4 Special warnings and precautions for use

Agranulocytosis

Clozaril can cause agranulocytosis. The incidence of agranulocytosis and the fatality rate in those developing agranulocytosis have decreased markedly since the institution of white blood cell (WBC) counts and absolute neutrophil count (ANC) monitoring. The following precautionary measures are therefore mandatory and should be carried out in accordance with official recommendations.

Because of the risks associated with Clozaril, its use is limited to patients in whom therapy is indicated as set out in section 4.1 and:

• who have initially normal leukocyte findings (WBC count ≥ 3500/mm^3 ($3.5x10^9$/l) and ANC ≥ 2000/mm^3 ($2.0x10^9$/l), and

• in whom regular WBC counts and ANC can be performed weekly for the first 18 weeks and at least 4-week intervals thereafter. Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of Clozaril.

Before initiating clozapine therapy patients should have a blood test (see " agranulocytosis") and a history and physical examination. Patients with history of cardiac illness or abnormal cardiac findings on physical examination should be referred to a specialist for other examinations that might include an ECG, and the patient treated only if the expected benefits clearly outweigh the risks (see section 4.3). The treating physician should consider performing a pre-treatment ECG.

Prescribing physicians must comply fully with the required safety measures.

Prior to treatment initiation, physicians must ensure, to the best of their knowledge, that the patient has not previously experienced an adverse haematological reaction to clozapine that necessitated its discontinuation. Prescriptions should not be issued for periods longer than the interval between two blood counts.

Immediate discontinuation of Clozaril is mandatory if either the WBC count is less than 3000/mm^3 ($3.0x10^9$/l) or the ANC is less than 1500/mm^3 ($1.5x10^9$/l) at any time during Clozaril treatment. Patients in whom Clozaril has been discontinued as a result of either WBC or ANC deficiencies must not be re-exposed to Clozaril.

At each consultation, a patient receiving Clozaril must be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention should be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia. Patients and their caregivers must be informed that, in the event of any of these symptoms, they must have a blood cell count performed immediately. Prescribers are encouraged to keep a record of all patients' blood results and to take any steps necessary to prevent these patients from accidentally being rechallenged in the future.

Patients with a history of primary bone marrow disorders may be treated only if the benefit outweighs the risk. They should be carefully reviewed by a haematologist prior to starting Clozaril.

Patients who have low WBC counts because of benign ethnic neutropenia should be given special consideration and may only be started on Clozaril with the agreement of a haematologist.

White Blood Cell (WBC) counts and Absolute Neutrophil Count (ANC) monitoring

WBC and differential blood counts must be performed within 10 days prior to initiating Clozaril treatment to ensure that only patients with normal WBC counts and ANC (WBC count ≥ 3500/mm^3 ($3.5x10^9$/l) and ANC ≥ 2000/mm^3 ($2.0x10^9$/l)) will receive Clozaril. After the start of Clozaril treatment regular WBC count and ANC must be performed and monitored weekly for the first 18 weeks, and at least at four-week intervals thereafter.

Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of Clozaril or until haematological recovery has occurred (see " Low WBC count/ANC" below). At each consultation, the patient must be reminded to contact the treating physician immediately if any kind of infection, fever, sore throat or other flu-like symptoms develop. WBC and differential blood counts must be performed immediately if any symptoms or signs of an infection occur.

Low WBC count/ANC

If, during Clozaril therapy, either the WBC count falls to between 3500/mm^3 ($3.5x10^9$/l) and 3000/mm^3 ($3.0x10^9$/l) or the ANC falls to between 2000/mm^3 ($2.0x10^9$/l) and 1500/mm^3 ($1.5x10^9$/l), haematological evaluations must be performed at least twice weekly until the patient's WBC count and ANC stabilise within the range 3000-3500/mm^3 (3.0-$3.5x10^9$/l) and 1500-2000/mm^3 (1.5-$2.0x10^9$/l), respectively, or higher.

Immediate discontinuation of Clozaril treatment is mandatory if either the WBC count is less than 3000/mm^3 ($3.0x10^9$/l) or the ANC is less than 1500/mm^3 ($1.5x10^9$/l) during Clozaril treatment. WBC counts and differential blood counts should then be performed daily and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection. Confirmation of the haematological values is recommended by performing two blood counts on two consecutive days; however, Clozaril should be discontinued after the first blood count.

Following discontinuation of Clozaril, haematological evaluation is required until haematological recovery has occurred.

Table 1

Blood cell count	Action required

WBC/mm^3 (/l)	ANC/mm^3 (/l)	
≥ 3500 (≥ $3.5x10^9$)	≥ 2000 (≥ $2.0x10^9$)	Continue Clozaril treatment
Between ≥ 3000 and < 3500 (≥ $3.0x10^9$ and < $3.5x10^9$)	Between ≥ 1500 and < 2000 (≥ $1.5x10^9$ and < $2.0x10^9$)	Continue Clozaril treatment, sample blood twice weekly until counts stabilise or increase
< 3000 (< $3.0x10^9$)	< 1500 (< $1.5x10^9$)	Immediately stop Clozaril treatment, sample blood daily until haematological abnormality is resolved, monitor for infection. Do not re-expose the patient.

If Clozaril has been withdrawn and either a further drop in the WBC count below 2000/mm^3 ($2.0x10^9$/l) occurs or the ANC falls below 1000/mm^3 ($1.0x10^9$/l), the management of this condition must be guided by an experienced haematologist.

Discontinuation of therapy for haematological reasons

Patients in whom Clozaril has been discontinued as a result of either WBC or ANC deficiencies (see above) must not be re-exposed to Clozaril.

Prescribers are encouraged to keep a record of all patients' blood results and to take any steps necessary to prevent the patient being accidentally rechallenged in the future.

Discontinuation of therapy for other reasons

Patients who have been on Clozaril for more than 18 weeks and have had their treatment interrupted for more than 3 days but less than 4 weeks should have their WBC count and ANC monitored weekly for an additional 6 weeks. If no haematological abnormality occurs, monitoring at intervals not exceeding 4 weeks may be resumed. If Clozaril treatment has been interrupted for 4 weeks or longer, weekly monitoring is required for the next 18 weeks of treatment and the dose should be re-titrated (see section 4.2).

Other precautions

This medicinal product contains lactose monohydrate.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Eosinophilia

In the event of **eosinophilia**, discontinuation of Clozaril is recommended if the eosinophil count rises above 3000/mm^3 ($3.0x10^9$/l); therapy should be restarted only after the eosinophil count has fallen below 1000/mm^3 ($1.0x10^9$/l).

Thrombocytopenia

In the event of **thrombocytopenia**, discontinuation of Clozaril therapy is recommended if the platelet count falls below 50 000/mm^3 ($50x10^9$/l).

Cardiovascular disorders

Orthostatic hypotension, with or without syncope, can occur during Clozaril treatment. Rarely, collapse can be profound and may be accompanied by cardiac and/or respiratory arrest. Such events are more likely to occur with concurrent use of a benzodiazepine or any other psychotropic agent (see section 4.5) and during initial titration in association with rapid dose escalation; on very rare occasions they may occur even after the first dose. Therefore, patients starting Clozaril treatment require close medical supervision. Monitoring of standing and supine blood pressure is necessary during the first weeks of treatment in patients with Parkinson's disease.

Analysis of safety databases suggests that the use of Clozaril is associated with an increased risk of **myocarditis** especially during, but not limited to, the first two months of treatment. Some cases of myocarditis have been fatal. **Pericarditis/pericardial effusion** and **cardiomyopathy** have also been reported in association with Clozaril use; these reports also include fatalities. Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first two months of treatment, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (e.g. unexplained fatigue, dyspnoea, tachypnoea), or symptoms that mimic myocardial infarction. Other symptoms which may be present in addition to the above include flu-like symptoms. If myocarditis or cardiomyopathy is suspected, Clozaril treatment should be promptly stopped and the patient immediately referred to a cardiologist.

In patients who are diagnosed with cardiomyopathy while on Clozaril treatment, there is potential to develop mitral valve

incompetence. Mitral valve incompetence has been reported in cases of cardiomyopathy related to Clozaril treatment. These cases of mitral valve incompetence reported either mild or moderate mitral regurgitation on two-dimensional echocardiography (2DEcho) (see section 4.8).

Patients with clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to Clozaril.

Myocardial infarction

There have been post marketing reports of **myocardial infarction** including fatal cases. Causality assessment was difficult in the majority of these cases because of serious pre-existing cardiac disease and plausible alternative causes.

QT interval prolongation

As with other antipsychotics, caution is advised in patients with known cardiovascular disease or family history of **QT prolongation**.

As with other antipsychotics, caution should be exercised when clozapine is prescribed with medicines known to increase QTc interval.

Cerebrovascular adverse events

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. Clozapine should be used with caution in patients with risk factors for stroke.

Risk of thromboembolism

Since Clozaril may be associated with **thromboembolism**, immobilisation of patients should be avoided.

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 Clozaril and preventive measures undertaken.

Seizures

Patients with a history of epilepsy should be closely observed during Clozaril therapy since dose-related convulsions have been reported. In such cases, the dose should be reduced (see section 4.2) and, if necessary, an anti-convulsant treatment should be initiated.

Anticholinergic effects

Clozaril exerts anticholinergic activity, which may produce undesirable effects throughout the body. Careful supervision is indicated in the presence of **prostatic enlargement** and **narrow-angle glaucoma**. Probably on account of its anticholinergic properties, Clozaril has been associated with varying degrees of **impairment of intestinal peristalsis**, ranging from **constipation** to **intestinal obstruction**, **faecal impaction, paralytic ileus, megacolon and intestinal infarction ischaemia** (see section 4.8). On rare occasions these cases have been fatal. Particular care is necessary in patients who are receiving concomitant medications known to cause constipation (especially those with anticholinergic properties such as some antipsychotics, antidepressants and antiparkinsonian treatments), have a history of colonic disease or a history of lower abdominal surgery as these may exacerbate the situation. It is vital that constipation is recognised and actively treated.

Fever

During Clozaril therapy, patients may experience transient **temperature elevations** above 38° C, with the peak incidence within the first 3 weeks of treatment. This fever is generally benign. Occasionally, it may be associated with an increase or decrease in the WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infection or the development of agranulocytosis. In the presence of high fever, the possibility of **neuroleptic malignant syndrome** (NMS) must be considered. If the diagnosis of NMS is confirmed, Clozaril should be discontinued immediately and appropriate medical measures should be administered.

Falls

Clozaril may cause seizures, 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.

Metabolic changes

Atypical antipsychotic drugs, including Clozaril, have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes may include hyperglycaemia, dyslipidemia, and body

weight gain. While atypical antipsychotic drugs may produce some metabolic changes, each drug in the class has its own specific profile.

Hyperglycaemia

Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus has been reported rarely during treatment with clozapine. A mechanism for this possible association has not yet been determined. Cases of severe hyperglycaemia with ketoacidosis or hyperosmolar coma have been reported very rarely in patients with no prior history of hyperglycaemia, some of which have been fatal. When follow-up data were available, discontinuation of clozapine resulted mostly in resolution of the impaired glucose tolerance, and reinstitution of clozapine resulted in its reoccurrence. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug. The discontinuation of clozapine should be considered in patients where active medical management of their hyperglycaemia has failed.

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics, including Clozaril. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using clozapine, is recommended.

Weight gain

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

Rebound, withdrawal effects

Acute withdrawal reactions have been reported following abrupt cessation of clozapine therefore gradual withdrawal is recommended. If abrupt discontinuation is necessary (e.g. because of leucopenia), the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound, such as profuse sweating, headache, nausea, vomiting and diarrhoea.

Special populations

Hepatic impairment

Patients with stable pre-existing liver disorders may receive Clozaril, but need regular liver function tests. Liver function tests should be performed in patients in whom symptoms of possible **liver dysfunction**, such as nausea, vomiting and/or anorexia, develop during Clozaril therapy. If the elevation of the values is clinically relevant (more than 3 times the UNL) or if symptoms of jaundice occur, treatment with Clozaril must be discontinued. It may be resumed (see “ Re-starting therapy” under section 4.2) only when the results of liver function tests are normal. In such cases, liver function should be closely monitored after re-introduction of Clozaril.

Patients aged 60 years and older

Initiation of treatment in patients aged 60 years and older is recommended at a lower dose (see section 4.2).

Orthostatic hypotension can occur with Clozaril treatment and there have been reports of tachycardia, which may be sustained. Patients aged 60 years and older, particularly those with compromised cardiovascular function, may be more susceptible to these effects.

Patients aged 60 years and older may also be particularly susceptible to the anticholinergic effects of Clozaril, such as urinary retention and constipation.

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 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.

Clozaril is not approved for the treatment of dementia-related behavioural disturbances.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindication of concomitant use

Substances known to have a substantial potential to depress bone marrow function must not be used concurrently with

Clozaril (see section 4.3).

Long-acting depot antipsychotics (which have myelosuppressive potential) must not be used concurrently with Clozaril because these cannot be rapidly removed from the body in situations where this may be required, e.g. neutropenia (see section 4.3).

Alcohol should not be used concomitantly with Clozaril due to possible potentiation of sedation.

Precautions including dose adjustment

Clozaril may enhance the central effects of CNS depressants such as narcotics, antihistamines and benzodiazepines. Particular caution is advised when Clozaril therapy is initiated in patients who are receiving a benzodiazepine or any other psychotropic agent. These patients may have an increased risk of circulatory collapse, which, on rare occasions, can be profound and may lead to cardiac and/or respiratory arrest. It is not clear whether cardiac or respiratory collapse can be prevented by dose adjustment.

Because of the possibility of additive effects, caution is essential in the concomitant administration of substances possessing anticholinergic, hypotensive, or respiratory depressant effects.

Owing to its anti-alpha-adrenergic properties, Clozaril may reduce the blood-pressure-increasing effect of norepinephrine or other predominantly alpha-adrenergic agents and reverse the pressor effect of epinephrine.

Concomitant administration of substances known to inhibit the activity of some cytochrome P450 isozymes may increase the levels of clozapine, and the dose of clozapine may need to be reduced to prevent undesirable effects. This is more important for CYP 1A2 inhibitors such as caffeine (see below), perazine and the selective serotonin reuptake inhibitor fluvoxamine. Some of the other serotonin reuptake inhibitors such as fluoxetine, paroxetine, and, to a lesser degree, sertraline, are CYP 2D6 inhibitors and, as a consequence, major pharmacokinetic interactions with clozapine are less likely. Similarly, pharmacokinetic interactions with CYP 3A4 inhibitors such as azole antimycotics, cimetidine, erythromycin and protease inhibitors are unlikely, although some have been reported. Hormonal contraceptives (including combinations of estrogen and progesterone or progesterone only) are CYP 1A2, CYP 3A4 and CYP 2C19 inhibitors. Therefore initiation or discontinuation of hormonal contraceptives, may require dose adjustment of clozapine according to the individual medical need. Because the plasma concentration of clozapine is increased by caffeine intake and decreased by nearly 50% following a 5-day caffeine-free period, dosage changes of clozapine may be necessary when there is a change in caffeine-drinking habit. In cases of sudden cessation of smoking, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects.

Cases have been reported of an interaction between citalopram and clozapine, which may increase the risk of adverse events associated with clozapine. The nature of this interaction has not been fully elucidated.

Concomitant administration of substances known to induce cytochrome P450 enzymes may decrease the plasma levels of clozapine, leading to reduced efficacy. Substances known to induce the activity of cytochrome P450 enzymes and with reported interactions with clozapine include, for instance, carbamazepine (not to be used concomitantly with clozapine, due to its myelosuppresive potential), phenytoin and rifampicin. Known inducers of CYP1A2, such as omeprazole, may lead to decreased clozapine levels. The potential for reduced efficacy of clozapine should be considered when it is used in combination with these substances.

Other

Concomitant use of lithium or other CNS-active agents may increase the risk of development of neuroleptic malignant syndrome (NMS).

Rare but serious reports of seizures, including onset of seizures in non-epileptic patients, and isolated cases of delirium where Clozaril was co-administered with valproic acid have been reported. These effects are possibly due to a pharmacodynamic interaction, the mechanism of which has not been determined.

Caution is called for in patients receiving concomitant treatment with other substances which are either inhibitors or inducers of the cytochrome P450 isozymes. With tricyclic antidepressants, phenothiazines and type 1_C anti-arrhythmics, which are known to bind to cytochrome P450 2D6, no clinically relevant interactions have been observed thus far.

As with other antipsychotics, caution should be exercised when clozapine is prescribed with medicines known to increase QTc interval, or causing electrolyte imbalance.

An outline of drug interactions believed to be most important with Clozaril is given in Table 2 below. The list is not exhaustive.

Table 2: Reference to the most common drug interactions with Clozaril

Drug	Interactions	Comments

Bone marrow suppressants (e.g. carbamazepine, chloramphenicol), sulphonamides (e.g. co-trimoxazole), pyrazolone analgesics (e.g. phenylbutazone), penicillamine, cytotoxic agents and long-acting depot injections of antipsychotics	Interact to increase the risk and/or severity of bone marrow suppression.	Clozaril **must not be used** concomitantly with other agents having a well known potential to suppress bone marrow function (see section 4.3).
Benzodiazepines	Concomitant use may increase risk of circulatory collapse, which may lead to cardiac and/or respiratory arrest.	Whilst the occurrence is rare, caution is advised when using these agents together. Reports suggest that respiratory depression and collapse are more likely to occur at the start of this combination or when Clozaril is added to an established benzodiazepine regimen.
Anticholinergics	Clozaril potentiates the action of these agents through additive anticholinergic activity.	Observe patients for anticholinergic side-effects, e.g. constipation, especially when using to help control hypersalivation.
Antihypertensives	Clozaril can potentiate the hypotensive effects of these agents due to its sympathomimetic antagonistic effects.	Caution is advised if Clozaril is used concomitantly with antihypertensive agents. Patients should be advised of the risk of hypotension, especially during the period of initial dose titration.
Alcohol, MAOIs, CNS depressants, including narcotics and benzodiazepines	Enhanced central effects. Additive CNS depression and cognitive and motor performance interference when used in combination with these substances.	Caution is advised if Clozaril is used concomitantly with other CNS active agents. Advise patients of the possible additive sedative effects and caution them not to drive or operate machinery.
Highly protein bound substances (e.g. warfarin and digoxin)	Clozaril may cause an increase in plasma concentration of these substances due to displacement from plasma proteins.	Patients should be monitored for the occurrence of side effects associated with these substances, and doses of the protein bound substance adjusted, if necessary.
Phenytoin	Addition of phenytoin to Clozaril regimen may cause a decrease in the clozapine plasma concentrations.	If phenytoin must be used, the patient should be monitored closely for a worsening or recurrence of psychotic symptoms.
Lithium	Concomitant use can increase the risk of development of neuroleptic malignant syndrome (NMS).	Observe for signs and symptoms of NMS.
CYP1A2 inducing substances (e.g. omeprazole)	Concomitant use may decrease clozapine levels	Potential for reduced efficacy of clozapine should be considered.
CYP1A2 inhibiting substances e.g. fluvoxamine, caffeine, ciprofloxacin, perazine or hormonal contraceptives (CYP1A2, CYP3A4, CYP2C19)	Concomitant use may increase clozapine levels	Potential for increase in adverse effects. Care is also required upon cessation of concomitant CYP1A2 or CYP3A4 inhibiting medications as there may be a decrease in clozapine levels. The effect of CYP2C19 inhibition may be minimal.

4.6 Fertility, pregnancy and lactation

Pregnancy

For clozapine, there are only limited clinical data on exposed pregnancies. Animal studies do not indicate direct or

indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3). Caution should be exercised when prescribing to pregnant women.

Neonates exposed to antipsychotics (including Clozaril) 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.

Breastfeeding

Animal studies suggest that clozapine is excreted in breast milk and has an effect in the nursing infant; therefore, mothers receiving Clozaril should not breast-feed.

Fertility

Limited data available on the effects of clozapine on human fertility are inconclusive. In male and female rats, clozapine did not affect fertility when administered up to 40 mg/kg, corresponding to a human equivalence dose of 6.4 mg/kg or approximately a third of the maximum permissible adult human dose.

Women of child-bearing potential

A return to normal menstruation may occur as a result of switching from other antipsychotics to Clozaril. Adequate contraceptive measures must therefore be ensured in women of childbearing potential.

4.7 Effects on ability to drive and use machines

Owing to the ability of Clozaril to cause sedation and lower the seizure threshold, activities such as driving or operating machinery should be avoided, especially during the initial weeks of treatment.

4.8 Undesirable effects

Summary of the safety profile

For the most part, the adverse event profile of clozapine is predictable from its pharmacological properties. An important exception is its propensity to cause agranulocytosis (see section 4.4). Because of this risk, its use is restricted to treatment-resistant schizophrenia and psychosis occurring during the course of Parkinson's disease in cases where standard treatment has failed. While blood monitoring is an essential part of the care of patients receiving clozapine, the physician should be aware of other rare but serious adverse reactions, which may be diagnosed in the early stages only by careful observation and questioning of the patient in order to prevent morbidity and mortality.

The most serious adverse reactions experienced with clozapine are agranulocytosis, seizure, cardiovascular effects and fever (see section 4.4). The most common side effects are drowsiness/sedation, dizziness, tachycardia, constipation, and hypersalivation.

Data from the clinical trials experience showed that a varying proportion of clozapine-treated patients (from 7.1 to 15.6%) were discontinued due to an adverse event, including only those that could be reasonably attributed to clozapine. The more common events considered to be causes of discontinuation were leukopenia, somnolence, dizziness (excluding vertigo) and psychotic disorder.

Blood and lymphatic system

Development of granulocytopenia and agranulocytosis is a risk inherent to Clozaril treatment. Although generally reversible on withdrawal of treatment, agranulocytosis may result in sepsis and can prove fatal. Because immediate withdrawal of treatment is required to prevent the development of life-threatening agranulocytosis, monitoring of the WBC count is mandatory (see section 4.4). Table 3 below summarises the estimated incidence of agranulocytosis for each Clozaril treatment period.

Table 3: Estimated incidence of agranulocytosis[1]

Treatment period	Incidence of agranulocytosis per 100,000 person-weeks[2] of observation
Weeks 0-18	32.0
Weeks 19-52	2.3
Weeks 53 and higher	1.8

[1] From the UK Clozaril Patient Monitoring Service lifetime registry experience between 1989 and 2001.

[2] Person-time is the sum of individual units of time that the patients in the registry were exposed to Clozaril before

experiencing agranulocytosis. For example, 100,000 person-weeks could be observed in 1,000 patients who were in the registry for 100 weeks (100*1000=100,000), or in 200 patients who were in the registry for 500 weeks (200*500=100,000) before experiencing agranulocytosis.

The cumulative incidence of agranulocytosis in the UK Clozaril Patient Monitoring Service lifetime registry experience (0-11.6 years between 1989 and 2001) is 0.78%. The majority of cases (approximately 70%) occur within the first 18 weeks of treatment.

Metabolic and nutritional disorders

Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus has been reported rarely during treatment with clozapine. On very rare occasions, severe hyperglycaemia, sometimes leading to ketoacidosis/ hyperosmolar coma, has been reported in patients on Clozaril treatment with no prior history of hyperglycaemia. Glucose levels normalised in most patients after discontinuation of Clozaril and in a few cases hyperglycaemia recurred when treatment was reinitiated. Although most patients had risk factors for non-insulin-dependent diabetes mellitus, hyperglycaemia has also been documented in patients with no known risk factors (see section 4.4).

Nervous system disorders

The very common adverse reactions observed include drowsiness/sedation, and dizziness.

Clozaril can cause EEG changes, including the occurrence of spike and wave complexes. It lowers the seizure threshold in a dose-dependent manner and may induce myoclonic jerks or generalised seizures. These symptoms are more likely to occur with rapid dose increases and in patients with pre-existing epilepsy. In such cases the dose should be reduced and, if necessary, anticonvulsant treatment initiated. Carbamazepine should be avoided because of its potential to depress bone marrow function, and with other anticonvulsant the possibility of a pharmacokinetic interaction should be considered. In rare cases, patients treated with Clozaril may experience delirium.

Very rarely, tardive dyskinesia has been reported in patients on Clozaril who had been treated with other antipsychotic agents. Patients in whom tardive dyskinesia developed with other antipsychotics have improved on Clozaril.

Cardiac disorders

Tachycardia and postural hypotension with or without syncope may occur, especially in the initial weeks of treatment. The prevalence and severity of hypotension is influenced by the rate and magnitude of dose titration. Circulatory collapse as a result of profound hypotension, in particular related to aggressive titration, with the possible serious consequences of cardiac or pulmonary arrest, has been reported with Clozaril.

A minority of Clozaril-treated patients experience ECG changes similar to those seen with other antipsychotics, including S-T segment depression and flattening or inversion of T waves, which normalise after discontinuation of Clozaril. The clinical significance of these changes is unclear. However, such abnormalities have been observed in patients with myocarditis, which should therefore be considered.

Isolated cases of cardiac arrhythmias, pericarditis/pericardial effusion and myocarditis have been reported, some of which have been fatal. The majority of the cases of myocarditis occurred within the first 2 months of initiation of therapy with Clozaril. Cardiomyopathy generally occurred later in the treatment.

Eosinophilia has been co-reported with some cases of myocarditis (approximately 14%) and pericarditis/pericardial effusion; it is not known, however, whether eosinophilia is a reliable predictor of carditis.

Signs and symptoms of myocarditis or cardiomyopathy include persistent tachycardia at rest, palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (e.g. unexplained fatigue, dyspnoea, tachypnoea), or symptoms that mimic myocardial infarction. Other symptoms which may be present in addition to the above include flu-like symptoms.

Sudden, unexplained deaths are known to occur among psychiatric patients who receive conventional antipsychotic medication but also among untreated psychiatric patients. Such deaths have been reported very rarely in patients receiving Clozaril.

Vascular disorders

Rare cases of thromboembolism have been reported.

Respiratory system

Respiratory depression or arrest has occurred very rarely, with or without circulatory collapse (see sections 4.4 and 4.5).

Gastrointestinal system

Constipation and hypersalivation have been observed very frequently, and nausea and vomiting frequently. Very rarely ileus may occur (see section 4.4). Rarely Clozaril treatment may be associated with dysphagia. Aspiration of ingested food may occur in patients presenting with dysphagia or as a consequence of acute overdosage.

Hepatobiliary disorders

Transient, asymptomatic elevations of liver enzymes and, rarely, hepatitis and cholestatic jaundice may occur. Very rarely, fulminant hepatic necrosis has been reported. If jaundice develops, Clozaril should be discontinued (see section 4.4). In rare cases, acute pancreatitis has been reported.

Renal disorders

Isolated cases of acute interstitial nephritis have been reported in association with Clozaril therapy.

Reproductive and breast disorders

Very rare reports of priapism have been received.

General disorders

Cases of neuroleptic malignant syndrome (NMS) have been reported in patients receiving Clozaril either alone or in combination with lithium or other CNS-active agents.

Acute withdrawal reactions have been reported (see section 4.4).

Tabulated list of adverse reactions:

The table below (Table 4) summarises the adverse reactions accumulated from reports made spontaneously and during clinical studies.

Table 4: Treatment-emergent adverse experience frequency estimate from spontaneous and clinical trial reports

Adverse reactions are ranked under headings of frequency, 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).

Infections and infestations	
Not known:	Sepsis*
Blood and lymphatic system disorders	
Common:	Leukopenia/decreased WBC/neutropenia, eosinophilia, leukocytosis
Uncommon:	Agranulocytosis
Rare:	Anaemia
Very rare:	Thrombocytopenia, thrombocythaemia
Immune system disorders	
Not known:	Angioedema*, leukocytoclastic vasculitis*, Drug rash with eosinophilia and systemic symptoms (DRESS)*
Endocrine disorders	
Not known:	Pseudophaeochromocytoma*
Metabolism and nutrition disorders	
Common:	Weight gain
Rare:	Diabetes mellitus, impaired glucose tolerance, obesity*
Very rare:	Hyperosmolar coma, ketoacidosis, severe hyperglycaemia, hypercholesterolemia, hypertriglyceridemia
Psychiatric disorders	

Common:	Dysarthria
Uncommon:	Dysphemia
Rare:	Agitation, restlessness
Nervous system disorders	
Very common:	Drowsiness/sedation, dizziness
Common:	Seizures/convulsions/myoclonic jerks, extrapyramidal symptoms, akathisia, tremor, rigidity, headache
Uncommon:	Neuroleptic malignant syndrome
Rare:	Confusion, delirium
Very rare:	Tardive dyskinesia, obsessive compulsive symptoms
Not known:	Cholinergic syndrome (after abrupt withdrawal)*, EEG changes*, pleurothotonus*, restless leg syndrome*
Eye disorders	
Common:	Blurred vision
Cardiac disorders	
Very common:	Tachycardia
Common:	ECG changes
Rare:	Circulatory collapse, arrhythmias, myocarditis, pericarditis/ pericardial effusion
Very rare:	Cardiomyopathy, cardiac arrest
Not known:	Myocardial infarction*,**, myocarditis*,**, chest pain/angina pectoris*, atrial fibrillation*, palpitations*, mitral valve incompetence associated with clozapine related cardiomyopathy*
Vascular disorders	
Common:	Syncope, postural hypotension, hypertension
Rare:	Thromboembolism
Not known:	Hypotension*, Venous thromboembolism
Respiratory, thoracic and mediastinal disorders	
Rare:	Aspiration of ingested food, pneumonia and lower respiratory tract infection which may be fatal, sleep apnoea syndrome*
Very rare:	Respiratory depression/arrest
Not known:	Pleural effusion*, nasal congestion*
Gastrointestinal disorders	
Very common:	Constipation, hypersalivation
Common:	Nausea, vomiting, anorexia, dry mouth
Rare:	Dysphagia

Very rare:	Intestinal obstruction/paralytic ileus/faecal impaction, parotid gland enlargement
Not known:	Megacolon*,**, intestinal infarction/ischaemia*,**, intestinal necrosis*,**, intestinal ulceration*,** and intestinal perforation*,**, diarrhoea*, abdominal discomfort/ heartburn/dyspepsia*, colitis*
Hepatobiliary disorders	
Common:	Elevated liver enzymes
Rare:	Pancreatitis, hepatitis, cholestatic jaundice
Very rare:	Fulminant hepatic necrosis
Not known:	Hepatic steatosis*, hepatic necrosis*, hepatotoxicity*, hepatic fibrosis*, hepatic cirrhosis*, liver disorders including those hepatic events leading to life-threatening consequences such as liver injury (hepatic, cholestatic and mixed), liver failure which may be fatal and liver transplant*.
Skin and subcutaneous tissue disorders	
Very rare:	Skin reactions
Not known	Pigmentation disorder*
Musculoskeletal and connective tissue disorders	
Not known:	Rhabdomyolysis*, muscle weakness*, muscle spasms*, muscle pain*, systemic lupus erythematosus*
Renal and urinary disorders	
Common:	Urinary retention, urinary incontinence
Very rare:	Tubulointerstitial nephritis
Not known:	Renal failure*, Nocturnal enuresis*
Pregnancy, puerperium and perinatal conditions	
Not known	Drug withdrawal syndrome neonatal (see 4.6)
Reproductive system and breast disorders	
Very rare:	Priapism
Not known	Retrograde ejaculation*
General disorders and administration site conditions	
Common:	Benign hyperthermia, disturbances in sweating/temperature regulation, fever, fatigue
Very rare:	Sudden unexplained death
Not known:	Polyserositis*
Investigations	
Rare:	Increased CPK
Injury, poisoning and procedural complications	
Uncommon:	Falls (associated with clozapine-induced seizures, somnolence, postural hypotension, motor and sensory instability)*

* Adverse drug reactions derived from post-marketing experience via spontaneous case reports and literature cases.

** These adverse drug reactions were sometimes fatal.

Very rare events of ventricular tachycardia and QT prolongation which may be associated with Torsades De Pointes have been observed although there is no conclusive causal relationship to the use of this medicine.

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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In cases of acute intentional or accidental Clozaril overdose for which information on the outcome is available, mortality to date is about 12%. Most of the fatalities were associated with cardiac failure or pneumonia caused by aspiration and occurred at doses above 2000 mg. There have been reports of patients recovering from an overdose in excess of 10 000 mg. However, in a few adult individuals, primarily those not previously exposed to Clozaril, the ingestion of doses as low as 400 mg led to life-threatening comatose conditions and, in one case, to death. In young children, the intake of 50 to 200 mg resulted in strong sedation or coma without being lethal.

Signs and symptoms

Drowsiness, lethargy, areflexia, coma, confusion, hallucinations, agitation, delirium, extrapyramidal symptoms, hyperreflexia, convulsions; hypersalivation, mydriasis, blurred vision, thermolability; hypotension, collapse, tachycardia, cardiac arrhythmias; aspiration pneumonia, dyspnoea, respiratory depression or failure.

Treatment

There are no specific antidotes for Clozaril.

Gastric lavage and/or administration of activated charcoal within the first 6 hours after the ingestion of the drug. Peritoneal dialysis and haemodialysis are unlikely to be effective. Symptomatic treatment under continuous cardiac monitoring, surveillance of respiration, monitoring of electrolytes and acid-base balance. The use of epinephrine should be avoided in the treatment of hypotension because of the possibility of a 'reverse epinephrine' effect.

Close medical supervision is necessary for at least 5 days because of the possibility of delayed reactions.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antipsychotics; Diazepines, oxazepines and thiazepines, ATC code N05A H02

Mechanism of action

Clozaril has been shown to be an antipsychotic agent that is different from classic antipsychotics.

In pharmacological experiments, the compound does not induce catalepsy or inhibit apomorphine- or amphetamine-induced stereotyped behaviour. It has only weak dopamine-receptor-blocking activity at D_1, D_2, D_3 and D_5 receptors, but shows high potency for the D_4 receptor.

Pharmacodynamic effects

Clozaril has potent anti-alpha-adrenergic, anticholinergic, antihistaminic, and arousal-reaction-inhibiting effects. It has also been shown to possess antiserotoninergic properties.

Clinical efficacy and safety

Clinically Clozaril produces rapid and marked sedation and exerts antipsychotic effects in schizophrenic patients resistant to other drug treatment. In such cases, Clozaril has proven effective in relieving both positive and negative schizophrenic symptoms mainly in short-term trials. In an open clinical trial performed in 319 treatment resistant patients treated for 12 months, a clinically relevant improvement was observed in 37% of patients within the first week of treatment and in an additional 44% by the end of 12 months. The improvement was defined as about 20% reduction from baseline in Brief Psychiatric Rating Scale Score. In addition, improvement in some aspects of cognitive dysfunction has been described.

Compared to classic antipsychotics, Clozaril produces fewer major extrapyramidal reactions such as acute dystonia, parkinsonian-like side effects and akathisia. In contrast to classic antipsychotics, Clozaril produces little or no prolactin elevation, thus avoiding adverse effects such as gynaecomastia, amenorrhoea, galactorrhoea and impotence.

A potentially serious adverse reaction caused by Clozaril therapy is granulocytopenia and agranulocytosis occurring at an estimated incidence of 3% and 0.7%, respectively. In view of this risk, the use of Clozaril should be limited to patients who are treatment-resistant or patients with psychosis in Parkinson's disease when other treatment strategies have failed (see section 4.1) and in whom regular haematological examinations can be performed (see sections 4.4 and 4.8).

5.2 Pharmacokinetic properties

Absorption

The absorption of orally administered Clozaril is 90 to 95%; neither the rate nor the extent of absorption is influenced by food.

Clozaril is subject to moderate first-pass metabolism, resulting in an absolute bioavailability of 50 to 60%.

Distribution

In steady-state conditions, when given twice daily, peak blood levels occur on an average at 2.1 hours (range: 0.4 to 4.2 hours), and the volume of distribution is 1.6 l/kg. Clozaril is approximately 95% bound to plasma proteins.

Biotransformation/metabolism

Clozaril is almost completely metabolised before excretion by CYP1A2 and CYP3A4, and to some extent by CYP2C19 and CYP2D6. Of the main metabolites only the demethyl metabolite was found to be active. Its pharmacological actions resemble those of clozapine, but are considerably weaker and of short duration.

Elimination

Its elimination is biphasic, with a mean terminal half-life of 12 hours (range: 6 to 26 hours). After single doses of 75 mg the mean terminal half-life was 7.9 hours; it increased to 14.2 hours when steady-state conditions were reached by administering daily doses of 75 mg for at least 7 days.

Only trace amounts of unchanged drug are detected in the urine and faeces, approximately 50% of the administered dose being excreted as metabolites in the urine and 30% in the faeces.

Linearity/non-linearity

Dosage increases from 37.5 mg to 75 mg and 150 mg given twice daily were found to result during steady state in linearly dose-proportional increases in the area under the plasma concentration/time curve (AUC), and in the peak and minimum plasma concentrations.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential (for reproductive toxicity, see section 4.6).

6. Pharmaceutical particulars

6.1 List of excipients

Magnesium stearate

Silica, colloidal anhydrous

Povidone K30

Talc

Maize starch

Lactose monohydrate

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 precautions.

6.5 Nature and contents of container

PVC/PVDC/Aluminium or PVC/PE/PVDC/Aluminium blister

Pack size: 7, 14, 20, 28, 30, 40, 50, 60, 84, 98, 100 tablets.

Hospital pack size: 500 (10x50) and 5000 (100x50) tablets.

PVC/PVDC/Aluminium or PVC/PE/PVDC/Aluminium perforated unit-dose blister:

Pack size: 7x1, 14x1, 20x1, 28x1, 30x1, 40x1, 50x1, 60x1, 84x1, 98x1, 100x1 tablets.

Hospital pack size: 500 (10x50x1) and 5000 (100x50x1) tablets.

White polyethylene (PE) bottles with polypropylene (PP), inner sealed and child-resistant closures.

Pack size: 100 tablets.

Hospital pack size: 500 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements

7. Marketing authorisation holder

Mylan Products Ltd.

20 Station Close

Potters Bar

Herts

EN6 1TL

United Kingdom

8. Marketing authorisation number(s)

PL 46302/0057

9. Date of first authorisation/renewal of the authorisation

14/04/2014

10. Date of revision of the text

May 2023

Company Contact Details

Mylan

Address

Building 4, Trident Place, Mosquito Way, Hatfield,
Hertfordshire, AL10 9UL

Fax

+44 (0)1707 261 803

Medical Information Fax

+44 (0)1707 261 803

Customer Care direct line

+44 (0)1707 853 000 select option 2

WWW

http://www.mylan.com

Telephone

+44 (0)1707 853 000

Medical Information Direct Line
+44 (0)1707 853 000

Medical Information e-mail
info@mylan.co.uk

Stock Availability
+44 (0)1707 853 000 select option 2