**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 Clearance (CrCl) $\geq$ 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 (P-gp) 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 first, 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). 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<br>Eosinophilia | Neutropenia | |
| **Immune system disorders** | | | | Hypersensitivity | |
| **Endocrine disorders** | | | Blood thyroid stimulating hormone decreased | Hypothyroidism | |
| **Metabolism and nutrition** | | Dyslipidaemia<br>Weight increased | Blood sodium abnormal<br>Diabetes | | |

| | | | | | |
|---|---|---|---|---|---|
| **disorders** | | Decreased appetite<br>Increased appetite | mellitus<br>Blood glucose increased | | |
| **Psychiatric disorders** | | Sleep disorders[1]<br>Anxiety | Suicidal behaviour<br>Delirium<br>Depression<br>Libido decreased<br>Libido increased<br>Erectile dysfunction | | |
| **Nervous system disorders** | Akathisia[2]<br>Parkinsonism[3] | Sedation<br>Dizziness<br>Dystonia[4]<br>Other extrapyramidal diseases and abnormal movement disorders[5] | Tardive dyskinesia<br>Dyskinesia[6]<br>Dysaesthesia<br>Lethargy | Seizures/ Convulsion<br>Amnesia<br>Aphasia | Neuroleptic malignant syndrome |
| **Eye disorders** | | Vision blurred | Intraocular pressure increased<br>Accommodation disorder<br>Visual acuity reduced<br>Eye irritation | Cataract<br>Photophobia | |
| **Ear and labyrinth disorders** | | | Vertigo | | |
| **Cardiac disorders** | | Tachyarrhythmia | Cardiac conduction disorders<br>Bradyarrhythmia<br>Electrocardiogram QT prolonged<br>Electrocardiogram T wave abnormal | | |
| **Vascular disorders** | | Hypertension | Hypotension | | |
| **Respiratory, thoracic and mediastinal disorders** | | | Hiccups | | |
| **Gastrointestinal disorders** | | Vomiting<br>Nausea<br>Constipation | Gastrooesophageal reflux disease | Dysphagia | |
| **Hepatobiliary disorders** | | Hepatic enzymes increased | Blood bilirubin increased | | Toxic hepatitis |

| | | | | | |
|---|---|---|---|---|---|
| **Skin and subcutaneous tissue disorders** | | | Pruritus<br>Rash | | |
| **Musculoskeletal and connective tissue disorders** | | Blood creatine phosphokinase increased | | Rhabdomyolysis | |
| **Renal and urinary disorders** | | | Dysuria<br>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 (defined as increase ≥ 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-$HT_{2C}$ and adrenergic α1 receptors (Ki values of 134 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 25$^{th}$ 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 score for negative symptoms ≥ 24, a score of ≥ 4 on 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 (PANSS FSNS ≥ 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 ($AUC_{0-\infty}$ 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 function (creatinine clearance (CrCl) ≥ 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.
Gyömrői út 19-21.
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 Clearance (CrCl) ≥ 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.
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 (P-gp) 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 first, 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). 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<br>Eosinophilia | Neutropenia | |
| **Immune system disorders** | | | | Hypersensitivity | |
| **Endocrine disorders** | | | Blood thyroid stimulating hormone decreased | Hypothyroidism | |
| **Metabolism and nutrition disorders** | | Dyslipidaemia<br>Weight increased<br>Decreased appetite<br>Increased appetite | Blood sodium abnormal<br>Diabetes mellitus<br>Blood glucose increased | | |
| **Psychiatric disorders** | | Sleep disorders[1]<br>Anxiety | Suicidal behaviour<br>Delirium<br>Depression<br>Libido decreased | | |

| | | | | | |
|---|---|---|---|---|---|
| | | | Libido increased<br>Erectile dysfunction | | |
| **Nervous system disorders** | Akathisia[2]<br>Parkinsonism[3] | Sedation<br>Dizziness<br>Dystonia[4]<br>Other extrapyramidal diseases and abnormal movement disorders[5] | Tardive dyskinesia<br>Dyskinesia[6]<br>Dysaesthesia<br>Lethargy | Seizures/ Convulsion<br>Amnesia<br>Aphasia | Neuroleptic malignant syndrome |
| **Eye disorders** | | Vision blurred | Intraocular pressure increased<br>Accommodation disorder<br>Visual acuity reduced<br>Eye irritation | Cataract<br>Photophobia | |
| **Ear and labyrinth disorders** | | | Vertigo | | |
| **Cardiac disorders** | | Tachyarrhythmia | Cardiac conduction disorders<br>Bradyarrhythmia<br>Electrocardiogram QT prolonged<br>Electrocardiogram T wave abnormal | | |
| **Vascular disorders** | | Hypertension | Hypotension | | |
| **Respiratory, thoracic and mediastinal disorders** | | | Hiccups | | |
| **Gastrointestinal disorders** | | Vomiting<br>Nausea<br>Constipation | Gastrooesophageal reflux disease | Dysphagia | |
| **Hepatobiliary disorders** | | Hepatic enzymes increased | Blood bilirubin increased | | Toxic hepatitis |
| **Skin and subcutaneous tissue disorders** | | | Pruritus<br>Rash | | |
| **Musculoskeletal and connective tissue disorders** | | Blood creatine phosphokinase increased | | Rhabdomyolysis | |

| | | | | | |
|---|---|---|---|---|---|
| **Renal and urinary disorders** | | | Dysuria<br>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 (defined as increase ≥ 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-$HT_{2C}$ and adrenergic α1 receptors (Ki values of 134 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 25$^{th}$ 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 score for negative symptoms ≥ 24, a score of ≥ 4 on 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 (PANSS FSNS ≥ 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 ($AUC_{0-\infty}$ 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 renal function (creatinine clearance (CrCl) ≥ 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

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

3 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.
Gyömrői út 19-21.
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.
Gyömrői út 19-21
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.
Gyömrői út 19-21.
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.
Gyömrői út 19-21.
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.
Gyömrői út 19-21.
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.
Gyömrői út 19-21.
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.
Gyömrői út 19-21.
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.
Gyömrői út 19-21.
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.
Gyömrői út 19-21.
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.
Gyömrői út 19-21.
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 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 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.
Gyömrői út 19-21
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

**България**
ТП „Гедеон Рихтер АД”
Тел.: + 359 2 8129063

**Česká republika**
Gedeon Richter Marketing ČR, s.r.o.
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**
Gedeon Richter Plc. atstovybė Lietuvoje
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

**Ελλάδα**
Recordati Hellas Pharmaceuticals S.A.
Τηλ: + 30 210-6773822

**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

**Κύπρος**
C.G. PAPALOISOU LTD.
Τηλ: + 357 22 490305

**Latvija**
Gedeon Richter Plc. pārstāvniecība Latvijā
Tel: +371 67845338

Recordati AB
Tlf: + 46 8 545 80 230 (Sverige)

**Österreich**
Recordati Austria GmbH
Tel: + 43 664 128 4879

**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.

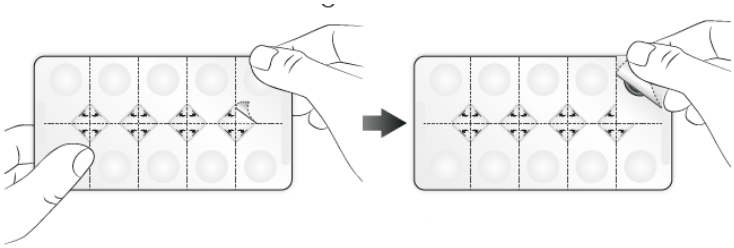
**Reagila orodispersible tablets contain sodium**
This medicine contains less than 1 mmol sodium (23 mg) per orodispersible tablet, that is to say essentially ‘sodium-free’.

## 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.
Gyömrői út 19-21
1103 Budapest
Hungary

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

**België/Belgique/Belgien/Danmark/Deutschland /Ελλάδα/España/France/Ireland/Ísland/Italia/ Κύπρος/Luxembourg/Luxemburg/ Magyarország/Malta/Nederland/Norge/ Österreich/Portugal/Suomi/Finland/Sverige/ United Kingdom (Northern Ireland)**
Richter Gedeon Nyrt.
Tél/Tel/Tlf/Τηλ/Sími/Puh: +36 1 505 7032

**Lietuva**
Gedeon Richter Plc. atstovybė Lietuvoje
Tel: +370 5 261 01 54

**България**
ТП „Гедеон Рихтер АД”
Тел.: + 359 2 8129063

**Polska**
GEDEON RICHTER POLSKA Sp. z o.o.
Tel.: + 48 (22)755 96 48

**Česká republika**
Gedeon Richter Marketing ČR, s.r.o.
Tel: +420 261 141 200

**România**
Gedeon Richter România S.A.
Tel: +40-265-257 011

**Eesti**
Richter Gedeon Eesti filiaal
Tel: +372 608 5301

**Slovenija**
Gedeon Richter d.o.o.
Tel: + +386 8 205 68 70

**Hrvatska**
Gedeon Richter Croatia d.o.o.
Tel: + 385 1 5625 712

**Latvija**
Gedeon Richter Plc. pārstāvniecība Latvijā
Tel: +371 67845338

**Slovenská republika**
Gedeon Richter Slovakia, s.r.o.
Tel: +421 2 5020 5801

**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.