ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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.

Excipients 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.

Excipients 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.

Excipients 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 dosage 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).

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.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Concomitant administration of strong or moderate 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 is a frequently occurring adverse reaction 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-EPS medication. 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 neuroleptic malignant syndrome (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 cerebrovascular adverse reactions has been seen in randomised placebo controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. 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.

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 trial designed to assess QT prolongation (see section 5.1). In clinical trials, 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 venous thromboembolism 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 trials, glucose-related adverse reactions have been reported with cariprazine (see section 5.1).

Women of childbearing potential

Women of childbearing potential must use highly effective contraception while taking cariprazine and at least for 10 weeks after stopping treatment (see sections 4.5 and 4.6). Women using systemically acting hormonal contraceptives should add a second barrier method.

Weight change

Significant weight gain has been observed with the use of cariprazine. Patients should have their weight monitored regularly (see section 4.8).

Excipients

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 or moderate inhibitors of CYP3A4 (e.g. boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, diltiazem, erythromycin, fluconazole verapamil) is contraindicated (see section 4.3). 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
It is currently unknown whether cariprazine may reduce the effectiveness of systemically acting hormonal contraceptives, and therefore women using systemically acting hormonal contraceptives should add a second barrier method.

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. It is currently unknown if cariprazine may reduce the effectiveness of systemically acting hormonal contraceptives and therefore women using systemically acting hormonal contraceptives should add a barrier method (see section 4.5).

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 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

Adverse drug reactions (ADRs) based upon pooled data from cariprazine schizophrenia studies are shown by system organ class and by preferred term.

Adverse reactions are ranked 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.

Adverse drug reactions occurring in patients with schizophrenia

MedDRA System Organ Class	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Frequency not known**
Blood and lymphatic system disorders			Anaemia Eosinophilia	Neutropenia	
Immune system disorders				Hypersensitivity	
Endocrine disorders			Blood thyroid stimulating hormone decreased	Hypothyroidism	
Metabolism and nutrition disorders		Weight increased Decreased appetite Increased appetite Dyslipidaemia	Blood sodium abnormal Blood glucose increased Diabetes mellitus		
Psychiatric disorders		Sleep disorders1 Anxiety	Suicidal behaviour Delirium Depression Libido decreased Libido increased Erectile dysfunction		
Nervous system disorders	Akathisia[2] Parkinsonism[3]	Sedation Dizziness Dystonia[4] Other	Lethargy Dysaesthesia Dyskinesia[6] Tardive	Seizures/ Convulsion Amnesia Aphasia	Neuroleptic malignant syndrome

		extrapyramidal diseases and abnormal movement disorders[5]	dyskinesia		
Eye disorders		Vision blurred	Eye irritation Intraocular pressure increased Accommodation disorder Visual acuity reduced	Photophobia Cataract	
Ear and labyrinth disorders			Vertigo		
Cardiac disorders		Tachyarrhytmia	Cardiac conduction disorders Bradyarrhytmia Electrocardiogram QT prolonged Electrocardiogram T wave abnormal		
Vascular disorders		Hypertension	Hypotension		
Respiratory, thoracic and mediastinal disorders			Hiccups		
Gastrointestinal disorders		Nausea Constipation Vomiting	Gastrooesophageal reflux disease	Dysphagia	
Hepatobiliary disorders		Hepatic enzymes increased	Blood bilirubin increased		Toxic hepatitis
Skin and subcutaneous tissue disorders			Pruritus Rash		
Musculoskeletal and connective tissue disorders		Blood creatine phosphokinase increased		Rhabdomyolysis	
Renal and urinary disorders			Dysuria Pollakisuria		
Pregnancy, puerperium and perinatal conditions					Drug withdrawal syndrome neonatal (see

					section 4.6)
General disorders and administration site conditions		Fatigue	Thirst		

[1]Sleep disorders: Insomnia, Abnormal dreams/nightmare, Circadian rhythm sleep disorder, Dyssomnia, Hypersomnia, Initial insomnia, Middle insomnia, Nightmare, Sleep disorder, Somnambulism, Terminal insomnia
[2]Akathisia: Akathisia, Psychomotor hyperactivity, Restlessness
[3]Parkinsonism: Akinesia, Bradykinesia, Bradyphrenia, Cogwheel rigidity, Extrapyramidal disorder, Gait disturbance, Hypokinesia, Joint stiffness, Tremor, Masked facies, Muscle rigidity, Musculoskeletal stiffness, Nuchal rigidity, Parkinsonism
[4]Dystonia: Blepharospasm, Dystonia, Muscle tightness, Oromandibular dystonia, Torticollis, Trismus
[5]Other extrapyramidal diseases and abnormal movement disorders: Balance disorder, Bruxism, Drooling, Dysarthria, Gait deviation, Glabellar reflex abnormal, Hyporeflexia, Movement disorder, Restless legs syndrome, Salivary hypersecretion, Tongue movement disturbance
[6]Dyskinesia: Choreoathetosis, Dyskinesia, Grimacing, Oculogyric crisis, Protrusion tongue

Description of selected adverse reactions

Lens opacity/Cataract
Development of cataracts was observed in cariprazine non-clinical studies (see section 5.3). Therefore, cataract formation was closely monitored with slit lamp examinations in the clinical studies and patients with existing cataracts were excluded. During the schizophrenia clinical development program of cariprazine, few cataract cases were reported, characterized with minor lens opacities with no visual impairment (13/3192; 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: 22/2048; 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 venous thromboembolism, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotics - Frequency unknown.

Elevated liver transaminases
Elevated liver transaminases (ALT, 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 trial designed to assess QT prolongation (see section 5.1). In other clinical trials, 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} > 1000 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 drug.

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

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 trials 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 1 below. Results for the secondary outcome parameter (CGI) and additional endpoints were supportive of the primary endpoint.

Table 1. 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 trial 49.0% of placebo-treated patients versus 21.6% of cariprazine-treated patients had a relapse of schizophrenic symptoms. Time to relapse (92 vs. 326 days-based on the 25th percentile) was therefore significantly longer in the cariprazine group than in the placebo group (p=0.009).

Efficacy in predominantly negative symptoms of schizophrenia
The efficacy of cariprazine for the treatment of predominantly negative symptoms of schizophrenia was investigated in a 26-week, multi-centre, double-blind, and active-controlled clinical trial. 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 2). 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 2).*
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 2 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 paediatric population. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Cariprazine has two pharmacologically active metabolites with similar activites 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 feces.

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 4.8 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 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 NUMBER(S)

EU/1/17/1209/001-040

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

13 July 2017

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.