PROFESSIONAL INFORMATION

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

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 (E129).

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 (E129).

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 (E129).

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules

Reagila 1,5 mg hard capsules

Size 4’ (approximately 14,3 mm in length) hard gelatine capsules 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 gelatine capsules 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 gelatine capsules 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 gelatine capsules 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

-Treatment of acute relapses of schizophrenia and maintenance therapy in adult patients.

-Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.

-Treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults.

4.2 Posology and method of administration

Posology

Schizophrenia

The recommended starting dose of Reagila 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 healthcare professional. 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 Reagila and after each dosage change (see section 5.2).

Manic or Mixed Episodes Associated with Bipolar I Disorder

The starting dose of Reagila is 1,5 mg and should be increased to 3 mg once daily on Day 2. The recommended dosage range is 3 mg to 6 mg once daily. Depending upon clinical response and tolerability, further dose adjustments can be made in 1,5 mg or 3 mg increments. The maximum recommended dosage is 6 mg daily. In short-term controlled trials, dosages above 6 mg daily did not result in increased effectiveness sufficient to outweigh dose-related adverse reactions.

Depressive episodes associated with Bipolar I Disorder (Bipolar Depression)

The starting dose of Reagila is 1,5 mg once daily. Depending upon clinical response and tolerability, the dosage can be increased to 3 mg once daily on Day 15. Maximum recommended dosage is 3 mg once daily.

The efficacy of Reagila for long-term use has not been adequately evaluated in controlled studies for bipolar mania and depression. The medical practitioner who choose to use Reagila for extended periods should periodically re-evaluate the long-term efficacy and safety of the drug for the individual patient.

Switching from other antipsychotics to cariprazine

When switching from another antipsychotic to Reagila gradual cross-titration should be considered, with gradual discontinuation of the previous treatment while Reagila treatment is initiated.

Switching to another antipsychotic from cariprazine

When switching to another antipsychotic from Reagila, no gradual cross-titration is needed, the new antipsychotic should be initiated in its lowest dose while Reagila is discontinued. It should be considered that plasma concentration of cariprazine and its active metabolites will decline by 50 % in approximately 1 week (see section 5.2).

Special populations

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 Reagila 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 Reagila have not been evaluated in patients with severe hepatic impairment (Child-Pugh score between 10 and 15). Use of Reagila is not recommended in patients with severe hepatic impairment (see section 5.2).

Elderly population

Available data in elderly patients aged ≥ 65 years treated with Reagila is 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 Reagila in children and adolescents aged less than 18 years have not been established. No data is 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).

Pregnancy and lactation (see 4.6).

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 characterised 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 Reagila 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 Reagila, or medicines used for treatment of extrapyramidal symptoms. 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 Reagila, discontinuation should be considered.

Parkinson's disease

If prescribed to patients with Parkinson's disease, antipsychotic medicines such as Reagila may exacerbate the underlying disease and worsen symptoms of Parkinson’s disease.

Ocular symptoms/cataract

In the preclinical studies of Reagila, 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 Reagila 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, Reagila must be discontinued immediately.

Seizures and convulsions

Reagila should be used cautiously in patients with history of seizures or with conditions that potentially lower the seizure threshold.

Elderly patients with dementia

Reagila 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. Reagila should be used with caution in patients with risk factors for stroke.

Cardiovascular disorders

Blood pressure changes

Reagila can cause orthostatic hypotension as well as hypertension (see section 4.8). Reagila 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 Reagila 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, Reagila 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 medicines that might cause QT prolongation (see section 5.1).

Venous thromboembolism (VTE)

Cases of venous thromboembolism have been reported with antipsychotic medicines. 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 Reagila 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 Reagila (see section 5.1).

Dyslipidaemia

Atypical antipsychotics, including Reagila cause adverse alterations in lipids. Before or soon after initiation of antipsychotic medication, a fasting lipid profile at baseline should be obtained and monitored periodically during treatment.

Women of childbearing potential

Women of childbearing potential must use highly effective contraception while taking Reagila and at least for 10 weeks after stopping treatment (see sections 4.5 and 4.6).

Weight change

Significant weight gain has been observed with the use of Reagila. 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 (E129), which may cause allergic reactions.

4.5 Interaction with other medicines and other forms of interaction

Potential for other medicines 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 plus 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, phenobarbitone, 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 medicines

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 are 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 (ethinyl estradiol 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 medicines 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 (see section 4.3). 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 is 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 should not be used 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.

Administration of cariprazine to rats during the period of organogenesis caused malformations and lower pup survival. Cariprazine caused foetal developmental toxicity at all dose levels (0,5 to 7,5 mg/kg/day) and included reduced foetal body weight, decreased male anogenital distance and skeletal malformations of bent limb bones, scapula and humerus.

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.

Breastfeeding

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. Breastfeeding should be discontinued during treatment with cariprazine (see section 4.3).

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

Reagila has an influence on the ability to drive and use machines, e.g., somnolence, fatigue, vertigo, dyskinesia. 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 Reagila in all three indications identified from clinical trials were akathisia, extrapyramidal symptoms, insomnia, nausea, restlessness vomiting and somnolence. Most ADRs were mild to moderate in severity. The most serious ADRs were extrapyramidal symptoms, tachy-dysrhythmia, tachycardia, cardiac conduction disorders, brady-dysrhythmia, suicidal behaviour, hypertension and hypotension (section 4.4).

Tabulated list of adverse reactions

ADRs based upon pooled data from Reagila schizophrenia studies are shown by system organ class and by preferred term in Table 1.

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.

Table 1. Adverse drug reactions occurring in patients with schizophrenia

MedDRA System Organ Class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to <1/10)**	**Uncommon (≥ 1/1 000 to < 1/100)**	**Rare (≥ 1/10 000 to < 1 / 1 000)**	**Frequency not known**
Blood and lymphatic system disorders			Anaemia Eosinophilia	Neutropenia	
Immune system disorders				Hypersensitivity	
Endocrine disorders			Blood thyroid stimulating hormone decreased	Hypothyroidism	
Metabolism and nutrition disorders		Weight increased Decreased appetite Increased appetite Dyslipidaemia	Blood sodium abnormal Blood glucose increased Diabetes mellitus		
Psychiatric disorders		Sleep disorders[1] Anxiety	Suicidal behaviour Delirium Depression Libido decreased Libido increased		

			Erectile dysfunction	
Nervous system disorders	Akathisia[2] Parkinsonism[3]	Sedation Dizziness Dystonia[4] Other extrapyramidal diseases and abnormal movement disorders[5]	Lethargy Dysaesthesia Dyskinesia[6] Tardive dyskinesia	Seizures/ Convulsion Amnesia Aphasia
Eye disorders		Vision blurred	Eye irritation Intraocular pressure increased Accommodation disorder Visual acuity reduced	Photophobia Cataract
Ear and labyrinth disorders			Vertigo	
Cardiac disorders		Tachy-dysrhythmia	Cardiac conduction disorders Brady-dysrhythmia	

			Electrocardiogram QT prolonged Electrocardiogram T wave abnormal	
Vascular disorders		Hypertension	Hypotension	
Respiratory, thoracic and mediastinal disorders			Hiccups	
Gastrointestinal disorders		Nausea Constipation Vomiting	Gastroesophageal reflux disease	Dysphagia
Hepatobiliary disorders		Hepatic enzymes increased	Blood bilirubin increased	
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				

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.

Table 2. Adverse drug reactions occurring in patients with manic or mixed episodes associated with Bipolar I disorder.

The safety profile of cariprazine has been evaluated based on three placebo-controlled, 3-week bipolar mania trials with cariprazine doses ranging from 3 to 6 mg once daily. The maximum recommended dosage is 6 mg daily.

MedDRA System Organ Class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to <1/10)**	**Uncommon (≥ 1/1 000 to < 1/100)**
Cardiac disorders		Tachycardia[a]	
Eye disorders		Vision blurred	

Gastrointestinal disorders	Nausea Vomiting	Constipation Dyspepsia Abdominal pain[b] Dry mouth Diarrhoea[c] Toothache	
General disorders and administration site conditions		Fatigue[d]	Pyrexia[e]
Metabolism and nutrition disorders		Decreased appetite	
Psychiatric disorders		Sleep disorders[j] Restlessness	
Nervous system disorders	Akathisia Extrapyramidal Symptoms[g] Headache[h]	Dizziness Somnolence[i]	
Vascular disorders		Hypertension[k]	
Respiratory, thoracic and mediastinal disorders			Oropharyngeal pain
Investigations		Blood creatine phosphokinase increased Weight increased	Hepatic enzymes increased[f]
Musculoskeletal and connective tissue disorders		Pain in extremity	Back pain

*****Data shown by modal daily dose, defined as most frequently administered dose per patient

[a]Tachycardia terms: heart rate increased, sinus tachycardia, tachycardia

[b]Abdominal pain terms: abdominal discomfort, abdominal pain, abdominal pain upper, abdominal tenderness

[c]Diarrhea: diarrhea, frequent bowel movements

[d]Fatigue terms: asthenia, fatigue

[e]Pyrexia terms: body temperature increased, pyrexia

[f]Hepatic enzymes increased terms: alanine amitatenotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, transaminases increased

[g]Extrapyramidal Symptoms terms: bradykinesia, drooling, dyskinesia, dystonia, extrapyramidal disorder, hypokinesia, muscle rigidity, muscle tightness, musculoskeletal stiffness, oromandibular dystonia, parkinsonism (tremors, muscle rigidity and slowness of movement), salivary hypersecretion, tremor

[h]Headache terms: headache, tension headache

[i]Somnolence terms: hypersomnia, sedation, somnolence

[j]Insomnia terms: initial insomnia, insomnia, middle insomnia

[k]Hypertension terms: blood pressure diastolic increased, blood pressure increased, hypertension

[o]The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions (not included).

Table 3. Adverse drug reactions occurring in patients with Bipolar depression

The safety profile of cariprazine has been evaluated based on three placebo-controlled, two 6-week and one 8-week bipolar depression trials with cariprazine doses 1,5 mg and 3 mg once daily.

MedDRA System Organ Class	**Very common (≥ 1/10)**	**Common (≥ 1/100 to <1/10)**	**Uncommon (≥ 1/1 000 to < 1/100)**
Metabolism and nutrition disorders		Increased appetite	
Psychiatric disorders		Insomnia[d] restlessness	
Nervous system disorders		Akathisia Extrapyramidial symptoms[a]	

		Somnolence[b] Dizziness	
Gastrointestinal disorders		Nausea Vomiting	
General disorders and administration site conditions		Fatigue[c]	
Investigations		Weight increased	

[a]Extrapyramidal symptoms terms: akinesia, drooling, dyskinesia, dystonia, extrapyramidal disorder, hypokinesia, muscle tightness, musculoskeletal stiffness, myoclonus, oculogyric crisis, salivary hypersecretion, tardive dyskinesia, tremor

[b]Somnolence terms: hypersomnia, sedation, somnolence

[c]Fatigue terms: asthenia, fatigue, malaise

[d]Insomnia terms: initial insomnia, insomnia, insomnia related to another mental condition, middle insomnia, sleep disorder, terminal insomnia

Post marketing Experience

The following adverse reaction has been identified with unknown frequency during post approval use of cariprazine:

Skin and subcutaneous tissue disorders – Stevens-Johnson syndrome

Description of selected adverse reactions

Lens opacity/Cataract

Development of cataracts was observed in Reagila nonclinical 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 Reagila, few cataract cases were reported, characterised 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 %).

The development of cataracts was observed in nonclinical studies [see section 5.3]. Cataracts were reported during the premarketing clinical trials of cariprazine; however, the duration of trials was too short to assess any association to cariprazine usage.

In the two 6-week and one 8-week bipolar depression trials, there were no clinically meaningful differences between cariprazine-treated patients and placebo-treated patients in mean change from baseline to endpoint in supine systolic and diastolic blood pressure. cariprazine-treated patients' supine blood pressure increased by 0,1 to 0,3 mmHg; placebo-treated patients' supine blood pressure increased by 0,2 mmHg.

Extrapyramidal symptoms (EPS)

In the short-term schizophrenia studies the incidence of EPS was observed in 27 %; 11,5 %; 30,7 % and 15,1 % in patients treated with cariprazine, placebo and two comparator molecules respectively. Akathisia was reported in 13,6 %; 5,1 %; 9,3 % and 9,9 % in patients treated with cariprazine, placebo and two comparator molecules respectively. Parkinsonism was experienced in 13,6 %; 5,7 %; 22,1 % and 5,3 % in patients treated with cariprazine, placebo and two comparator molecules respectively. Dystonia was observed in 1,8 %; 0,2 %; 3,6 % and 0,7 % in patients on cariprazine, placebo and two comparator molecules 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 reported in 7,8 % and 1,0 % in cariprazine and placebo group respectively.

In the schizophrenia negative symptom study EPS was reported in 14,3 % in the cariprazine group and 11,7 % in the comparator treated patients. Akathisia was reported in 10,0 % in patients treated with cariprazine and 5,2 % in the comparator group. Parkinsonism was experienced in 5,2 % and 7,4 % in cariprazine and comparator treated patients respectively. Most EPS cases were mild to moderate in intensity and could be handled with common anti-EPS medicines. The rate of discontinuation due to EPS related ADRs was low.

In 3-week bipolar mania trials, the incidence of reported adverse reactions related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness, was 28 % for cariprazine-treated patients versus 12 % for placebo-treated patients. These reactions led to a discontinuation in 1 % of cariprazine-treated patients versus 0,2 % of placebo-treated patients. The incidence of akathisia was 20 % for cariprazine treated patients versus 5 % for placebo-treated patients. These reactions led to discontinuation in 2 % of cariprazine-treated patients versus 0 % of placebo-treated patients.

In the two 6-week and one 8-week bipolar depression trials, the incidence of reported adverse reactions related to EPS, excluding akathisia and restlessness was 4 % for cariprazine-treated patients versus 2 % for placebo-treated patients. These reactions led to discontinuation in 0,4 % of cariprazine-treated patients versus 0 % of placebo-treated patients. The incidence of akathisia was 8% for cariprazine-treated patients versus 2 % for placebo-treated patients. These reactions led to discontinuation in 1,5 % of cariprazine treated patients versus 0 % of placebo-treated patients.

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.

Changes in Laboratory Test

Elevated liver transaminases (ALT, AST) are frequently observed with antipsychotic treatment. In the cariprazine clinical studies in schizophrenia the incidence of ALT, AST elevation adverse events occurred in 2,2 % of cariprazine-, 1,6 % of comparator and 0,4 % of placebo-treated patients. None of the cariprazine-treated patients had any liver damage.

The proportions of patients with transaminase elevations of ≥ 3 times the upper limits of the normal reference range in 3-week bipolar mania trials ranged between 2 % and 4 % for cariprazine-treated patients depending on dose group administered and 2 % for placebo-treated patients. The proportions of patients with transaminase elevations of ≥ 3 times the upper limits of the normal reference range in 6-week and 8-week bipolar depression trials ranged between 0 % and 0,5 % for cariprazine-treated patients depending on dose group administered and 0.,4 % for placebo-treated patients.

The proportions of patients with elevations of CPK greater than 1000 U/L in 3-week bipolar mania trials was about 4 % in cariprazine and placebo-treated patients. The proportions of patients with elevations of CPK greater than 1000 U/L in 6-week and 8-week bipolar depression trials ranged between 0,2 % and 1 % for cariprazine-treated patients versus 0,2 % for placebo treated patients.

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 in schizophrenia, 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 randomised 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 the comparator and PCS weight gain was observed in 6 % of the cariprazine group while 7,4 % of the comparator 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 schizophrenia, 3 patients (0,4 %) had QTcB > 500 ms, one of whom also had QTcF > 500 ms. A > 60 ms 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 in schizophrenia, during the open-label phase, > 60 ms 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 ms increases from baseline in QTcB were observed in 3 cariprazine-treated patients (3,1 %) and 2 placebo-treated patients (2 %).

Other Adverse Reactions Observed During the Pre-marketing Evaluation of Cariprazine

Adverse reactions listed below were reported by patients treated with cariprazine at doses of ≥ 1,5 mg once daily within the premarketing database of 5,763 cariprazine-treated patients. The reactions listed are those that could be of clinical importance, as well as reactions that are plausibly drug-related on pharmacologic or other grounds. Reactions that appear elsewhere in the cariprazine label are not included.

Reactions are further categorized by organ class and listed in order of decreasing frequency, according to the following definition: those occurring in at least 1/100 patients (common) [only those not already listed in the tabulated results from placebo-controlled studies appear in this listing]; those occurring in 1/100 to 1/1000 patients (uncommon); and those occurring in fewer than 1/1,000 patients (rare).

Gastrointestinal Disorders: Uncommon: gastroesophageal reflux disease, gastritis

Hepatobiliary Disorders: Rare: hepatitis

Metabolism and Nutrition Disorders: Common: decreased appetite; Rare: hyponatremia

Musculoskeletal and Connective Tissue Disorders: Rare: rhabdomyolysis

Nervous System Disorders: Rare: ischemic stroke

Psychiatric Disorders: Uncommon: suicide ideation; Rare: completed suicide, suicide attempts

Renal and Urinary Disorders: Uncommon: pollakiuria

Skin and Subcutaneous Tissue Disorders: Uncommon: hyperhidrosis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms

Accidental acute overdose (48 mg/day) was reported in one patient. This patient experienced orthostasis and sedation.

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 dysrhythmias. In case of severe extrapyramidal symptoms, anticholinergic medicines 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

Class: A 2.6.5 Antipsychotic – miscellaneous structures.

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, 0,49 – 0,71 nM and 0,69 nM (D2S) respectively) and serotonin 5 HT1A receptors (Ki values of 1,4-2,6 nM), and antagonist activity at serotonin 5-HT_{2B}, 5-HT_{2A} and histamine H1 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 α1A 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.

Effect on QTc Interval

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 ms from baseline, nor did any patient experience a QTc of > 500 ms in the study.

At a dose three-times the maximum recommended dose, cariprazine does not prolong the QTc interval to clinically relevant extent.

Clinical efficacy and safety

Schizophrenia

Efficacy with short-term use

The efficacy of cariprazine for the treatment of acute schizophrenia was studied in three multi-centre, multinational, randomised, 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 6,0 mg of comparator molecule A 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 of comparator molecule B 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 summarised in Table 4 below. Results for the secondary outcome parameter (CGI) and additional endpoints were supportive of the primary endpoint.

Table 4. 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**
Comparator molecule A 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**
Comparator molecule B 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 randomised-withdrawal, long-term clinical study. In total, 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. Stabilised 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 comparator molecule A (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 comparator-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 the comparator molecule was observed from Week 14 onward (Table 5). Both cariprazine- and comparator-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 the comparator molecule was observed from Week 10 onward (Table 5).

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 5. Summary of results in study RGH-188-005

Efficacy parameter	Cariprazine LS mean	Comparator 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

Bipolar I disorder

Manic or mixed episodes associated with bipolar I disorder

The efficacy of cariprazine in the acute treatment of bipolar mania was established in three, 3-week placebo-controlled trials in patients (mean age of 39 years, range 18 to 65 years; 40 % were female; and 48 % were Caucasian), who met DSM-IV-TR criteria for bipolar I disorder with manic or mixed episodes with or without psychotic features. In all three trials, cariprazine was superior to placebo.

The Young Mania Rating Scale (YMRS) and Clinical Global Impressions-Severity scale (CGI-S) were used as the primary and secondary efficacy measures, respectively, for assessing psychiatric signs and symptoms in each trial.

● The YMRS is an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology. YMRS total score may range from 0 to 60 with a higher score reflecting greater severity.

● The CGI-S is validated clinician-related scale that measures the patient’s current illness

state and overall clinical state on a 1 (normal, not at all ill) to 7-point (extremely ill) scale.

In each study, the primary endpoint was decrease from baseline in YMRS total score at the end of week 3. The change from baseline for each cariprazine dose group was compared to placebo The results of the trials are shown in Table 6.

Study 4: In a 3-week placebo-controlled (N = 492) trial involving two flexible-dose range groups of cariprazine (3 to 6 mg/day or 6 to 12 mg/day), both cariprazine dose groups were superior to placebo on the YMRS total score and the CGI-S. The 6 to 12 mg/day dose group showed no additional advantage.

Study 5: In a 3-week placebo-controlled trial (N = 235) involving a flexible-dose range of cariprazine (3 to 12 mg/day), cariprazine was superior to placebo on the YMRS total score and the CGI-S.

Study 6: In a 3-week, placebo-controlled trial (N = 310) involving a flexible-dose range of cariprazine (3 to 12 mg/day), cariprazine was superior to placebo on the YMRS total score and the CGI-S.

The efficacy of cariprazine was established at doses ranging from 3 to 12 mg/day. Doses above 6 mg did not appear to have additional benefit over lower doses (Table 6) and there was a dose-related increase in certain adverse reactions. Therefore, the maximum recommended dose is 6 mg/day.

Examination of population subgroups based on age (there were few patients over 55), sex, and race did not suggest any clear evidence of differential responsiveness.

Table 6. Primary Analysis Results from Manic or Mixed Episodes Associated with Bipolar I Disorder Trials

Study Number	**Treatment Group (# ITT patients)**	**Primary Efficacy Endpoint: YMRS Total**		
		Mean Baseline Score (SD)	**LS Mean Change from Baseline (SE)**	**Placebo-subtracted Difference[a] (95 % CI)**
Study 4	Cariprazine (3-6 mg/day)* (n=165)	33,2 (5,6)	-18,6 (0,8)	-6,1 (-8,4, -3,8)
	Cariprazine (6-12 mg/day)*[b] (n=167)	32,9 (4,7)	-18,5 (0,8)	-5,9 (-8,2, -3,6)

	Placebo (n=160)	32,6 (5,8)	-12,5 (0,8)	--
Study 5	Cariprazine (3-12 mg/day)*[b] (n=118)	30,6 (5,0)	-15,0 (1,1)	-6,1 (-8,9, -3,3)
	Placebo (n=117)	30,2 (5,2)	-8,9 (1,1)	--
Study 6	Cariprazine (3-12 mg/day)*[b] (n=158)	32,3 (5,8)	-19,6 (0,9)	-4,3 (-6,7, -,.9)
	Placebo (n=152)	32,1 (5,6)	-15,3 (0,9)	--

ITT: intent-to-treat; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval

[a]Difference (drug minus placebo) in least-squares mean change from baseline

*Doses that are statistically significantly superior to placebo

[b]The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

Depressive episodes associated with Bipolar I disorder (Bipolar Depression)

The efficacy of cariprazine in the treatment of depressive episodes associated with bipolar I disorder (bipolar depression) was established in one 8-week and two 6-week fixed-dose placebo-controlled trials in patients (mean age of 43 years, range 18 to 65 years; 61% were female; and 75% were Caucasian) who met DSM-IV-TR or DSM-5 criteria for depressive episodes associated with bipolar I disorder.

In each study, the primary endpoint was change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) total score at the end of Week 6. The secondary endpoint was change from baseline to Week 6 in CGI-S.

Study 7: In the 8-week, placebo-controlled trial involving three-fixed doses of cariprazine (0,75 mg/day, 1,5 mg/day, and 3 mg/day), cariprazine 1.5 mg was superior to placebo at end of Week 6 on the MADRS total score and the CGI-S.

Study 8: In a 6-week, placebo-controlled trials, involving two-fixed doses of cariprazine (1,5 mg/day and 3 mg/day), cariprazine 1,5 mg and 3 mg were superior to placebo at end of Week 6 on the MADRS total score.

Study 9: In a 6-week, placebo-controlled trial involving two-fixed doses of cariprazine (1,5 mg/day and 3 mg/day), cariprazine 1.5 mg was superior to placebo at end of Week 6 on the MADRS total score and the CGI-S.

Examination of population subgroups based on age (there were few patients over 55), sex, and race did not suggest any clear evidence of differential responsiveness.

Table 9. Primary Analysis Results from Bipolar Depression Trials

Study Number	**Treatment Group (# ITT patients)**	**Primary Efficacy Endpoint: MADRS Total**		
		Mean Baseline Score (SD)	**LS Mean Change from Baseline (SE)**	**Placebo-subtracted Difference[a] (95 % CI)**
Study 7	Cariprazine (1,5 mg/day)* (n=145)	30,3 (4,4)	-15,1 (0,8)	-4,0 (-6,3, -1,6)
	Cariprazine (3 mg/day) (n=145)	30,6 (4,7)	-13,7 (0,9)	-2,5 (-4,9, -0,1)
	Placebo (n=141)	30,4 (4,6)	-11,1 (0,9)	--
Study 8	Cariprazine (1.5 mg/day)* (n=154)	30,7 (4,3)	-15,1 (0,8)	-2,5 (-4,6, -0,4)
	Cariprazine (3 mg/day)* (n=164)	31,0 (4,9)	-15,6 (0,8)	-3,0 (-5,1, -0,9)
	Placebo (n=156)	30,2 (4,4)	-12,6 (0,8)	--

Study 9	Cariprazine (1.5 mg/day)* (n=162)	31,5 (4,3)	-14,8 (0,8)	-2,5 (-4,6, -0,4)
	Cariprazine (3 mg/day) (n=153)	31,5 (4,8)	-14,1 (0,8)	-1,8 (-3,9, 0,4)
	Placebo (n=163)	31,4 (4,5)	-12,4 (0,8)	--
ITT: intent-to-treat; SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval [a]Difference (drug minus placebo) in least-squares mean change from baseline *Doses that are statistically significantly superior to placebo				

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 approximately 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 metabolised by CYP3A4 and, to a lesser extent, by CYP2D6, to DCAR and HCAR. DCAR is further metabolised 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 approximately 2 days for cariprazine and DCAR, 8 days for DDCAR and is approximately 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 approximately 1 week and greater than 90 % decline in total cariprazine concentration occurs in approximately 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 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 medicines

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 (E171)

Gelatine

Capsule shell (3 mg capsule)

Allura red AC (E129)

Brilliant blue FCF (E133)

Titanium dioxide (E171)

Yellow iron oxide (E172)

Gelatine

Capsule shell (4,5 mg capsule)

Allura red AC (E129)

Brilliant blue FCF (E133)

Titanium dioxide (E171)

Yellow iron oxide (E172)

Gelatine

Capsule shell (6 mg capsule)

Brilliant blue FCF (E133)

Allura red AC (E129)

Titanium dioxide (E171)

Gelatine

Printing ink (black: 1,5 mg, 3 mg and 6 mg capsules)

Shellac

Black iron oxide (E172)

Propylene glycol

Potassium hydroxide

Printing ink (white: 4,5 mg capsule)

Shellac

Titanium dioxide (E171)

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.

Store at or below 25 °C.

6.5 Nature and contents of container

Transparent hard PVC/PE/PVDC blister heat-sealed with hard aluminium foil backing in an outer carton.

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 medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Date of Approval: 27 July 2026

Adcock Ingram Limited

1 New Road

Erand Gardens

Midrand 1685

Customer Care: 0860 ADCOCK/232625

8. REGISTRATION NUMBER

Reagila 1,5 mg capsules: 55/2.6.5/0097

Reagila 3 mg capsules: 55/2.6.5/0098

Reagila 4,5 mg capsules: 55/2.6.5/0099

Reagila 6 mg capsules: 55/2.6.5/0100

9. DATE OF FIRST AUTHORISATION

19 July 2022.

10. DATE OF REVISION OF THE TEXT

27 July 2026