Australian Product Information - REAGILA® (CARIPRAZINE) HARD CAPSULES

1. NAME OF THE MEDICINE

Cariprazine

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

REAGILA contains cariprazine, a novel atypical antipsychotic agent. Each REAGILA® hard capsule contains cariprazine hydrochloride corresponding to 1.5 mg, 3 mg, 4.5 mg or 6 mg of cariprazine

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3. PHARMACEUTICAL FORM

Hard capsule that is filled with white to yellowish white powder mixture.

REAGILA® 1.5 mg: Hard gelatin capsule with white opaque cap and white opaque body imprinted with “GR 1.5” on the capsule body with black ink.

REAGILA® 3 mg: Hard gelatin capsule with green opaque cap and white opaque body imprinted with “GR 3” on the capsule body with black ink.

REAGILA® 4.5 mg: Hard gelatin capsule with green opaque cap and green opaque body imprinted with “GR 4.5” on the capsule body with white ink.

REAGILA® 6 mg: Hard gelatin capsule with purple opaque cap and white opaque body imprinted with “GR 6” on the capsule body with black ink.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

REAGILA® is indicated for the treatment of schizophrenia in adult patients.

4.2 DOSE AND METHOD OF ADMINISTRATION

REAGILA® hard capsules are intended for oral administration only.

REAGILA® is to be taken once daily at the same time of the day with or without food. Alcohol should be avoided when taking cariprazine (see Section 4.5 Interactions with other medicines and other forms of interactions).

The recommended starting dose of REAGILA® is 1.5 mg once daily. Thereafter the dose can be increased in 1.5 mg increments according to efficacy and tolerability 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 REAGILA® and after each dosage change (see Section 5.2 Pharmacokinetic properties).

Switching from other antipsychotics to REAGILA®

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.

Discontinuation of treatment

REAGILA® can be stopped immediately. If discontinuing treatment with cariprazine, because of the long half-life of REAGILA® and its active metabolites, it may take 3 to 4 weeks for REAGILA® to be excreted from the body.

Missed dose

If the patient misses a dose, the patient should take the missed dose as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped and the next dose should be taken according to the regular schedule. It is not recommended to take a double dose to make up for the forgotten dose.

Switching to another antipsychotic from REAGILA®

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.

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 Pharmacokinetic properties).

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 REAGILA® is not recommended in patients with severe hepatic impairment (see Section 5.2 Pharmacokinetic properties).

Elderly Patients

Available data in elderly patients aged ≥ 65 years treated with REAGILA® are not sufficient to determine whether or not they respond differently from younger patients (see Section 5.2 Pharmacokinetic properties). Dose selection for an elderly patient should be more cautious.

Paediatric Patients

The safety and efficacy of REAGILA® in children and adolescents aged less than 18 years have not been established. No data are available.

4.3 CONTRAINDICATIONS

REAGILA® (cariprazine) is contraindicated in any patient with a known hypersensitivity to cariprazine or any component in the formulation (listed in Section 6.1 List of excipients).

REAGILA® is contraindicated with concomitant administration of strong or moderate CYP3A4 inhibitors (see Section 4.5 Interactions with other medicines and other forms of interactions) and strong or moderate CYP3A4 inducers (see Section 4.5 Interactions with other medicines and other forms of interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

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 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 anti-EPS medication. The dose can be modified based on individual response and tolerability (see Section 4.8 Adverse effects).

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 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 REAGILA® to patients with Parkinson's disease.

Ocular symptoms/cataract

In the preclinical studies of REAGILA® lens opacity/cataract was detected in dogs (see Sections 4.8 Adverse effects and 5.3 Preclinical safety data). 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 have an ophthalmologic examination and be re-evaluated for treatment continuation.

Neuroleptic malignant syndrome (NMS)

A potentially fatal symptom complex referred to as NMS has been reported in association with antipsychotic treatment. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, elevated serum creatine phosphokinase levels, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, REAGILA® must be discontinued immediately.

Seizures

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

Risk of cerebrovascular accidents (CVA)

An approximately 3-fold increased risk of CVA 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 Adverse effects). REAGILA® should be used with caution in patients with known cardiovascular disease predisposing to blood pressure changes. Blood pressure should be monitored.

Electrocardiogram (ECG) changes

QT prolongation can develop in patients treated with antipsychotics.

With REAGILA® no QT interval prolongation was detected compared to placebo in a clinical trial designed to assess QT prolongation (see Section 5.1 Pharmacodynamic properties). In clinical trials, only a few, non-serious, QT- prolongations have been reported with REAGILA® (see Section 4.8 Adverse effects). Therefore, REAGILA® should be used cautiously in patients with known cardiovascular disease or a family history of QT prolongation and in patients treated with medicinal products that might cause QT prolongation (see Section 5.1 Pharmacodynamic properties).

Venous thromboembolism (VTE)

Cases of VTE have been reported with antipsychotic medicinal products. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with 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 assessed for fasting plasma glucose before, or soon after, initiation of antipsychotic medication, and monitored periodically during long-term treatment. In clinical studies, glucose-related adverse reactions have been reported with REAGILA® (see Section 4.8 Adverse effects).

In clinical studies with REAGILA®,changes from baseline to endpoint in fasting serum glucose for cariprazine were comparable to placebo.

Weight change

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended (see Section 4.8 Adverse effects).

Excipients

REAGILA® 3 mg, 4.5 mg and 6 mg hard capsules contain Allura red AC (E 129), which may cause allergic reactions.

Use in the elderly

Available data in elderly patients aged ≥ 65 years treated with REAGILA® are not sufficient to determine whether or not they respond differently from younger patients (see Section 5.2 Pharmacokinetic properties).

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.

Paediatric use

The safety and efficacy of REAGILA® in children and adolescents aged less than 18 years have not been established. No data are available.

Effects on laboratory tests

The use of REAGILA® has been associated with increases in levels of liver enzymes and creatine phosphokinase and abnormal amounts of lipids (e.g. cholesterol and/or fat). Regular monitoring of lipids and liver function tests is recommended.

Elevated prolactin levels have been reported with other medicines that antagonise dopamine D2 receptors. In clinical trials, REAGILA® did not cause hyperprolactinaemia.

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. In clinical trials of REAGILA®, changes in metabolic profile and hyperlipidaemia, were comparable to placebo.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Potential for other medicinal products to affect REAGILA®

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 REAGILA® a further increase in plasma exposure of total cariprazine can be expected during longer co-administration. Therefore, co- administration of REAGILA® 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 Contraindications). Consumption of grapefruit juice should be avoided.

CYP3A4 inducers

Co-administration of REAGILA® with strong and moderate inducers of CYP3A4 may result in a significant decrease in total cariprazine exposure, therefore the co-administration of REAGILA® 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 Contraindications).

CYP2D6 inhibitors

CYP2D6 mediated pathway plays a minor role in the metabolism of REAGILA®, the major pathway is via CYP3A4 (see Section 5.2 Pharmacokinetic properties). Therefore, CYP2D6 inhibitors are unlikely to have a clinically relevant effect on REAGILA® metabolism.

P-gp, OATP1B1, OATP1B3 and BCRP

REAGILA® and its major active metabolites are not substrates of P-glycoprotein (P-gp), the organic anion transporting polypeptide 1B1 and 1B3 (OATP1B1 and OATP1B3), or the breast cancer resistance protein (BCRP). This suggests that an interaction of cariprazine with inhibitors of P-gp, OATP1B1, OATP1B3 and BCRP is unlikely.

Potential for REAGILA® 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 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.

Cytochrome P450 (CYP450) substrates

Based on the results of in vitro studies, cariprazine and its major metabolites are not expected to inhibit the metabolism of co-administered medicines that are substrates for CYP1A2, CYP2A6, CYP2B6, CYP2D6, CYP2C8, CYP2C9 or CYP3A4, CYP2C19 or CYP2E1.

Neither cariprazine, DCAR nor DDCAR showed potential to induce the activities of CYP1A2, CYP2B6 or CYP3A4.

Hormonal contraceptives

In a drug interaction study, 28 days of treatment with cariprazine at 6 mg daily had no clinically relevant effect on the pharmacokinetics of oral contraceptives (ethinylestradiol and levonorgestrel).

Pharmacodynamic interactions

Given the primary central nervous system effects of cariprazine, REAGILA® should be used with caution in combination with other centrally acting medicinal products and alcohol

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effect of REAGILA® on human fertility has not been evaluated.

Animal Data

Fertility was reduced in female rats given oral daily doses of 1 mg/kg (1.5 times the human dose in mg/m2) from 4 weeks prior to mating through gestation day 7. Reductions in conception indices were evident at 10 mg/kg/day (15 times the human dose in mg/m2).

Cariprazine had no effect on fertility in male rats given oral daily doses up to 10 mg/kg/day from 70 days prior to mating (up to 4 times the maximal recommended human dose (MRHD) of 6 mg/day based on AUC of total cariprazine, i.e. sum of AUC values of cariprazine, DCAR and DDCAR).

Use in pregnancy – Pregnancy Category D

There are no or limited amount of data from the use of cariprazine in pregnant women.

REAGILA® is not recommended during pregnancy and in women of childbearing potential not using effective contraception. After discontinuation of REAGILA® treatment contraception should be used for at least 10 weeks due to the slow elimination of active moieties.

Non-teratogenic class effect: 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 hospitalisation. Consequently, newborns should be monitored carefully.

Animal Data

Oral administration of cariprazine to rats at doses of 0.5 mg/kg/day and above during the period of organogenesis caused malformations, lower pup survival, and developmental delays at drug exposures 0.2 times the MRHD of 6 mg/day based on AUC of total cariprazine, i.e. sum of AUC values of cariprazine, DCAR and DDCAR).

Oral administration of cariprazine to pregnant rats during the period of organogenesis, throughout pregnancy and lactation at 1 mg/kg/day (0.4 times the MRHD based on AUC of total cariprazine) 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.

In rabbits, cariprazine caused maternal toxicity, but no fetal toxicity, developmental effects or malformations at oral doses of 5 mg/kg/day (exposures 5 times the clinical exposure at the MRHD based on AUC of total cariprazine).

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®.

Use in lactation

It is unknown whether REAGILA® or its major active metabolites are excreted in human milk. Cariprazine and its metabolites are excreted in milk of rats during lactation. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with REAGILA®.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

REAGILA® 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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

Summary of the safety profile

The most frequently reported adverse drug reactions (ADRs) with REAGILA® in the dose range (1.5-6 mg) were akathisia (19%) and parkinsonism (17.5%). Most events were mild to moderate in severity.

Tabulated list of adverse reactions

ADRs based upon pooled data from cariprazine schizophrenia studies are shown by system organ class and by preferred term (Refer 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

Blood and lymphatic system disorders	**uncommon:** anaemia, eosinophilia; rare: neutropenia
Immune system disorders	**rare:** hypersensitivity
Endocrine disorders	**uncommon:** blood thyroid stimulating hormone decreased; **rare:** hypothyroidism
Metabolism and nutrition disorders	**common:** dyslipidaemia, weight increased; decreased appetite; increased appetite; **uncommon:** blood sodium abnormal; blood glucose increased; diabetes mellitus
Psychiatric disorders	**common:** sleep disorders[1]; anxiety; **uncommon:** suicidal behavior;delirium; depression; libido decreased; libido increased; erectile dysfunction
Nervous system disorders	**very common:** akathisia[2] ; Parkinsonism[3]; **common:** sedation; dizziness; dystonia[4] ; Other extrapyramidal disorders and abnormal movement disorders[5]; **uncommon:** tardive dyskinesia, dyskinesia[6]; dysaesthesia, lethargy; **rare:** seizures/ convulsion, amnesia, aphasia; **frequency not known:** neuroleptic malignant syndrome
Eye disorders	**common:** vision blurred; **uncommon:** intraocular pressure increased; accommodation disorder; visual acuity reduced; eye irritation; **rare:** cataract, photophobia
Ear and labyrinth disorders	**uncommon:** vertigo
Cardiac disorders	**common:** tachyarrhythmia; **uncommon:** cardiac conduction disorders; bradyarrhythmia; electrocardiogram QT prolonged; electrocardiogram T wave abnormal
Vascular disorders	**common:** hypertension; **uncommon:** hypotension
Respiratory, thoracic and mediastinal disorders	**uncommon:** hiccups
Gastrointestinal disorders	**common:** vomiting, nausea; constipation; **uncommon:** gastrooesophageal reflux disease; **rare:** dysphagia
Hepatobiliary disorders	**common:** hepatic enzymes increased; **uncommon:** blood bilirubin increased; **frequency not known:** toxic hepatitis
Skin and subcutaneous tissue disorders	**uncommon:** pruritus, rash
Musculoskeletal and connective tissue disorders	**common:** blood creatine phosphokinase increased; rare: rhabdomyolysis
Renal and urinary disorders	**uncommon:** dysuria, pollakisuria

Pregnancy, puerperium and perinatal conditions	**frequency not known:** drug withdrawal syndrome neonatal (see Section 4.6 Fertility, pregnancy and lactation)
General disorders and administration site conditions	**common:** fatigue; **uncommon:** 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	

Adverse events reported with the use of REAGILA (incidence of 2 % or greater) that occurred during pooled schizophrenia studies (Safety Population) are presented in Table 2.

Table 2: Treatment-emergent adverse events (≥ 2% in the cariprazine 1.5-6mg group) during pooled schizophrenia studies (Safety population)

System Organ Class Preferred Term	Placebo N = 683, n (%)	Cariprazine 1.5-6 mg N = 2048, n (%)
Patients with at least one TEAE	**467 (68.4)**	**1569 (76.6)**
Nervous system disorders	**171 (25.0)**	**843 (41.2)**
Akathisia	23 (3.4)	299 (14.6)
Headache	81 (11.9)	247 (12.1)
Extrapyramidal disorder	22 (3.2)	143 (7.0)
Tremor	11 (1.6)	112 (5.5)
Dizziness	15 (2.2)	92 (4.5)
Sedation	21 (3.1)	75 (3.7)
Somnolence	13 (1.9)	63 (3.1)
Psychiatric disorders	**201 (29.4)**	**684 (33.4)**
Insomnia	69 (10.1)	287 (14.0)
Restlessness	20 (2.9)	126 (6.2)
Anxiety	27 (4.0)	141 (6.9)
Schizophrenia	60 (8.8)	101 (4.9)
Agitation	27 (4.0)	78 (3.8)
Psychotic disorder	19 (2.8)	44 (2.1)
Gastrointestinal disorders	**162 (23.7)**	**548 (26.8)**
Nausea	31 (4.5)	141 (6.9)
Constipation	32 (4.7)	113 (5.5)
Dyspepsia	21 (3.1)	100 (4.9)
Vomiting	24 (3.5)	91 (4.4)
Diarrhoea	23 (3.4)	72 (3.5)
Toothache	22 (3.2)	61 (3.0)
Abdominal discomfort	16 (2.3)	41 (2.0)
Investigations	**50 (7.3)**	**303 (14.8)**
Weight increased	10 (1.5)	104 (5.1)
Blood creatine phosphokinase increased	11 (1.6)	54 (2.6)
Infections and infestations	**66 (9.7)**	**238 (11.6)**
Nasopharyngitis	10 (1.5)	49 (2.4)
Musculoskeletal and connective tissue disorders	**82 (12.0)**	**253 (12.4)**
Back pain	14 (2.0)	65 (3.2)
Pain in extremity	16 (2.3)	42 (2.1)
Metabolism and nutrition disorders	**28 (4.1)**	**115 (5.6)**
Decreased appetite	13 (1.9)	52 (2.5)
[5] **Other extrapyramidal disorders 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 Preclinical safety data). 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, 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%).

Extrapyramidal symptoms (EPS)

In the short term studies EPS was observed in 27%; 11.5%; 30.7% and 15.1% of patients treated with cariprazine, placebo, risperidone and aripiprazole respectively. Akathisia was reported in 13.6%; 5.1%; 9.3% and 9.9% of patients treated with cariprazine, placebo, risperidone and aripiprazole respectively. Parkinsonism was experienced in 13.6%; 5.7%; 22.1% and 5.3% of patients treated with cariprazine, placebo, risperidone and aripiprazole respectively. Dystonia was observed in 1.8%; 0.2%; 3.6% and 0.7% of 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% of the cariprazine group compared to 3.0% of the placebo treated patients. Akathisia was reported in 3.9% of patients treated with cariprazine, versus 2.0% of 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% of the cariprazine group and 11.7% of the risperidone treated patients. Akathisia was reported in 10.0% of patients treated with cariprazine and 5.2% of the risperidone group. Parkinsonism was experienced in 5.2% and 7.4% in cariprazine and risperidone treated patients respectively. Most EPS cases were mild to moderate in intensity and could be handled with common anti-EPS medicinal products. The rate of discontinuation due to EPS related ADRs was low.

Venous thromboembolism (VTE)

Cases of VTE, including cases of pulmonary embolism and cases of deep vein thrombosis have been reported with antipsychotics - Frequency unknown.

Elevated liver transaminases

Elevated liver transaminases (Alanine Aminotransferase [ALT], Aspartate Aminotransferase [AST]) are frequently observed with antipsychotic treatment. In the cariprazine clinical studies the incidence of ALT and 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, within the recommended dose range of 1.5 - 6 mg/day 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. The proportion of patients with potentially clinically significant (PCS) weight gain (defined as increase ≥ 7%) was 7.6 and 7.7% for the 1.5–3 and 4.5–6 mg/day cariprazine groups respectively, compared with 16.7% in the risperidone 4mg group, 6.0% in the aripiprazole 10mg group and 4.7% in the placebo group.

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 in the total study population (1.1 kg for cariprazine 3 – 9 mg and 0.9 kg for placebo). At the dose range of 3-6mg/day cariprazine, during the open-label phase of the study during 20 weeks cariprazine treatment, 9.0% of patients developed PCS weight gain, while during the double-blind phase, 9.8 % of the patients who continued with cariprazine treatment had PCS weight gain versus 7.1% of the patients who were 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 risperidone and PCS weight gain was observed in 6% of the cariprazine group while 7.4% of the risperidone group.

QT- prolongation

With cariprazine no QT interval prolongation was detected compared to placebo in a clinical study designed to assess QT prolongation (see Section 5.1 Pharmacodynamic properties). In other clinical studies, only a few, non-serious, QT-prolongations have been reported with cariprazine. During the long- term, open-label treatment period, 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%).

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

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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

There is no specific antidote to REAGILA®, therefore, 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 REAGILA® 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Psycholeptics, other antipsychotics, ATC code: N05AX15 REAGILA® is an atypical antipsychotic. It is an orally active and potent dopamine D_3 /D_2 receptor partial agonist with preferential binding to D_3 receptors and partial agonist at serotonin 5-HT_{1A} receptors.

Mechanism of action

The mechanism of action of cariprazine, as with other medicines having efficacy in schizophrenia, is not fully understood. However, the therapeutic effect of cariprazine may be mediated through a combination of partial agonist activity at dopamine D_3, D_{2L} and D_{2S} receptors and serotonin 5-HT_{1A} receptors, and antagonist activity at serotonin 5-HT_{2B}, 5-HT_{2A} and histamine H_1 receptors.

In vitro receptor binding studies revealed that cariprazine binds with high affinity (Ki < 1 nM) at dopamine D_3 (Ki = 0.085-0.3 nM), D_{2L} (Ki = 0.49-0.71 nM), D_{2S} (Ki = 0.69 nM) (ie. cariprazine displays 2-8 fold selectivity for D_3 over D_2 receptors) and serotonin 5-HT2B (Ki values of 0.58-1.1 nM) receptors, and with medium affinity (1nM <Ki < 20nM) at serotonin 5-HT1A (Ki = 1.4-2.6 nM) and 5-HT2A (Ki = 18.8 nM) receptors.

Cariprazine has low affinity (20nM < Ki < 200nM) for histamine H1 receptors (Ki = 23.3 nM), serotonin 5-HT_{2C} (Ki = 134 nM) and adrenergic α1 receptors (Ki = 155 nM).

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 active substance.

Pharmacodynamic effects

In vivo non-clinical studies demonstrated that cariprazine occupies D_3 receptors to a similar extent as D_2 receptors at pharmacologically effective doses. There was a dose-dependent occupancy of brain dopamine D_3 and D_2 receptors (with preferential occupancy in regions with higher D_3 expression) in patients with schizophrenia within the therapeutic dose range of cariprazine for 15 days.

The effects of cariprazine on the QT interval were evaluated in patients with schizophrenia or schizoaffective disorder. Holter monitor-derived electrocardiographic assessments were obtained in 129 patients over a twelve-hour period at baseline and steady state. No QT interval prolongation was detected following supratherapeutic doses (9 mg/day or 18 mg/day). No patients treated with cariprazine experienced QTc increases ≥ 60 msec from baseline, nor did any patient experience a QTc of > 500 msec in the study.

Clinical trials

Efficacy with short-term use

The efficacy of REAGILA® for the treatment of acute schizophrenia was studied in three multi-centre, multinational, randomised, double-blind, placebo-controlled 6-week studies including 1,754 patients with the age of 18 to 60 years. The primary endpoint was change from baseline to week 6 in the Positive and Negative Syndrome Scale (PANSS) total score and the secondary endpoint was change from baseline to week 6 in the Clinical Global Impressions-Severity (CGI-S) score in all acute schizophrenia studies.

In a multinational placebo-controlled study using fixed doses of 1.5 mg, 3.0 mg and 4.5 mg REAGILA® and 4.0 mg risperidone for assay sensitivity, all REAGILA® 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 REAGILA® 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 REAGILA®, both REAGILA® doses groups showed statistically significant improvement in both primary as well as secondary endpoint compared to placebo.

Results for the primary outcome parameter, analysed using mixed effects model for repeated measures (MMRM), are summarised in Table 3: Change From Baseline to Week 6 in the PANSS Total Score in Studies of Acute Exacerbations of Schizophrenia—ITT Population and are comparable to analysis using analysis of covariance (ANCOVA) with last observation carried forward (LOCF). Results for the secondary outcome parameter (CGI) and additional endpoints were supportive of the primary endpoint.

Table 3: 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)	—	—
REAGILA® 1.5 mg/day	97.1 ± 9.13	–21.27 (1.77)	–7.97 (–12.94, –3.01)	0.0017
REAGILA® 3 mg/day	97.2 ± 8.66	–21.45 (1.74)	–8.16 (–13.09, –3.22)	0.0013
REAGILA® 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)	—	—

REAGILA® 3 mg/day	96.1 ± 8.7	–20.2 (1.5)	–6.0 (–10.1, –1.9)	0.0044
REAGILA® 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)	—	—
REAGILA® 3 to 6 mg/day	96.3 ± 9.3	–22.8 (1.6)	–6.8 (–11.3, –2.4)	0.0029
REAGILA® 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; MMRM = mixed effects model for repeated measures *compared to placebo				

Efficacy with long-term use

The efficacy of REAGILA® for maintaining antipsychotic effect was investigated in a randomized, withdrawal, long-term clinical study. In total, 751 patients with acute symptoms of schizophrenia were treated with REAGILA® 3-9mg/d during 20-week open-label treatment consisting of an 8-week, flexible-dose run-in phase and a 12-week fixed-dose stabilization phase. 337 of these patients received REAGILA® in the dose-range of 3 or 6mg/day.

Stable patients who completed open-label treatment could be randomised to continue REAGILA® (3, 6, or 9mg/d) or placebo for double-blind treatment (up to 72 weeks). A total of 264 patients completed open label treatment; 200 eligible patients were randomised to double-blind placebo (n=99) or REAGILA® (n=101). The primary efficacy parameter was time to relapse (worsening of symptom scores, psychiatric hospitalisation, aggressive/violent behaviour, or suicidal risk) in the pooled REAGILA® group (3-9 mg) vs placebo.

By the end of the double-blind treatment, time to relapse was significantly longer in the REAGILA® group (3-9mg) than in the placebo group (p = 0.0010). The 25th percentile for time to relapse was 92 days in the placebo group, compared to 224 days in the REAGILA® group. 47.5% (47/99) of placebo-treated patients and 24.8% (25/101) of REAGILA®-treated patients had a relapse of schizophrenia symptoms. The hazard of relapse for REAGILA®- treated patients was estimated to be less than half that of placebo-treated patients (hazard ratio [95% CI] = 0.45 [0.28, 0.73]) (Figure 1). For REAGILA® 3-6 mg, time to relapse was also significantly longer in the REAGILA® group than in the placebo group (p = 0.0091). The 25th percentile for time to relapse was 92 days in the placebo group, compared to 326 days in the REAGILA® group. 49.0% (25/51) of placebo-treated patients versus 21.6% (11/51) of REAGILA®-treated patients had a relapse of schizophrenic symptoms (hazard ratio [95% CI] = 0.40 [0.20, 0.82]) (Figure 2).

Figure 1: Cumulative Rate of Relapse During the Double-Blind Treatment Period- Double-Blind Intent-to-Treat Population

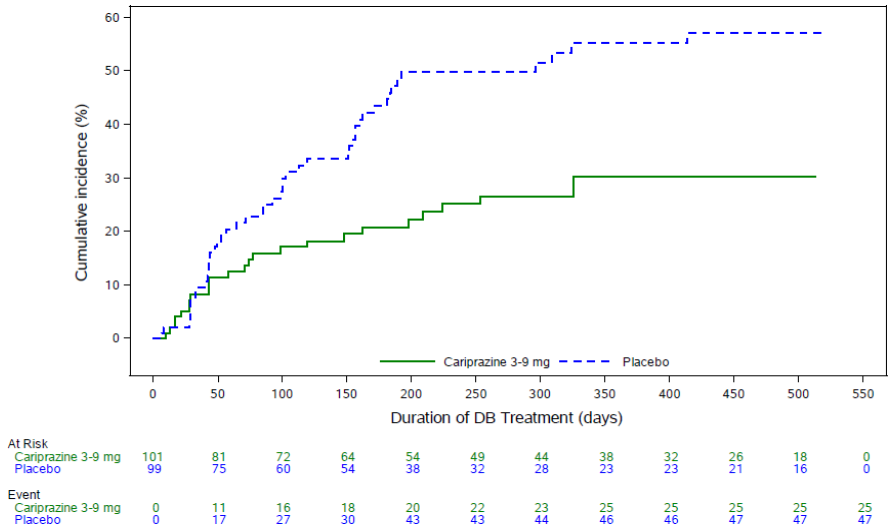
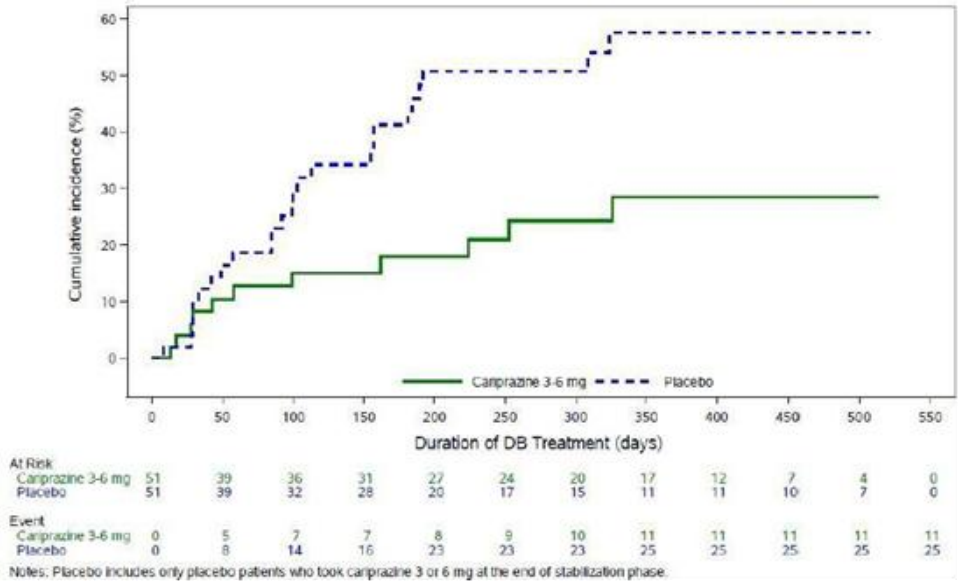


Figure 2: Kaplan Meier Curves of Cumulative Rates of Relapse during Double-Blind Treatment Period Cariprazine 3-6mg vs Corresponding Placebo Double-Blind Intention-To-Treat Population



Efficacy in predominantly negative symptoms of schizophrenia

The efficacy of REAGILA® for the treatment of predominantly negative symptoms of schizophrenia was investigated in a 26-week, multi-centre, double-blind, and active- controlled clinical study. REAGILA® (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 REAGILA®- 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=0.002). However, a statistically significant difference (p=0.008) in favour of REAGILA® over risperidone was observed from Week 14 onward (Table 4: Summary of results in study RGH-188-005 (MMRM analysis).

Both REAGILA® 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=0.005) in favour of REAGILA® over risperidone was observed from Week 10 onward (Table 4: Summary of results in study RGH-188-005 (MMRM analysis).

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. The results were analysed using MMRM and were consistent with the analysis using ANCOVA with LOCF.

Table 4: Summary of results in study RGH-188-005 (MMRM analysis)

Efficacy parameter	REAGILA® LS	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

PANSS-FSNS = PANSS factor score for negative symptoms

CfB = change from baseline

PSP = Personal and Social Performance

5.2 PHARMACOKINETIC PROPERTIES

Cariprazine has two pharmacologically active metabolites with similar activities as cariprazine, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR). Total cariprazine (sum of cariprazine + DCAR and DDCAR) exposure approaches 50% of steady state exposure in ~1 week of daily dosing while 90% of steady state is achieved in 3 weeks. At steady state, exposure to DDCAR is approximately two to three- fold higher than to cariprazine, and exposure to DCAR is approximately 30% of cariprazine exposure.

Absorption

Absolute bioavailability of REAGILA® is unknown. REAGILA® 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 REAGILA® 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%, Cmax decreased by < 5% under fed condition versus fasting). The effect of food on the exposure of the metabolites DCAR and DDCAR was also minimal.

REAGILA® 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 96% for DCAR and 92% to 94% for DDCAR) to plasma proteins.

Metabolism

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.

REAGILA® 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.

Excretion

Elimination of cariprazine and its major active metabolites is mainly through hepatic metabolism. Following administration of 12.5 mg/day REAGILA® 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 REAGILA®, 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.

REAGILA® has not been evaluated in patients with severe (CrCl < 30 mL/min) renal impairment (see Section 4.2 Dose and method of administration).

Hepatic impairment

A 2-part study (a single dose of 1 mg REAGILA® [Part A] and a daily dose of 0.5 mg REAGILA® 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 REAGILA® or 0.5 mg REAGILA® 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 REAGILA®.

REAGILA® has not been evaluated in patients with severe hepatic impairment (Child-Pugh Class C) (see Section 4.2 Dose and method of administration).

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 Dose and method of administration). 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 REAGILA® 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 could be a P-gp inhibitor in the intestine (see Section 4.5 Interactions with other medicines and other forms of Interactions).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Cariprazine was not mutagenic in the in vitro bacterial reverse mutation assay, nor clastogenic in the in vitro human lymphocyte chromosomal aberration assay or in the in vivo mouse bone marrow micronucleus assay. However, cariprazine increased the mutation frequency in the in vitro mouse lymphoma assay under conditions of metabolic activation at cytotoxic concentrations.

The major human metabolite DDCAR was not mutagenic in the in vitro bacterial reverse mutation assay, but induced a small increase in chromosomal aberrations in the in vitro human lymphocyte chromosomal aberration assay at cytotoxic concentrations in the presence of metabolic activation.

Based on the weight of evidence, cariprazine and its major metabolite DDCAR have negligible genotoxic potential.

Carcinogenicity

There was no increase in the incidence of tumours following daily oral administration of cariprazine to rats for 2 years and to Tg.rasH2 mice for 6 months at doses that are up to 4 and 19 times respectively, the MRHD based on AUC of total cariprazine, (i.e. sum of AUC values of cariprazine, DCAR and DDCAR).

Rats were administered cariprazine at oral doses of 0.25, 0.75, and 2.5 (males)/1, 2.5, and 7.5 mg/kg/day (females) which are 0.2 to 1.8 (males)/ 0.8 to 4.1 (females) times the MRHD based on AUC of total cariprazine.

Tg.rasH2 mice were administered cariprazine at oral doses of 1, 5, and 15 (males)/5, 15, and 50 mg/kg/day (females) which are 0.6 to 7.9 (males)/2.6 to 19 (females) times the MRHD based on AUC of total cariprazine.

Animal Toxicology

Retinal Pathology

REAGILA® 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 (2 mg/kg/day) was 4.2-fold the clinical AUC exposure for total cariprazine at the MRHD. Increased incidence and severity of retinal degeneration/atrophy was observed in albino rats in the 2-year study at 0.75 mg/kg/day (0.6 times the clinical AUC exposure for total cariprazine at the MRHD). Cataracts were not observed in other repeat dose studies in pigmented mice or albino rats.

Phospholipidosis

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 of 1 mg/kg/day (approximately 2 times the MRHD based on AUC of total

cariprazine). No inflammation was observed at the end of 2-month drug-free period at an exposure 4 times the clinical exposure at the MRHD; however, inflammation was still present at higher doses.

Effects on Adrenal Gland

Hypertrophy of the adrenal gland cortex was observed in rats (females only) and in mice following daily oral administration of cariprazine for 2 years and 6 months, respectively. Reversible hypertrophy/hyperplasia and vacuolation/vesiculation of the adrenal gland cortex were observed following daily oral administration of cariprazine to dogs for 1 year. The NOAEL was 2 mg/kg/day which is 4 times the MRHD based on AUC of total cariprazine. The relevance of these findings to human risk is unknown

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

This medicine does not contain lactose, sucrose, gluten or tartrazine.

Capsule contents

Pregelatinised maize starch

Magnesium stearate

Capsule shell (1.5 mg capsule)

Titanium dioxide

Gelatin

Capsule shell (3 mg capsule)

Allura red AC

Brilliant blue FCF

Titanium dioxide

Iron oxide yellow

Gelatin

Capsule shell (4.5 mg capsule)

Allura red AC

Brilliant blue FCF

Titanium dioxide

Iron oxide yellow

Gelatin

Capsule shell (6 mg capsule)

Brilliant blue FCF

Allura red AC

Titanium dioxide

Gelatin

Printing ink (black: 1.5 mg, 3 mg and 6 mg capsules)

Shellac

Iron oxide black

Propylene glycol

Potassium hydroxide

Printing ink (white: 4.5 mg capsule)

Shellac

Titanium dioxide

Propylene glycol

Simethicone

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Keep the blister in the outer carton in order to protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Transparent hard PVC/PE/PVDC blister heat-sealed with hard aluminum foil backing packed in folded carton box.

REAGILA® 1.5 mg and REAGILA® 3 mg hard capsules

Cartons contain 10 (starter pack), 30, 60 or 90 hard capsules. Not all pack sizes may be marketed.

REAGILA® 4.5 mg and REAGILA® 6 mg hard capsules

Cartons contain 30, 60 or 90 hard capsules. Not all pack sizes may be marketed

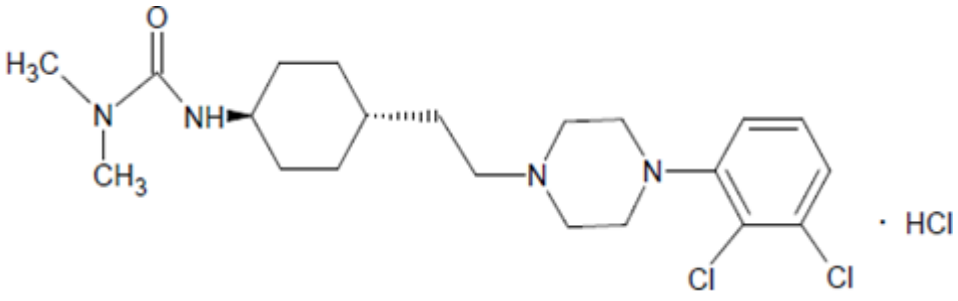
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Cariprazine HCl (active entity) is a white or almost white crystalline powder. It is freely soluble in methanol, slightly soluble in dichloromethane and, ethanol, very slightly soluble in acetone, acetonitrile and water, and practically insoluble in isopropyl alcohol and N,N- dimethylformamide and has a pKa of 8.2.

Chemical structure



CAS number

Cariprazine: [839712-12-8]

Cariprazine hydrochloride: [1083076-69-0]

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription only medicine

8. SPONSOR

Atnahs Pharma Australia Pty Ltd

Level 10 / 10 Shelley Street,

Sydney, NSW, 2000, Australia

Ph: 1800 899 005

9. DATE OF FIRST APPROVAL

18 November 2020

DATE OF REVISION

05 December 2025

Summary table of changes

Section changed	Summary of new information
8	Update to Sponsor details

REAGILA® is a registered trademark of Atnahs Pharma Australia Pty Ltd.