Australian Public Assessment Report for Cariprazine hydrochloride

Proprietary Product Name: Reagila

Sponsor: Gedeon Richter Australia Pty Ltd

May 2021

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.

- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.

- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.

- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.

- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.

- AusPARs are prepared and published by the TGA.

- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.

- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.

- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
5-HT	5-hydroxytryptamine (serotonin)
ACM	Advisory Committee on Medicines
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ARTG	Australian Register of Therapeutic Goods
ASA	Australian specific annex
AUC	Area under the plasma concentration time curve
AUC_{0-24}	Area under the plasma concentration time curve during 24 hours
AusPAR	Australian Public Assessment Report
BBB	Blood brain barrier
BMI	Body mass index
BW	Body weight
CFB	Change from Baseline
CGI-S	Clinical Global Impression – Severity score
CI	Confidence interval
C_{max}	Maximum plasma concentration
CNS	Central nervous system
DB	Double blind
DBP	Double blind period
DCAR	Desmethyl cariprazine (metabolite)
DDCAR	Didesmethyl cariprazine (metabolite)
DLP	Data lock point
EMA	European Medicines Agency (European Union)
E_{max}	Maximum effect value

Abbreviation	Meaning
EPS	Extrapyramidal symptoms
ET	Early termination
FSNS	PANSS Factor Score Negative Symptoms
GIT	Gastrointestinal tract
GVP	Good pharmacovigilance practices
HR	Hazard ratio
IEC	Independent ethics committee
IRB	Independent review board
ITT	Intent to treat
LOCF	Last observation carried forward
LS	Least square
LSMD	Least square mean difference
MMRM	Mixed-effect model repeated measure
NONMEM	Non-linear mixed effects modelling
OL	Open label
PANSS	Positive and Negative Syndrome Scale
PD	Pharmacodynamic(s)
PET	Positron emission tomography
PI	Product Information
PK	Pharmacokinetic(s)
PNS	Predominant negative symptoms
Pop PK	Population pharmacokinetic(s)
PP	Per protocol
PSP	Personal and Social Performance scale
PSUR	Periodic safety update report
RMP	Risk management plan

Abbreviation	Meaning
SAE	Serious adverse events
SAP	Statistical analysis plan
SD	Standard deviation
SFU	Safety follow-up
SOC	System Organ Class
SP	Stabilisation phase
$T_{1/2}$	Half-life
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration
T_{max}	The time after administration of a drug when the maximum plasma concentration is reached
USA	United States of America
V_d	Volume of distribution

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Product name:	Reagila
Active ingredient:	Cariprazine hydrochloride
Decision:	Approved
Date of decision:	12 November 2020
Date of entry onto ARTG:	18 November 2020
ARTG numbers:	325476, 325477, 325478, 325479
, *Black Triangle Scheme:[1]*	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Sponsor's name and address:	Gedeon Richter Australia Pty Ltd Unit 33-34/23 Narabang Way Belrose, NSW, 2085
Dose form:	Hard capsule
Strengths:	1.5 mg, 3 mg, 4.5 mg and 6 mg
Container:	Blister pack
Pack sizes:	1.5 mg and 3 mg strengths: 10 (starter pack), 30, 60 and 90 capsules 4.5 mg and 6 mg strengths: 30, 60 and 90 capsules
Approved therapeutic use:	*Reagila is indicated for the treatment of schizophrenia in adult patients*
Route of administration:	Oral
Dosage:	Reagila is to be taken once daily at the same time of the day and can be taken with or without food. 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

---

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

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.

For further information regarding dosage, refer to the Product Information.

Pregnancy category:	D

Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Seqirus (Australia) Pty Limited (the agent) to register Reagila (cariprazine hydrochloride) 1.5 mg, 3 mg, 4.5, and 6 mg, hard capsule for the following proposed indication:

> *Reagila is indicated for the treatment of schizophrenia in adult patients.*

Seqirus (Australia) Pty Ltd is the authorised agent whom acts on behalf of the sponsor: Gedeon Richter Australia Pty Ltd.

Schizophrenia is a lifelong, disabling psychiatric disorder that affects approx. 7 per 1000 of the adult population, with a worldwide prevalence of approximately 1%.[2,3] Based on the World Health Organization (WHO) prevalence ranges, lifetime prevalence estimates for schizophrenia in Australia (in 2001) were approximately between 10 to 18 per 1000 persons. The frequency of schizophrenia in Indigenous Australian communities is unknown, but higher rates of admission to psychiatric hospitals suggest prevalence may be higher among Aboriginal Australians than in the wider Australian population.[4]

The disorder usually manifests during adolescence or in young adulthood. The cardinal symptoms fall into three domains: positive symptoms, such as delusions and

---

[2] World Health Organization Health Topics, Schizophrenia (cited 21 October 2015). Available from: http://www.who.int/topics/schizophrenia/en/

[3] NICE Guideline CG178, Psychosis and schizophrenia in adults: prevention and management. National Institutes of Clinical Excellence (NICE; United Kingdom) 2014. Cited 21 October 2015.. Available from: http://www.nice.org.uk/guidance/cg178/chapter/introduction

[4] Galletly C et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. Aust N Z J Psychiatry 2016; 50(5):410-72.

hallucinations; negative symptoms, such as lack of drive and social withdrawal (absence or reduction in normal behaviours); and cognitive symptoms, such as problems with attention and memory. Many patients with schizophrenia have psychiatric comorbid conditions such as depression, anxiety and a high proportion have a lifetime history of alcohol, illicit substance and/or nicotine abuse. Physical disease is also common in patients with schizophrenia, including respiratory and cardiovascular disorders, and diabetes mellitus. In 2005 in Australia, life expectancy for patients with a primary diagnosis of schizophrenia was shorter for both males (by 16.4 years) and females (by 12.5 years) compared with the population average.[5]

Schizophrenia with negative symptoms is a form of schizophrenia, when negative symptoms dominate the clinical features. The negative symptoms may be due to the disease (primary symptoms) or caused by other factors (secondary symptoms), for example, depression, extrapyramidal side-effects of antipsychotics, positive symptoms or environmental understimulation. Primary negative symptoms appear to be more pervasive and seem to fluctuate less over time. These symptoms tend to persist during clinical periods of stability, do not respond well to treatment and interfere with the ability to perform normal functions.[6] Severity of negative symptoms is a predictor of poor patient functioning. It affects the patient's ability to live independently, to perform activities of daily living, to be socially active, maintain personal relationships, and to work and study.[7,8,9,10,11] Higher severity of symptoms is related to a lower quality of life.[12]

Antipsychotic medicines treat the symptoms of schizophrenia, but not its underlying causes. Antipsychotic medicines are the cornerstone of both acute and maintenance therapy for schizophrenia. In patients with schizophrenia or related psychoses, antipsychotic medicines diminish positive symptoms such as hallucinations, delusions and thought disorder, via dopamine receptor blockade. They also decrease symptoms of excitement, including hostility.

Although atypical antipsychotics (often referred to as 'atypicals') represent an improvement over classic typical antipsychotics in their adverse event profiles, atypicals generally fail to demonstrate superiority in addressing negative or cognitive symptoms, or treatment resistance. To date no effective therapy is available for negative symptoms of schizophrenia in Australia , although amisulpride is approved for treatment of negative symptoms in some European countries (mainly based on placebo-comparative data from studies in the 1990s). Some antipsychotics such as clozapine, amisulpride, olanzapine and risperidone have been described to have better efficacy on negative symptoms than

---

[5] Royal Australian and New Zealand College of Psychiatrists 2016. The economic cost of serious mental illness and comorbidities in Australia and New Zealand.

[6] Buchanan RW. Persistent Negative symptoms in schizophrenia: an overview. Schizophr Bull. 2007 Jul; 33(4): 1013–1022.

[7] Alonso J, Croudace T, Brown J, Gasquet I, Knapp MR, Suárez D, et al. Health-related quality of life (HRQL) and continuous antipsychotic treatment: 3-year results from the Schizophrenia Health Outcomes (SOHO) study. Value Health. 2009 Jun;12(4):536-43.

[8] Harvey PD, Heaton RK, Carpenter WT, Green MF, Gold JM, Schoenbaum M. Functional impairment in people with schizophrenia: focus on employability and eligibility for disability compensation. Schizophr Res. 2012 September; 140(1-3): 1–8.

[9] Rabinowitz J, Levine SZ, Garibaldi G, Bugarski-Kirola D, Berardo CG, Kapur S. Negative symptoms have greater impact on functioning than positive symptoms in schizophrenia: analysis of CATIE data. Schizophr Res. 2012 May;137(1-3):147-50.

[10] Rabinowitz J, Berardo CG, Bugarski-Kirola D, Marder S. Association of prominent positive and prominent negative symptoms and functional health, well-being, healthcare-related quality of life and family burden: a CATIE analysis. Schizophr Res. 2013 Nov;150(2-3):339- 42.

[11] Kirkpatrick B and Buchanan RW. Anhedonia and the deficit syndrome of schizophrenia. Psychiatry Research 1990;31:25-30.

[12] Rudnick A. The impact of coping on the relation between symptoms and quality of life in schizophrenia. Psychiatry. 2001 Winter;64(4):304-8.

others. However, their impact is not sufficient. No information is currently available to guide clinicians on the effectiveness of the various antipsychotic agents to treat negative symptoms. This leads physicians to prescribe various medications, including anxiolytics and anticonvulsants, and for predominantly negative symptoms, antidepressants as adjunctive treatment, given the overlap between negative and depressive symptoms. However, supportive evidence for adjunctive treatments for negative symptoms is limited.

Blockade of dopamine D_2 receptor is believed to have a central role in the antipsychotic action (efficacy for positive symptoms) of current schizophrenia medications.[13,14,15] Although the dopamine D_3 receptor has emerged as a possible target for improving antipsychotic drug treatment with respect to cognitive deficits and negative symptoms,[16] its role in schizophrenia is less understood, especially since no clinically used antipsychotic differentiates dopamine D_2 from D_3 receptors *in vitro.*[17] Moreover, currently used antipsychotics favour dopamine D_2 over D_3 receptor occupancy in the brain following systemic administration in rodents.[18,19] Several currently used antipsychotics fail to significantly occupy dopamine D_3 receptors in schizophrenia patients at therapeutic doses.[20,21] Affinity of cariprazine to dopamine D_3 receptors is so strong it can displace dopamine in the living cell. This feature is unique to cariprazine over currently used antipsychotics. Other distinct features of cariprazine include its relatively lower affinity for serotonin (5-hydroxytryptamine) 5-HT_{2C} and adrenergic $\alpha1$ receptors. These are targets considered to be related to the cardiovascular and metabolic side effects of antipsychotic agents. Cariprazine is a partial agonist and the first and only atypical antipsychotic that demonstrates a balanced dual engagement of the dopamine D_3 and D_2 receptor systems, which may confer additional benefits such as enhanced cognition, and may be the underlying mechanism for improvement in negative symptoms in schizophrenia. Both remain areas of an unmet medical need.

The efficacy and tolerability of currently approved antipsychotics are heterogeneous and individual responses to treatment can vary widely. Therefore, despite the availability of a number of approved atypical antipsychotics for the treatment of schizophrenia, the need for additional therapeutic options remains.

[13] Baldessarini RJ, Tarazi FI. Pharmacotherapy of psychosis and mania. In: Brunton LL, Lazo JS, Parker KL, editors. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 11th ed. New York, NY: McGraw-Hill; 2005. p. 461–500.

[14] Kapur S and Mamo D. Half a century of antipsychotics and still a central role for dopamine D2 receptors. Prog Neuropsychopharmacol Biol Psychiatry. 2003 Oct;27(7):1081-90.

[15] Seeman P. Dopamine D2 receptors as treatment targets in schizophrenia. Clin Schizophr Relat Psychoses. 2010 Apr;4(1):56-73.

[16] Joyce JN. and Millan MJ. Dopamine D3 receptor antagonists as therapeutic agents. Drug Discov Today. 2005 Jul 1;10(13):917-25.

[17] Millan MJ. and Brocco M. Cognitive impairment in schizophrenia: a review of developmental and genetic models, and pro-cognitive profile of the optimised D(3) > D(2) antagonist, S33138. Therapie. 2008 May-Jun;63(3):187-229.

[18] Gyertyán I, Kiss B, Sághy K, Laszy J, Szabó G, Szabados T et al. Cariprazine (RGH-188), a potent D3/D2 dopamine receptor partial agonist, binds to dopamine D3 receptors in vivo and shows antipsychotic-like and procognitive effects in rodents. Neurochem Int. 2011 Nov;59(6):925-35.

[19] McCormick PN, Kapur S, Graff-Guerrero A, Raymond R, Nobrega JN, Wilson AA. The antipsychotics olanzapine, risperidone, clozapine, and haloperidol are D2-selective ex vivo but not in vitro. Neuropsychopharmacology. 2010 Jul;35(8):1826-35.

[20] Graff-Guerrero A, Mamo D, Shammi CM, Mizrahi R, Marcon H, Barsoum P. et al. The effect of antipsychotics on the high-affinity state of D2 and D3 receptors: a positron emission tomography study With [11C]-(+)-PHNO. Arch Gen Psychiatry. 2009 Jun;66(6):606-15.

[21] Mizrahi R, Agid O, Borlido C, Suridjan I, Rusjan P, Houle S, Remington G et al. Effects of antipsychotics on D3 receptors: a clinical PET study in first episode antipsychotic naïve patients with schizophrenia using [11C]-(+)-PHNO. Schizophr Res. 2011 Sep;131(1-3):63-8.

Regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

At the time the TGA considered this application, Reagila had been approved in over 52 countries and was under consideration in over nine countries. Reagila was withdrawn from South Korea and Taiwan due to commercial reasons.

Table 1: Selected international regulatory status

Region	Status	Approved indications
United States of America	Approved on 17 September 2015	*Treatment of schizophrenia in adult patients* *Acute treatment of manic or mixed episodes associated with bipolar I disorder in adult patients.*
	Approved on 9 November 2017	*Maintenance of treatment of schizophrenia.*
	Approved on 24 May 2019	*Treatment of depressive episodes associated with bipolar I disorder in adult patients*
European Union	Approved on 13 July 2017	*Treatment of schizophrenia in adult patients.*
Switzerland	Approved on 19 June 2018	*Treatment of schizophrenia in adult patients*
Singapore	Approved on 11 July 2019	*Treatment of schizophrenia in adult patients.*
Montenegro	Approved on 21 February 2019	*Treatment of schizophrenia in adult patients*
Russia	Approved on 18 March 2019	*Treatment of schizophrenia in adult patients*
Moldova	Approved on 13 September 2018	*Treatment of schizophrenia in adult patients*
Azerbaijan	Approved on 16 July 2019	*Treatment of schizophrenia in adult patients*
Uzbekistan	Approved on 24 May 2019	*Treatment of schizophrenia in adult patients*
Belarus	Approved on 4 July 2019	*Treatment of schizophrenia in adult patients*
Kazakhstan	Approved on 24April 2019	*Treatment of schizophrenia in adult patients*

Region	Status	Approved indications
Ukraine	Approved on 12 August 2018	*Treatment of schizophrenia in adult patients*
Israel	Approved on 30 January 2020	*Treatment of schizophrenia in adult patients*
Singapore	Approved on 11 July 2019	*Treatment of schizophrenia in adult patients*
Thailand	Approved on 22 July 2019	*Treatment of schizophrenia in adult patients*
Malaysia	Approved on 6 August 2020	*Treatment of schizophrenia in adult patients*
Jordan	Approved on 2 July 2020	*Treatment of schizophrenia in adult patients*
Kingdom of Saudi Arabia	Approved on 16 November 2020	*Treatment of schizophrenia in adult patients*
South Korea	Withdrawn*	
Taiwan	Withdrawn*	

*The South Korean and the Taiwanese Authorities requested additional local clinical efficacy studies in order to get efficacy data on South Korean and Taiwanese populations, respectively. The applicant, Mitsubishi-Tanabe Pharma Co. decided to withdraw the applications in both countries for commercial reasons.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2019-04790-1-1

Description	Date
Submission dossier accepted and first round evaluation commenced	2 December 2019
First round evaluation completed	3 June 2020

Description	Date
Sponsor provides responses on questions raised in first round evaluation	29 July 2020
Second round evaluation completed	17 August 2020
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	1 September 2020
Sponsor's pre-Advisory Committee response	14 September 2020
Advisory Committee meeting	1 and 2 October 2020
Registration decision (Outcome)	13 November 2020
Completion of administrative activities and registration on the ARTG	18 November 2020
Number of working days from submission dossier acceptance to registration decision*	196

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.
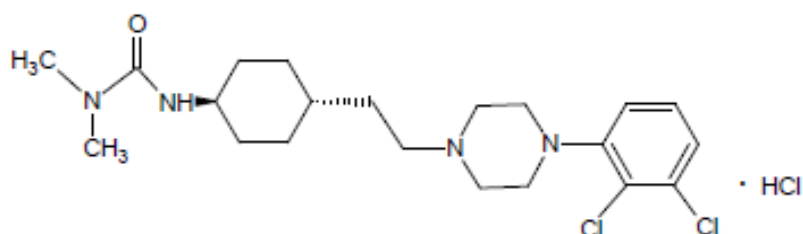
The following guidelines was referred to by the Delegate:

- Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia. EMA/CHMP/40072/2010 Rev. 1.[22]

Quality

Cariprazine hydrochloride (See Figure 1 below) is a partial dopamine D_3/D_2 receptor agonist and also shows some partial serotonin 5-HT$_{1A}$ receptor agonist activity.

Figure 1: Chemical structure of cariprazine hydrochloride

Cariprazine hydrochloride is stable during long term storage below 25°C for 60 months. Reagila (cariprazine hydrochloride) is available in 1.5 mg, 3 mg, 4.5 mg and 6 mg hard capsule in blister packet.

---

[22] Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia. EMA/CHMP/40072/2010 Rev. 1

No bridging bioequivalence data are required between the Phase III clinical formulation and the proposed formulation to be registered in Australia. The differences between the capsule used in the clinical formulation and proposed formulation are not considered significant and have been sufficiently bridged by comparable dissolution data across the pH range.

Approval for registration of the proposed product is recommended from a quality perspective.

Nonclinical

The nonclinical data submitted was of high quality and compliant with relevant guidelines. All pivotal toxicity studies were conducted under Good Laboratory Practice conditions using the proposed clinical route and dosing regimen.

The pharmacological profile and activity of cariprazine and its active metabolites in standard animal models support the proposed clinical use in patients with schizophrenia. No unique, clinically relevant hazards were identified in secondary pharmacodynamics and safety pharmacology studies.

Target organs identified in repeat-dose studies were the central nervous system (CNS), eye, lungs, adrenal gland, female reproductive tract, sciatic nerve, pancreas, pituitary gland and nasal mucosa. Reductions in serum concentrations of cholesterol and triglycerides were seen in all species. Many of these effects are characteristic of antipsychotic compounds active on dopamine D_2 and serotonin $5\text{-}HT_{1A}$ receptors including those mediated by hyperprolactinaemia. The most clinically significant toxicities were cataract formation in dogs and phospholipidosis (with or without inflammation and fibrosis) in the lungs and female reproductive toxicity. Cariprazine is not considered to pose a high genotoxic or carcinogenic hazard.

Female fertility was reduced at clinical exposures. Malformations (in rats, but not rabbits), reduced birth weight and developmental delay were associated with subclinical exposures in the absence of maternal toxicity. Pre/postnatal toxicity included reductions in litter size, birth weight, body weight gain and postnatal survival, adverse clinical signs and (in males) decreased auditory startle responsiveness, in the absence of maternal toxicity. Adverse fetal effects persisted in the second filial generation. A Pregnancy Category of D;[23] is recommended rather than the sponsor's proposed Pregnancy Category B3;[24] as the fetal malformations in rats and adverse effects in the first and second filial generations in the pre- and postnatal development study were associated with subclinical exposures and occurred in the absence of maternal toxicity. The Delegate agrees with the nonclinical evaluator that the Pregnancy Category D;[23] is appropriate for Reagila.

There are no nonclinical objections to registration. Clinical consideration should be given to the post-market monitoring of ocular effects.

Clinical

The clinical dossier consisted of:

• one bioequivalence study

---

[23] **Pregnancy Category D**: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
[24] **Pregnancy Category B3**: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

- 14 pharmacokinetics (PK) studies

- four pharmacodynamics (PD) studies

- two population pharmacokinetics (pop PK) studies

- ten clinical efficacy and safety via:

  – two Phase III and one Phase IIb pivotal efficacy and safety studies in acute schizophrenia (Studies RGH-MD-16, RGH-MD-04 and RGH-MD-05)

  – one Phase III pivotal efficacy and safety study in maintenance and relapse prevention in schizophrenia (Study RGH-MD-06)

  – one Phase III pivotal efficacy and safety study in predominantly negative symptoms of schizophrenia (RGH-188-005)

  – one Phase II confirmatory (proof-of-concept/dose-finding) efficacy and safety study in acute schizophrenia (Study RGH-MD-03)

  – two Phase III long-term, open-label (OL) safety studies (with efficacy data): Studies RGH-MD-11 and RGH-MD-17

  – two Phase III Japanese efficacy and safety studies (Studies A002-A7 and A002-A8)

  – Japan studies for safety data (schizophrenia): Studies A002-A7, A002-A8, A002-A3, and A002-A11; and two ongoing clinical studies (Studies A002-A4 and A002-A5).

Pharmacokinetics

Cariprazine is a relatively small molecule, which means it would be expected to pass through most biological membranes. This is supported by its dissociation constant (pKa) value of 8.2. Its positive partition coefficient indicates that the molecule has a greater affinity for a lipid environment than an aqueous one. This is supported by the large mean apparent volume of distribution of 916 L. Hence, cariprazine is likely to cross the blood brain barrier (BBB) at therapeutic dosing levels. This is a desirable feature of an antipsychotic agent, since the sites of action (dopamine D_3 and D_2 receptors) are within basal ganglia structures. However, the efficacy of a centrally acting agent needs to be balanced against its potential toxicity. This will be more fully addressed in the safety section.

The PK properties of cariprazine are characterised by relatively high absorption from the gastrointestinal tract (GIT), multi-exponential disposition and slow elimination. Study RGH-MD-01 showed that less than 4% of the daily dose was recovered in faeces as unchanged cariprazine. Median time to maximum plasma concentration (t_{max}) of oral cariprazine was approximately 3 to 4 hours in healthy adults. Cariprazine is extensively distributed into tissues, following a multi-exponential disposition, with an estimated volume of distribution (V_d) of 916 L. Cariprazine is highly bound (approximately. 96%) to human plasma proteins, independent of sex status.

The Delegate commented that about 70% of cariprazine and its metabolites are accounted for in the urine and faeces. The sponsor has been requested to response the below question, 'Can the tissue distribution and protein binding of the latter account for the remaining 30%?' in the section: Questions for the sponsor, located below.

Single doses of more than 2 mg and multiple doses of more than 1 mg/day were not well tolerated in healthy volunteers, characterisation of the PK of cariprazine, metabolites desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR) in standard (that is healthy volunteers) clinical pharmacology studies, at therapeutic doses, were not possible. The PKof cariprazine, and the metabolites DCAR and DDCAR were therefore characterised at therapeutic doses in schizophrenia patients, using standard non-compartmental

analyses. Generally, the PK of cariprazine was comparable between healthy adult subjects and adults with schizophrenia, except for dose-proportionality, which was nonlinear in healthy subjects at sub-therapeutic cariprazine doses and linear over the proposed dose-range in patients with schizophrenia.

No dose adjustments are needed due to PK differences in sex, race, body weight (BW), age, or due to mild or moderate hepatic or renal impairment. Also, cariprazine can be taken without regard to food.

Co-administration of cariprazine with strong and moderate cytochrome P450 (CYP)[25] 3A4 inhibitors, such as ketoconazole, are contraindicated.

Population pharmacokinetics

Study data: Rich and sparse plasma concentration cariprazine data were obtained from three Phase I, three Phase II and seven Phase III studies (which included three bipolar mania studies). The final model development dataset included 13,227 cariprazine samples collected from 2199 patients, 12,462 DCAR metabolite samples collected from 2180 patients, and 12,092 DDCAR metabolite samples collected from 2140 patients over the dose range 1.5 mg/day to 12.5 mg/day of cariprazine. Data were pooled using non-linear mixed effects modelling (NONMEM) version 7.1.2.

Study participants: Mean age was 40 years (range: 18 to 65), male 66.4%; Caucasian 45.6%, 1.7% Japanese; mean BW of 77.7 kg (range: 33.1 to 155.1); 17% (n = 377) had mild renal impairment; 0.9% (n = 20) had moderate renal impairment; 868 extensive metabolisers (ultra, extensive or intermediate) and 40 poor metabolisers.

Results: Mean BW, race and sex were statistically significant predictors of at least one of the parameters across the three analyte models (albeit all total cariprazine exposures were within 36% of the relevant comparator groups). Cariprazine and DCAR metabolite concentrations were approximately 3-fold and 6- to 8-fold higher after multiple dosing, respectively. Median time to achieve 90% steady state for cariprazine and the metabolite DCAR was 5 days, and 21 days for the metabolite DDCAR. Mean functional half-life ($t_{1/2}$) (from time to achieve 90% steady-state) was 1.5 days, 1.5 days and 7 days, respectively. No statistically significant differences in plasma clearance for cariprazine, and the metabolites DCAR or DDCAR were found due to concomitant administration of CYP;[25] 2D6 inhibitors, and following a steady-state dose of 6 mg/day, total cariprazine exposures (maximum concentration (C_{max}) and area under the plasma concentration time curve during 24 hours (AUC_{0-24})), after correction for molecular weight, were approximately 28.1% to 33.6% for cariprazine, 7.7% to 7.9% for the metabolite DCAR and 58.5% to 64.2% for the metabolite DDCAR, respectively.

Population pharmacokinetics results generally supported the results from individual PK studies. The methods, assumptions and conclusions derived from the PopPK evaluation appeared to be reasonable.

---

[25] **Cytochrome P450 (CYP) enzymes:** CYPs are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds.

Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

Pharmacodynamics

The pharmacodynamics (PD) data provided in the clinical dossier were sufficiently comprehensive to support the proposed indication of cariprazine in adults with schizophrenia.

Regarding the effect on dopamine D_3/D_2 receptor occupancy, administration of 1 mg cariprazine for two weeks displaced the specific binding of [^{11}C]-raclopride;[26] in the considered brain regions with known dopamine D_2/D_3 receptors (caudate, putamen and ventral striatum). Regional occupancies of around 73% were achieved at 1 mg steady-state. In Study RGH-MD-14, data for the striatal regions (that is, the caudate, putamen, and nucleus accumbens) showed a maximum occupancy (≥ 90%) at a target dose of cariprazine 3 mg following 14 days of once daily administration. Dopamine D_3/D_2 receptor occupancy in the striatal regions increased with increasing cariprazine doses of 0.5 mg to 3 mg following 14 days of once daily administration. Occupancy (76 to 86%) in the dorsal and ventral striatum at the 1.5 mg dose level in schizophrenia patients was similar to the receptor occupancy found at a 1 mg dose in healthy subjects. The maximum effect value (E_{max}) approached a 100% receptor occupancy in the dorsal striatum (the putamen and caudate nucleus), and in the ventral striatum (nucleus accumbens). Near complete receptor occupancy for the dopamine D_2 and D_3 receptors was observed in patients with schizophrenia at 12 mg/day after 15 days of cariprazine dosing, using labelled positron emission tomography (PET). At 3 mg/day, mean dopamine D_3 and D_2 receptor occupancy was 92% (range: 86% to 96%) and 79% (range: 68% to 88%), respectively. At the lowest dose of 1 mg/day, mean dopamine D_3 and D_2 receptor occupancy was 76% (range 58% to 89%) and 45% (range 14% to 64%), respectively.

Plasma concentration-effect relationships were defined for many important primary and secondary PD effects, including effects on dopamine D_3/D_2 receptor occupancy and the cardiac QT interval.[27] PD effects were generally consistent with C_{max} and total exposure (area under the plasma concentration time curve (AUC)), with dose-dependent RO of brain dopamine D_2 and D_3 receptors (with preferential RO in regions with high D_3 expression).

The dedicated thorough QT study and population PK/PD studies, did not reveal clinically meaningful effects of cariprazine treatment on QT prolongation.[27] The major anticipated clinical safety concern, based on the claimed mechanism of action, relate to possible CNS-related events. This will be evaluated further in the safety section.

Pivotal studies

Studies RGH-MD-04, RGH-MD-16 and RGH-MD-05 (acute exacerbation of schizophrenia)

- Study RGH-MD-04: A double-blind, placebo and active-controlled evaluation of the safety and efficacy of cariprazine in the acute exacerbation of schizophrenia;

- Study RGH-MD-16: Evaluation of the safety and efficacy of RGH-188 (cariprazine) in the acute exacerbation of schizophrenia; and

- Study RGH-MD-05: A double-blind, placebo-controlled evaluation of the safety and efficacy of cariprazine in the acute exacerbation of schizophrenia.

---

[26] ^{11}C-raclopride is a synthetic compound that acts as a selective antagonist on dopamine D_2 receptors
[27] The **QT interval** is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.

Study design

Each study had a seven day, no psychotropic washout period immediately prior to randomisation to double blinded (DB) treatment for 6 weeks, followed by a 2 week safety follow-up (SFU). The study objectives were to evaluate the safety, efficacy and tolerability of cariprazine relative to placebo in adult patients with acute exacerbation of schizophrenia.

The three studies are describes as follows:

- Study RGH-MD-04 was a Phase III multicentre, multinational, randomised, DB, placebo and active controlled, parallel group, fixed dose study, conducted between April 2010 and December 2011 in the USA (20 centres; 35% patients), Russia (14 centres; 30% patients), Ukraine (12 centres; 23% patients) and Romania (12 centres; 11% patients). Aripiprazole 10 mg/day was added as an active control for assay sensitivity.

- Study RGH-MD-16 was a Phase IIb, multicentre, randomised, DB, placebo and active controlled, parallel group, fixed dose study, conducted between June 2008 and August 2009 in the USA (18 centres; 38%), India (16 centres; 22%), Russia (15 centres; 22%), Ukraine (11 centres; 16%) and Malaysia (5 centres; 3%). Risperidone at 4 mg/day was added as an active control for assay sensitivity.

- Study RGH-MD-05 was a Phase III, multicentre, multinational, randomised, DB, placebo controlled, parallel group, fixed/flexible dose study, conducted between April 2010 and December 2011 in the US (15 centres; 52%), India (19 centres; 37%), Columbia (4 centres; 11%) and South Africa (2 centres; 1%).

An independent review board (IRB) or independent ethics committee (IEC) provided ethics approval for the study conduct, including three protocol amendments and one statistical analysis plan (SAP) amendment in each study. All participants provided written informed consent.

Conclusion

The study design, conduct and analyses used in the pivotal Phase II/III placebo and active controlled short term studies in acute schizophrenia were generally acceptable and consistent with the TGA-adopted Guideline for schizophrenia,[22] with no major deviations noted except that no per protocol (PP) analysis was performed in each study. The clinical evaluator requested that the sponsor provide clarification as to why no PP analysis was performed. The sponsor provided the requested data (not shown here) and the clinical evaluator concluded that the sponsor's response is acceptable. The results for the primary and secondary endpoints in the pivotal studies were generally consistent between the intent to treat (ITT) and the PP. This provides further evidence of the robustness of the results.

The entry criteria, use of established validated primary and secondary efficacy endpoints, the central randomisation and blinding methods used, sample size calculations and SAPs were generally acceptable. Confounding and selection bias are not considered to be significant factors within the study design. However, since the proportion of participants who did not complete the studies was relatively high (approximately 25% to 47% across treatment groups, across studies), this has potential to adversely impact internal validity.

The population investigated in the short term clinical trials is generally representative of a patient population with an acute exacerbation of schizophrenia. Patients were generally aged 30 to 50 years and most patients were male. Demographics across studies and treatments were generally similar except there were more Caucasian patients than other races in Studies RGH-MD-04 and RGH-MD-16, whereas more Black and Asian patients were included in Study RGH-MD-05. However, no clinically meaningful differences in treatment effect were observed across race groups, and so the results are expected to have reasonable external validity.

The baseline disease and efficacy characteristics were evenly distributed across treatments and studies, with a predominance of paranoid schizophrenia. Patients were generally markedly ill at Baseline (mean Clinical Global Impression – severity (CGI-S) scores close to 5.0), although the cariprazine 1.5 mg/day group in Study RGH-MD-16 had a statistically significantly lower (p = 0.037) CGI-S score (4.7) versus placebo treatment (4.9). However, since baseline score was a covariate in the ANCOVA model, this difference in CGI-S score is not expected to adversely affect the results in Study RGH-MD-16.

The clinical evaluator requested that the sponsor provide further information on the proportion of patients who deteriorated during randomised treatment during each study from the sponsor. The sponsor provided the requested data [beyond the scope for inclusion in this AusPAR] and the clinical evaluator concluded that the sponsor's response is acceptable. As expected, deterioration rates were typically higher in placebo treated subjects. No clear dose relationships were observed across the studies, and the proportion of non-responders at both defined endpoints were low (≤ 3.5%) for any cariprazine treatment group. These results provide further supportive evidence of efficacy for cariprazine across the proposed dose range.

The clinical evaluator requested that the sponsor provide further information on the treatment effect for the cariprazine 9 mg/day dose in Study RGH-MD-05.[28] The sponsor provided the requested data [beyond the scope for inclusion in this AusPAR] and the clinical evaluator concluded that the sponsor's response is acceptable. The results were generally consistent with the primary efficacy analyses in Study RGH-MD-05. The 9 mg/day cariprazine regimen demonstrated greatest efficacy versus placebo in the primary endpoint. No clear dose-response trend was observed between cariprazine doses for the second endpoint.

Study RGH-MD-06 (maintenance of effect and relapse prevention in schizophrenia)

Study RGH-MD-06 is a randomised, double blind, placebo controlled, parallel group study of cariprazine in the prevention of relapse in patients with schizophrenia.

Study design

Design: This was a Phase III, multicentre, randomised, DB, placebo-controlled, parallel group, flexible and fixed dose study conducted in the USA (25 centres), India (15 centres), Ukraine (15 centres), Slovakia (7 centres) and Romania (10 centres), between September 2011 and September 2014. Distribution of patients by country is as follows: 226 patients (30.1%) were from European countries (Romania, Slovakia and Ukraine), the others from India and the USA. The study was carried out in five phases, using a randomised withdrawal design.

The screening phase was drug-free for up to 7 days followed by a run-in period, in which patients received open label (OL) cariprazine, flexibly dosed at 3, 6 or 9 mg/day for the first six weeks, then fixed for two weeks. Patients continued to the stabilisation phase (SP) and received 12 weeks OL cariprazine at the same dose they received in the last two weeks of the run in period.

Conclusion

The study design (fixed dose, placebo controlled and withdrawal), conduct and analyses used in the pivotal Phase III maintenance/relapse prevention study were generally acceptable and consistent with the TGA-adopted Guideline for schizophrenia,[22] with no major deviations noted except that no PP analysis was performed.

---

[28] Clarification, while sponsor submitted data for 9 mg/day dosage, the sponsor has only applied for 1.5 mg to 6 mg/day dosage in the application. The sponsor has reemphasised that they are seeking approval for 1.5 to 6 mg in this application.

The entry criteria (inclusion and exclusion), primary efficacy endpoint (time to first relapse), and the central randomisation and blinding methods used were generally acceptable and consistent with the pivotal short-term acute schizophrenia studies. Demographic and patient characteristics of the study population were generally evenly distributed across treatments and representative of the target patient population.

While the sample size calculations and SAPs were generally acceptable, cariprazine results were not planned to be analysed by randomised dose (3, 6 or 9 mg/day). Instead, results were analysed as 'total cariprazine 3 to 9 mg/day'. Hence, the minimum effective dose to maintain the antipsychotic effect with cariprazine treatment could not be fully ascertained. The sponsor provided *post hoc* results to the European Medicines Agency (EMA) for the cariprazine 3 to 6 mg/day group versus. placebo comparison. The primary efficacy results of the *post hoc* analysis was generally consistent with the total cariprazine 3 to 9 mg/day results. The clinical evaluator requested further data on cariprazine 9 mg/day from sponsor. The sponsor provided further data on cariprazine 9 mg/day [inclusion beyond the scope of this AusPAR] and the clinical evaluator concluded that sponsor's response is acceptable. The results were generally consistent with those from the primary efficacy analysis. Any potential treatment benefit of a cariprazine 9 mg dose over a cariprazine 6 mg dose is not clinically meaningful. The cariprazine 3 mg dose provided greater efficacy than the cariprazine 6 mg dose.

While the need for use of rescue medication was reported to be reduced throughout the double blind period (DBP) for the total cariprazine 3 to 9 mg/day treatment group, it remains unclear whether particular dose-regimens of cariprazine (3, 6 and 9 mg) required more or less rescue medication. The sponsor was requested by the clinical evaluator to provide further data on the mean daily dose of rescue medication for Study RGH-MD-06.The sponsor provided the requested data [inclusion beyond the scope of this AusPAR] and the clinical evaluator concluded that sponsor's response is acceptable. In general, mean doses of permitted rescue medications (for insomnia, extrapyramidal symptoms (EPS) or akathisia, or for anxiety, agitation or restlessness) were comparable to doses used for placebo-treated subjects. No clear dose related trends were observed.

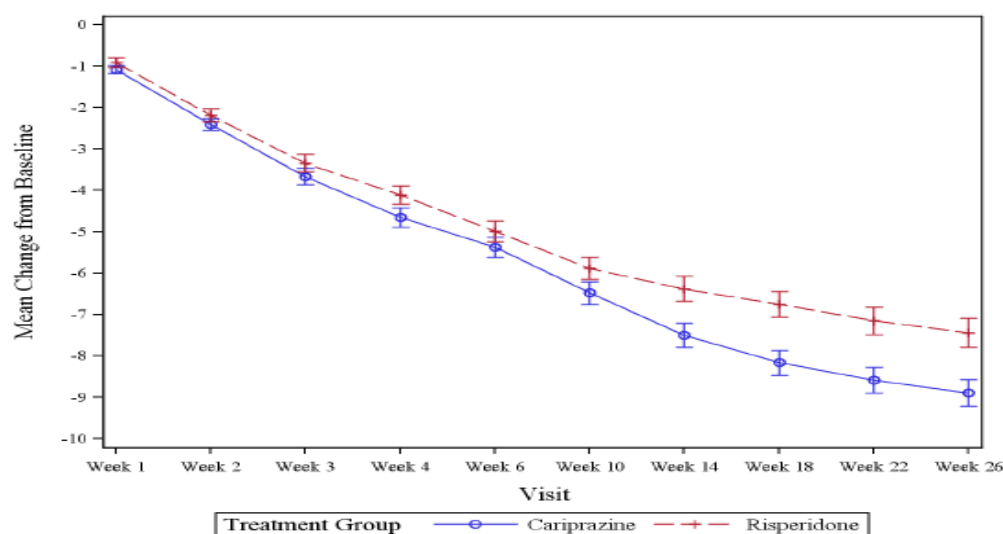### Study RGH-188-005 (predominant negative symptoms of schizophrenia)

Study RGH-188-005 is a randomised, double blind, parallel group study to investigate the efficacy, safety, and tolerability of cariprazine in patients with predominant negative symptoms of schizophrenia.

Study design

Clinical Design: This was a Phase IIIb, multinational, multicentre, randomised, DB, active controlled (risperidone), parallel group, fixed/flexible dosed study conducted across Europe (118 patients from Ukraine, 108 from Russia, 48 from Czech Republic, 46 from Serbia, 33 from Hungary, 32 from Bulgaria, 30 from Poland, 22 from France, 15 from Croatia, 7 from Romania and 1 from Spain), between May 2013 and November 2014.

The study consisted of three periods: a four week prospective lead in period (to down titrate antipsychotic medication), followed by a 26 week DB treatment period that comprised a two week (Part 1) up titration period to the target dose followed by a 24 week (Part 2) continuation phase, followed by a two week SFU period. No placebo arm was added, to control for positive symptoms. Risperidone was chosen as the active comparator.

Figure 2: Study RGH-188-005 Mean treatment profiles for the change from Baseline (± standard error) in Positive and Negative Syndrome Scale factor score for negative symptoms of schizophrenia (mixed-effect model repeated measure; intent to treat population)

Conclusion

The study design, conduct and analyses were generally acceptable and consistent with the TGA-adopted Guideline for schizophrenia,[22] with no major deviations noted except that no PP analysis was performed.

Risperidone was an acceptable choice of active comparator that is similar safety profile and dose range to cariprazine. The rationale for not including a placebo treatment arm, to control for positive symptoms and balance patient drop out rates, was reasonable. However, the short SFU period did not allow for adequate assessment of withdrawal phenomena (including potential relapse), since the plasma clearance of the metabolite DDCAR is expected to exceed four weeks.

The Delegate noted that risperidone ARTG entry does not particularly specify its use in the management of negative symptoms of schizophrenia. The Delegate believes that it is not acceptable to simply use risperidone as an active control. The Delegate questioned in the absence of a placebo arm, to exclude the effect of the actives regarding positive symptoms that is how was the contributory effect of either cariprazine or risperidone on the positive symptoms of schizophrenia, to the 'observed mild efficacy' on the negative symptoms delineated? The sponsor has been requested to respond to the above question in the 'Questions for the sponsor' section, located below.

Control of confounding factors allowed for a clearer interpretation of study treatment effects on the negative symptoms of schizophrenia, and explains, in part, why risperidone had a greater overall treatment effect on schizophrenia symptoms than cariprazine in Study RGH-MD-16, albeit the latter study was not powered to show equivalence.

Results in this study were not presented by final dose regimens, so it is uncertain whether there is a dose effect relationship and its relative magnitude. In addition, the target dose of 4.5 mg/day may have been inadequate to fully characterise cariprazine in this subgroup of patients with schizophrenia. It remains unknown whether greater benefit might be obtained from higher cariprazine dosing.

Other efficacy studies

Other efficacy studies included the following:

- Study RGH-MD-03: A double-blind placebo-controlled evaluation of the safety and efficacy of RGH-188 (cariprazine) in the acute exacerbation of schizophrenia (dose finding evaluation).

- Study RGH-MD-11: A Phase III, multicentre, OL, flexible dose study evaluating the long term safety, tolerability, and pharmacokinetics of cariprazine doses of 3 to 9 mg/day, in adult males or females (18 to 60 years) with a primary diagnosis of schizophrenia (Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)).[29]

- Study RGH-MD-17: A Phase IIb, multicentre, open label, flexible dose and outpatient, long term extension study of Study RGH-MD-16 with cariprazine doses of 1.5 to 4.5 mg/day in patients with schizophrenia.

- Study A002-A7: A Phase III, multicentre, randomised, open label, long term flexible dose study of cariprazine with risperidone as active reference, in patients with chronic phase or elderly schizophrenia.

- Study A002-A8: A Phase III, multicentre, unblinded, long-term variable dose study of cariprazine, in patients with schizophrenia receiving multiple drugs.

- Study A002-A11: A Phase II fixed dose clinical pharmacology study of cariprazine in Japanese adult patients with schizophrenia in which, patients were titrated to receive 9 mg/day cariprazine as tablets for 12 weeks as open label treatment.

- Study A002-A3: A Phase II fixed dose, randomised, unblinded study in schizophrenia Japanese adults, in which patients were titrated to receive cariprazine 3 mg/day, cariprazine 6 mg/day or cariprazine 12.5 mg/day, as tablets, for two weeks.

Conclusion

The design of the dose finding/proof of concept 'exploratory' study in acute schizophrenia (Study RGH-MD-03) was similar to that in the pivotal acute studies. However, the study was only conducted in the US and the latter, may affect the external validity of the study results. Also, like the confirmatory studies, there was a high overall dropout rate (46.3%), which although similar across treatments, could affect internal validity. Study results were presented by grouped cariprazine doses as opposed to individual cariprazine doses. That approach did not allow for an accurate assessment of the individual dose effect in the proposed dose range of 1.5 to 9 mg/day. Lack of significance for the post hoc pairwise comparison of cariprazine 6 to 12 mg/day versus. placebo, may in part, have been due to slower dose up titration compared with the confirmatory studies.

The Japanese studies, Study A002-A11 and A002-A3, provided supportive evidence of treatment effect over the cariprazine dose range 1.5 to 9 mg/day. Study A002-A11 provided evidence of maintenance of antipsychotic effect for cariprazine across the dose range of 3 to 9 mg/day in adults with stabilised (non-acute) schizophrenia over 12 weeks. Results by individual dose were not provided. The study population in Study A002-A3 were not as acutely ill as in the pivotal confirmatory studies, and study duration was too short (2 weeks) to provide clinically meaningful dose-effect data for cariprazine. Given the above, the results from both studies are considered only supportive of the results from the pivotal studies.

The long-term, open label, multi-national (United States of America (USA) and non-USA) extension studies, Studies RGH-MD-11 and RGH-MD-17, were similar in design, duration

---

[29] DSM-IV-TR codes are the classification found in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision, a manual published by the American Psychiatric Association that includes almost all currently recognized mental health disorders.

(48 weeks) and efficacy end points. While both studies consistently demonstrated maintenance of antipsychotic effect, for up to 48 weeks, across a broad range of efficacy parameters (including response rates) again, the results were presented by grouped cariprazine doses that is 3 to 9 mg/day and 1.5 to 4.5 mg/day in Studies RGH-MD-11 and RGH-MD-17, respectively. This approach did not allow for an accurate assessment of dose effect. The clinical evaluator requested further information on dose effects in Studies RGH-MD-11 and RGH-MD-17. The sponsor provided further data (not shown in this AusPAR) and the clinical evaluator concluded that sponsor response is acceptable. Across both studies, efficacy of cariprazine was generally maintained on long term treatment across the dose range 1.5 to 9 mg, for all three requested endpoints. The cariprazine 9 mg dose regimen in Study RGH-MD-11 did not provide additional efficacy to the cariprazine 6 mg dose regimen, whereas there appeared to be a dose response trend for all efficacy parameters between the 3 mg and 6 mg doses. There were no clear dose response trends in Study RGH-MD-17. However, the subject numbers were small (particularly for the 1.5 mg dose). Hence, caution is needed with results interpretation.

The long term open label Japanese studies, Studies A002-A7 and A002-A8, were similar in design, duration (48 weeks) and efficacy endpoints. Although both studies consistently demonstrated maintenance of antipsychotic effect, for up to 48 weeks, across a broad range of efficacy parameters (including response rates), the results were presented by grouped cariprazine doses that is 3 to 9 mg/day, and not by individual dose assignment. Given the differences in target populations and cariprazine formulations used, results from both studies are considered supportive of the results of the multi-national long-term extension Studies RGH-MD-11 and RGH-MD-17, and the results from the pivotal maintenance Study RGH-MD-06.

The Delegate comments that the data from the above other efficacy studies can only be rated as supporting data for the proposed indication, given their OL design.

Safety

The safety profile of cariprazine has been reasonably well established in a patient population of more than 3100 patients with schizophrenia and, more than 2000 patients with other indications (bipolar mania, bipolar depression, major depressive disorder). The extent of population exposure to assess clinical safety is generally consistent with the recommendations in the TGA-adopted Guideline for long-term studies.[22]

Across the cariprazine clinical program, the System Organ Class (SOC) with the highest incidence of treatment-emergent adverse events (TEAE) and adverse drug reactions (ADR) were the Nervous System Disorders and the Psychiatric Disorders SOCs.

The adverse events (AE) with the highest incidence were akathisia, insomnia and headache. Dose dependency was observed for extrapyramidal disorder, somnolence, restlessness, constipation, weight increased, elevations in blood creatine phosphokinase and nasopharyngitis. Akathisia was consistently the most common ADR reported following cariprazine dosing, across short and long term clinical studies in schizophrenia and other indications. Akathisia events were usually dose dependent, with peak incidence in the first 3 to 6 weeks of exposure (and decreased thereafter) and were rarely serious or led to study drug discontinuation.

During the cariprazine clinical development program 17 patients died by the data cut-off date. Of these deaths, 11 patients received one or more cariprazine doses: six in the schizophrenia program (three in Japanese studies) and five in other indications. Most cariprazine deaths were due to unrelated completed suicide events, with only one death considered cariprazine related (sudden death, cause unknown).

Serious adverse events (SAE) occurred most commonly in the Psychiatric Disorders and the Nervous System Disorders SOCs (see Table 2, below). Schizophrenia and psychotic

disorder (both indicated schizophrenia relapse) were the most commonly reported SAEs, with highest incidence in the placebo group. All other SAEs were reported in ≤ 1% of patients, including adverse events of special interest (AESI). Overall rates of SAEs were generally balanced between treatment groups, with no clear dose-dependency observed for any SAE up to 6 mg/day.

Table 2: Treatment-emergent adverse drug reactions (occurring in ≥ 1% of the cariprazine 1.5 to 6 mg treatment group) in the pooled schizophrenia studies (Safety population)

System organ class Preferred term	Placebo (N=683) n (%)	Cariprazine 1.5-6.0 mg (N=2048) n (%)
Eye disorders		
Vision blurred	1 (0.1)	22 (1.1)
Gastrointestinal disorders		
Nausea	22 (3.2)	109 (5.3)
Salivary hypersecretion	0 (0.0)	32 (1.6)
Investigations		
Weight increased	9 (1.3)	83 (4.1)
Alanine aminotransferase increased	2 (0.3)	28 (1.4)
Musculoskeletal and connective tissue disorders		
Musculoskeletal stiffness	2 (0.3)	28 (1.4)
Nervous system disorders		
Akathisia	19 (2.8)	288 (14.1)
Extrapyramidal disorder	19 (2.8)	137 (6.7)
Tremor	10 (1.5)	107 (5.2)
Dizziness	10 (1.5)	76 (3.7)
Somnolence	9 (1.3)	58 (2.8)
Psychiatric disorders		
Insomnia	28 (4.1)	177 (8.6)
Restlessness	13 (1.9)	97 (4.7)
Anxiety	8 (1.2)	59 (2.9)

Akathisia was consistently the most common AE that led to study drug discontinuation (other than symptom relapse in schizophrenia, bipolar mania or bipolar depression), across the clinical program. Overall rates of AEs that led to study drug discontinuation were low and comparable between cariprazine, aripiprazole and risperidone treatments. There appeared to be a small dose dependent trend for akathisia for the cariprazine 1.5 mg to 6 mg/day group compared to placebo treatment. The clinical evaluator requested that the sponsor provide further information on the serious adverse events that led to study drug discontinuation in the clinical schizophrenia program for the cariprazine 9 mg/day dose. The sponsor provided the requested data [inclusion is beyond the scope of this AusPAR] and the clinical evaluator concluded that the sponsor's response is acceptable.

There were no deaths or serious events associated with metabolic changes (hyperglycaemia, hypertriglyceridaemia or diabetes mellitus) following cariprazine administration. There appeared to be no dose-dependent or time-dependent effects of cariprazine on lipid parameters. In contrast, there appeared to be a time-dependent effect on fasting glucose, with higher incidence of AEs of increased glucose levels and diabetes mellitus reported.

Changes in bodyweight and body mass index (BMI) were observed with cariprazine treatment across most studies in the cariprazine clinical program (schizophrenia and other indications). There appeared to be both dose-dependent and time-dependent effects of cariprazine on weight indices. The frequency of reported weight related events, and study discontinuations, appeared to be relatively low compared to the frequency of

potentially clinically significant weight gain across studies and treatment groups. This suggests weight changes were generally manageable.

Elevated transaminases were consistently reported, across indications following cariprazine treatment, in general dose-dependent and time-dependent trends (particularly for alanine aminotransferase), both in short term and long term studies. Cariprazine treatment was not generally associated with clinically significant bilirubin elevations, and only a few isolated cases of hyperbilirubinaemia were reported. There was no evidence of drug-induced serious liver injury during the cariprazine clinical program, and no Hy's law cases.

There were no deaths, SAEs or AEs that led to study drug discontinuation in association with elevated prolactin levels. In fact, hyperprolactinaemia was not reported across the clinical cariprazine program. No safety issue was identified with cariprazine treatment for thyroid function. There was a dose effect trend for absolute neutrophil count decreased (absolute neutrophil count < 1.0×10^9/L) that is neutropenia. However, no AE, severe or serious, led to study drug discontinuation or was associated with fever, sore throat or infection. No case of hyponatraemia was accompanied by AE reports of lethargy or seizures. Cariprazine had little effect on renal parameters and did not appear to be nephrotoxic. There were no deaths, SAEs or AEs that led to study drug discontinuation associated with renal function. One case of rhabdomyolysis was associated with renal failure.

Blood pressure and pulse rate changes were reported in both directions across the schizophrenia clinical program, and were similar to those for aripiprazole and risperidone. This contrasted with dose related, albeit relatively small, increases in systolic blood pressure and diastolic blood pressure observed with cariprazine doses > 6 mg/day. Most potentially clinically significant shifts from normotension/pre-hypertension were upwards to Stage I hypertension. There was a dose dependent trend for incidence of increased blood pressure and a corresponding dose dependent trend for hypertension. Incidence of orthostatic hypotension was generally similar between treatments. Mean body temperature generally remained unchanged over the course of the studies.

There was no evidence that cariprazine exposure resulted in QTcF;[30] prolongation over the proposed dose range for cariprazine (and up to 18 mg/day in the dedicated QT study). Dose effect was observed for bradycardia and sinus tachycardia, for the cariprazine 1.5 to 6 mg/day group compared to placebo treatment. There were no AEs of torsade de pointes, ventricular fibrillation or ventricular tachycardia reported across the clinical program.

Cariprazine exposure was associated with dose dependent increases in creatine phosphokinase levels. Treatment emergent creatine phosphokinase levels were rarely accompanied by myoglobinuria and were not generally associated with altered renal function or renal failure. Few patients had concurrent myalgia, muscle pain, muscle weakness or muscle related AEs. There were four cases of rhabdomyolysis in the schizophrenia program.

Low incidence of cariprazine related hypersensitivity, immune related, tardive dyskinesia and neuroleptic malignant syndrome events were reported across the cariprazine clinical program. There were no reported cases of serotonin syndrome, serious skin reactions and no suggestion of withdrawal or rebound effects from cariprazine therapy.

---

[30] The **QT interval** is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.
The corrected QT interval (QTc) estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias. The **QTcF** is the QT interval corrected for heart rate according to Fridericia's formula.

Most seizures or convulsions across the cariprazine clinical program occurred after exposure of high dose cariprazine (9 mg/day). The results were inconclusive in respect of temporal associations between cariprazine exposure and onset of seizure or convulsion.

Six deaths occurred due to completed suicide, all unrelated to cariprazine exposure. Incidence of suicidality related treatment emergent adverse events, or suicidal ideation and behaviour based on Columbia-Suicide Severity Rating Scale (C-SSRS) scores, was low in cariprazine treated patients, with no clear dose or time effect trends observed across the clinical schizophrenia program.

In general, there were no clinically meaningful differences in cariprazine related AEs based on sex, race group or age category (< 55 years; ≥ 55 years). Caution should be exercised in patients aged 65 years and older, due to few study participants in this age group, as well as the potentially higher risk associated with dementia and other comorbid conditions and concomitant medications in older aged patients. In addition, the Delegate commented that the safety in patients with severe hepatic or renal impairment, and in pregnant or breastfeeding females, has not been established. Hence, cariprazine should be avoided in these groups of patients.

Post hoc analysis demonstrated no clear association between cariprazine treated patients with weight loss and AEs suggestive of adrenal hypofunction. The latter was flagged in nonclinical studies as a possible consequence of drug-induced phospholipidosis. Potentially clinically significant weight loss observed with placebo and other comparators is supportive of the sponsor's conclusion of lack of association between cariprazine exposure and drug induced adrenal hypofunction.

Due to the nonclinical finding of ocular side effects extensive ocular monitoring was applied in the long-term studies. Ophthalmologic testing in the cariprazine clinical development program revealed no evidence for retinal toxicity or lenticular changes of clinical significance. There were no ocular SAEs reported in the cariprazine clinical development program, no patient required ocular surgery and few patients discontinued treatment because of ocular AEs. The Class III positive lenticular shifts observed lacked the bilaterality and regional consistency that are the signature of drug induced changes.

In general, the safety profile for cariprazine in adults with schizophrenia is generally consistent with those of the other marketed atypical antipsychotics, approved for use in the treatment of schizophrenia in adults, such as risperidone. No new safety signal was identified. Cariprazine was generally well tolerated in patients with schizophrenia, at doses up to 1.5 mg to 6 mg/day. Cariprazine doses higher than 6 mg/day generally had poorer tolerability and higher incidence of akathisia, EPS, blood pressure elevation, elevation of aminotransferases and significant weight gain.

Clinical evaluator's recommendation

The benefit-risk balance of cariprazine, given the proposed usage is favourable.

Approval of cariprazine hydrochloride (Reagila) is recommended for the treatment of schizophrenia in adult patients by clinical evaluator.

Risk management plan

Seqirus (Australia) Pty Ltd is the agent and distributor of Reagila. Gedeon Richter Australia is the Sponsor. Seqirus (Australia) Pty Ltd submitted, on behalf of the Sponsor, has submitted the EU-risk management plan (RMP) version 1.7 (23 July 2019; data lock point (DLP) 11 July 2019) and Australian specific annex (ASA) version 1.0 (4 October 2019) in support of this application. In response to TGA questions, the sponsor Seqirus has submitted ASA version 1.1 (dated 22 June 2020). The EU-RMP 1.7 (23 July 2019; DLP

11 July 2019) was not updated. The sponsor provided ASA version 2.0 (dated 26 August 2020).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 3.[31]

Table 3: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Extrapyramidal symptoms including tardive dyskinesia	ü	–	ü	–
	Weight gain	ü	–	ü	–
Important potential risks	Neuroleptic Malignant Syndrome	ü	–	ü	–
	Ocular changes (lenticular changes and cataracts)	ü*†	–	ü	–
	Suicidal ideation and behaviour	ü	–	ü	–
	Interaction with CYP43A4 inhibitors and inducers	ü	ü‡	ü	–
	Developmental and reproductive toxicity	ü	–	ü	–
Missing information	Use in patient >65	ü*	–	ü	–

*Specific adverse reaction follow-up questionnaire

---

[31] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

†Half-yearly trend analysis

‡Clinical studies - EU only

The proposed summary of safety concerns is considered acceptable from an RMP perspective.

The sponsor has proposed routine pharmacovigilance activities for all safety concerns including follow up questionnaires and half yearly trend analysis for ocular changes (lenticular changes and cataracts) and a follow-up questionnaire for use in patients > 65 years. The sponsor has not proposed any additional pharmacovigilance activities in Australia. This is acceptable.

The sponsor has proposed routine risk minimisation activities for all safety concerns. The sponsor has not proposed any additional risk minimisation activities. This is acceptable.

Wording for conditions of registration

The suggested wording is:

The cariprazine hydrochloride EU-Risk Management Plan (RMP) (version 1.7, dated 23 July2019, data lock point 11 July 2019), with Australian Specific Annex (version 2.0, dated 26 August 2020), included with submission PM-2019-04790-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

The following wording is recommended for the periodic safety update report (PSUR) requirement:

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

As Reagila is a new chemical entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

Reagila (cariprazine hydrochloride) is to be included in the Black Triangle Scheme. The PI and consumer medicines information for Reagila must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

Risk-benefit analysis

Delegate's considerations

The submission is an application to register a new chemical entity, cariprazine hydrochloride (Reagila). Cariprazine is an orally active atypical antipsychotic, acting as a potent dopamine D_3/D_2 receptor partial agonist with preferential binding to D_3 receptors and a partial agonist at serotonin $5HT_{1A}$ receptor sites. The sponsor stated that '*cariprazine is the first and only atypical antipsychotic that demonstrates a balanced dual engagement of D_3 and D_2 receptor systems, which may confer additional benefits such as*

enhanced cognition, and may be the underlying mechanism for improvement in negative symptoms in schizophrenia'.

The sponsor submitted three pivotal short term (6 weeks duration) studies (Studies RGH-MD-04, RGH-MD -16 and RGH-MD-05) on acute exacerbation of schizophrenia; one pivotal study (RGH-MD-06) on maintenance of effect and relapse prevention of schizophrenia and one pivotal study (RGH-188-005) on predominant negative symptoms (PNS) of schizophrenia. All studies, except Study RGH-188-005, were DB and placebo controlled. In addition, Studies RGH-MD-04, RGH-MD-16 and RGH-188-005 had aripiprazole, risperidone and risperidone respectfully as active arms.

Acute exacerbation of schizophrenia

Analysis of the primary efficacy outcome that is change from Baseline (CFB) in PANSS total score at Week 6, either via last observation carried forward (LOCF) or mixed-effect model repeated measure (MMRM), for each dose/day range of cariprazine (1.5 mg, 3 mg, 4.5 mg, 6 mg and 9 mg) tested over placebo was significant, in the short term studies. However, the calculated least square mean difference (LSMD) from placebo in each case was only modest, ranging from -5.4 to -10.5 (see Table 4).

Table 4: Studies RGH-MD-04, RGH-MD-05 and RGH-MD-16 Change from Baseline in Positive and Negative Syndrome Scale total score at Week 6 (primary efficacy outcome)

Study	Baseline	LOCF				MMRM			
Treatment group	Mean ± SD	Change LS mean	LSMD	(95% CI)	P-value	Change LS mean	LSMD	(95% CI)	P-value
RGH-MD-04									
Placebo	96.5 ± 9.1	-11		n/a		-14.3		n/a	
Cariprazine 3 mg/day	96.1 ± 8.7	-16.4	-5.4	(-9.3, -1.4)	0.0078	-20.2	-6	(-10.1, -1.9)	0.0044
Cariprazine 6 mg/day	95.7 ± 9.4	-18.9	-7.9	(-11.8, -4.0)	< 0.0001	-23	-8.8	(-12.9, -4.7)	<0.0001
Aripiprazole 10 mg/day	95.6 ± 9.0	-18.8	-7.7	(-11.7, -3.8)	0.0001	-21.2	-7	(-11.0, -2.9)	0.0008
RGH-MD-16									
Placebo	97.3 ± 9.2	-9.5		n/a		-13.3		n/a	
Cariprazine 1.5 mg/day	97.1 ± 9.1	-17.3	-7.5	(-11.8, -3.3)	0.0005	-21.3	-8	(-12.9, -3.0)	0.0017
Cariprazine 3 mg/day	97.2 ± 8.7	-18.7	-8.8	(-13.1, -4.6)	< 0.0001	-21.5	-8.2	(-13.1, -3.2)	0.0013
Cariprazine 4.5 mg/day	96.7 ± 9.0	-20.2	-10.4	(-14.6, -6.2)	< 0.0001	-23.8	-10.5	(-15.4, -5.6)	< 0.0001
Risperidone 4 mg/day	98.1 ± 9.5	-25.3	-15	(-19.4, -10.8)	< 0.0001	-29.3	-16	(-20.9, -11.0)	< 0.0001
RGH-MD-05									
Placebo	96.6 ± 9.3	-12.3		n/a		-16		n/a	
Cariprazine 3 to 6 mg/day	96.3 ± 9.3	-18.6	-6.3	(-10.2, -2.4)	0.0016	-22.8	-6.8	(-11.3, -2.4)	0.0029
Cariprazine 6 to 9 mg/day	96.3 ± 9.0	-20.2	-8	(-11.9, -4.0)	< 0.0001	-25.9	-9.9	(-14.5, -5.3)	< 0.0001

CI = confidence interval; LOCF = last observation carried forward; LS = least square; LSMD = least square mean difference; MMRM = mixed-effect model repeated measure; n/a = not applicable; SD = standard deviation.

Moreover, it is worth noting that there was no particular dose proportionality pattern to the efficacy outcome, as evidenced by the recorded LSMDs for the cariprazine dose ranges

Furthermore, no cariprazine dose demonstrated better efficacy than either aripiprazole or risperidone, with regard to the primary outcome[32].

The Delegate was of the opinion that the 'gold standard' in defining response to treatment in acute exacerbation of schizophrenia is ideally to use at least 50% reduction from

---

[32]. Sponsor clarification: The acute trials were designed to show superiority to placebo (as per EMA Guidance EMA/CHMP/40072/2010 Rev. 11) and the active controls were included for assay sensitivity.

Baseline;[33] rather than use the lower thresholds in PANSS total score.[34] The derived percentage reductions from Baseline in PANSS for the tested cariprazine doses range from 5.6% to 10.75%. It is also noted, that the baseline PANSS for the patients included in the cariprazine trials ranged from 95.7 to 97.2. The latter will indicate that the baseline population depicted only marked but not severe schizophrenia.

All added together, it will be justifiable to state that cariprazine has only shown modest efficacy in the management of marked but not severe schizophrenia.

Sensitivity and subgroup analyses of the primary efficacy outcome between cariprazine and placebo mostly concur with the primary analysis findings above. The previously mentioned inconsistency in the cariprazine dose- effect was also manifested.

As for the primary efficacy PANSS endpoint, analysis of the key secondary efficacy CGI-S endpoint that is CFB to Week 6 , either via LOCF or MMRM, for each dose/day range of cariprazine (1.5 mg, 3 mg, 4.5 mg, 6 mg and 9 mg) studied over placebo was significant, in the short term studies. Again, the calculated LSMD from placebo in each case was only modest, ranging from -0.3 to -0.6, as per the table below:

Table 5: Studies RGH-MD-04, RGH-MD-05 and RGH-MD-16 Change from Baseline in Clinical Global Impression – severity scores at Week 6 (Key secondary efficacy outcome)

Study	Baseline	LOCF				MMRM			
Treatment group	Mean ± SD	Change LS mean	LSMD	(95% CI)	P-value	Change LS mean	LSMD	(95% CI)	P-value
RGH-MD-04									
Placebo	4.8 ± 0.6	-0.7		n/a		-1		n/a	
Cariprazine 3 mg/day	4.9 ± 0.6	-1.1	-0.4	(-0.6, -0.2)	0.0005	-1.4	-0.4	(-0.6, -0.2)	0.0004
Cariprazine 6 mg/day	4.8 ± 0.6	-1.2	-0.5	(-0.7, -0.2)	< 0.0001	-1.5	-0.5	(-0.7, -0.3)	< 0.0001
Aripiprazole 10 mg/day	4.8 ± 0.6	-1.2	-0.5	(-0.7, -0.3)	< 0.0001	-1.4	-0.4	(-0.6, -0.2)	0.0001
RGH-MD-16									
Placebo	4.9 ± 0.1	-0.6		n/a		-0.9		n/a	
Cariprazine 1.5 mg/day	4.7 ± 0.1	-0.9	-0.4	(-0.6, -0.1)	0.004	-1.2	-0.3	(-0.6, -0.0)	0.0253
Cariprazine 3 mg/day	4.9 ± 0.1	-1.1	-0.5	(-0.7, -0.2)	0.0003	-1.2	-0.3	(-0.6, -0.0)	0.0243
Cariprazine 4.5 mg/day	4.8 ± 0.1	-1.2	-0.6	(-0.9, -0.4)	< 0.0001	-1.5	-0.6	(-0.8, -0.3)	< 0.0001
Risperidone 4 mg/day	4.8 ± 0.1	-1.4	-0.8	(-1.1, -0.6)	< 0.0001	-1.6	-0.7	(-1.0, -0.4)	< 0.0001
RGH-MD-05									
Placebo	4.9 ± 0.7	-0.7		n/a		-1		n/a	
Cariprazine 3 to 6 mg/day	4.8 ± 0.7	-1	-0.3	(-0.5, -0.0)	0.0199	-1.4	-0.3	(-0.6, -0.1)	0.0115
Cariprazine 6 to 9 mg/day	4.9 ± 0.7	-1.2	-0.4	(-0.7, -0.2)	0.0003	-1.6	-0.5	(-0.8, -0.3)	0.0002

CI = confidence interval; LOCF = last observation carried forward; LS = least square; LSMD = least square mean difference; MMRM = mixed-effect model repeated measure; n/a = not applicable; SD = standard deviation.

Again, no clear dose proportionality pattern to the efficacy outcome was demonstrated as per the tabled LSMDs for the cariprazine dose ranges.

Furthermore, no cariprazine dose demonstrated better efficacy than either aripiprazole or risperidone, with regard to the CGI-S outcome.

---

[33] Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel RR. What does the PANSS mean? Schizophr Res. 2005 Nov 15;79(2-3):231-8.

[34] Per the TGA-accepted guideline: In short term trials in patients with acute/exacerbated symptoms at least a 30% reduction on the total PANSS score compared to Baseline is generally considered to be clinically relevant and can be accepted as a definition of responder. This figure may need adjustment in case of inclusion of more chronically ill patients, therefore a flexible approach can be taken.'
EMA/CHMP/40072/2010 Rev. 1: Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia.

It is also noted, that the baseline CGI-S for the patients included in the cariprazine trials ranged from 4.8 to4.9. The latter will indicate that the baseline population depicted only moderate to markedly ill, excluding severely ill schizophrenia.

In summary, it will be justifiable to state that cariprazine has only shown modest efficacy against placebo, in the management of rather marked but not severe schizophrenia.

Maintenance of effect and relapse prevention of schizophrenia

From the analysis of the primary efficacy endpoint, that is the time to first relapse during the DBP (defined as the number of days from the randomisation date to the relapse date), patients who received cariprazine 3 to 9 mg/day had a lower rate of schizophrenia relapse (24.8%) compared to placebo treatment (47.5%). Time to relapse was statistically significantly longer in the cariprazine group compared with the placebo group (p = 0.0010), with the 25th percentile for time to relapse of 224 days in the cariprazine group compared with 92 days in the placebo group. The hazard of relapse for cariprazine treated patients was estimated as a 55% reduction compared to placebo treated patients (hazard ratio (HR) (95% confidence interval (CI)); 0.45 (0.28, 0.73)).

Subgroup *post hoc* analysis as requested by the EMA, showed similar outcome for patients who received cariprazine, in a dose range of 3 to 6 mg/day over placebo.

The HR of 0.45 is interpreted as meaning that approximately half as many patients in the cariprazine group compared to the placebo group, did not experience relapse. The latter is a reflection of the modest efficacy of cariprazine in the maintenance/relapse trial given that, the enrolled baseline population in the DBP of the trial only had '*borderline to mild illness*' (CGI-S score = 2.8 cariprazine - 2.6 placebo; PANSS = 51.3 cariprazine - 50.5 placebo).[35]

It is worthwhile mentioning that the proposed indication is neither worded implicitly nor explicitly toward the use of cariprazine in either the maintenance or relapse prevention of schizophrenia.

Predominant negative symptoms of schizophrenia.

The main analyses of the primary efficacy variable, that is the CFB to endpoint (Week 26 or early termination (ET)) in the PANSS factor score for negative symptoms, revealed that there was a statistically significant difference (p = 0.002), which favoured cariprazine (3 to 6 mg/day; target dose 4.5 mg/day) over risperidone (2 to 6 mg/day; target dose 4 mg/day) in the CFB to Week 26 in the PANSS factor score for negative symptoms (MMRM).

The LS mean CFB values at Week 26 were -8.9 and -7.4 for cariprazine and risperidone, respectively. The pairwise difference was -1.5 (95% CI: -2.4, -0.5). The CFB always favoured cariprazine at each study visit, with statistically significant differences from Week 14 (p = 0.008) until Week 26.

The recorded LS mean CFB values were only modest for both cariprazine and risperidone in a population with what appears to be baseline middle of the range or mild to moderate negative symptoms via:

---

35 Sponsor clarification: Study RGH-MD-06 was designed to first stabilise patients, reduce their symptoms and increase their functioning to a level where in real clinical practice, patients could start considering treatment discontinuation, and to then examine what happens if they do. The baseline disease status of patients at the start of the DBP thus represents a patient population that has already been stabilised with 20 weeks of cariprazine treatment, rather than the more markedly ill original patient population in the open label phase (OLP), who had PANSS total score of 91.3 ± 10.1 It was a condition of entry into the DBP that patients had met the criteria of a PANSS total score ≤ 60 and a CGI-S score ≤ 4.'

- mean (± standard deviation (SD) PANSS factor score for negative symptoms were cariprazine 26.7 ± 2.8 and risperidone 26.5 ± 2.8;

- mean (± SD) CGI-S score were cariprazine 4.1 ± 0.8 and risperidone 4.2 ± 0.7.

The PNS study is considered as somewhat incomplete in the absence of a placebo arm. The rationale being that as the risperidone ARTG entry does not particularly specify its use in the management of negative symptoms of schizophrenia, it becomes unclear as to how the contributory effect of either cariprazine or risperidone, on the positive symptoms of schizophrenia to the observed post treatment PANSS score was controlled for. Simply including patients with minimal positive symptoms does not justify the placebo arm exclusion in the trial.

It is worthwhile mentioning here as well, that the proposed indication is neither worded implicitly nor explicitly toward the use of cariprazine for the negative symptoms of schizophrenia.

As earlier mooted, there is no substantive data evidence for a direct dose proportionality regarding the rather modest efficacy of cariprazine in acute exacerbation of schizophrenia. Cariprazine dose ranges of 1.5 mg, 3 mg, 4.5 mg, 6 mg and 9 mg did yield similar efficacy outcomes which are statistically significant over placebo, albeit modest in clinical terms.

For the maintenance/relapse study, the Delegate agrees with the clinical evaluator that the modest efficacy outcome recorded for the cariprazine tested doses of 3 mg,6 mg and 9 mg was '*bulk-delivered or pooled*' rather than analytically separated into the specific individual doses, making it impossible to ascertain the lowest effective dose for relapse prevention. In that regard, the *post hoc* analysis ordered by the EMA revealed similar modest efficacy outcome for the 3 to 6 mg range as for the 3 to 9 mg range. The Delegate agrees with the clinical evaluator that according to the sponsor's response, cariprazine 3 mg dose provided greater efficacy than the cariprazine 6 mg dose.

In sponsor's response to clinical evaluator questions, the clinical evaluator noted that most cariprazine-related SAEs in relation to the Psychiatric Disorders SOC were associated with the 9 mg dose (8.9%) compared to placebo (5.9%).The disorders were to do with relapse events, possibly reflecting the relative lack of efficacy of the cariprazine 9 mg dose.

The Delegate agrees with the clinical evaluator for the recommended maximum daily dose to be 6 mg that is 6 mg/day, titrated from 1.5 mg/day to the patient's tolerability .The latter is in line with evidence from the submitted data and provides, a much more favourable benefit-risk balance for cariprazine in the proposed indication.

Regarding safety, cariprazine is not an exemption to the many side effects associated with all the other anti-psychotic medications on the ARTG. These include akathisia, extra-pyramidal symptoms, weight gain and elevated blood pressure. Incidentally, some of those side effects (akathisia, EPS, elevated systolic blood pressure, weight gain, elevated transaminases ,decreased neutrophil count) manifest more prominently at the higher dose of cariprazine 9 mg/day than others, that could be time dependent (elevated glucose levels) regardless of dose or both (akathisia, EPS).

Proposed indication

> *Cariprazine is indicated for the treatment of schizophrenia in adult patients.*

Proposed action

Although cariprazine has only demonstrated modest efficacy, there is sufficient level of efficacy and safety data to consider its approvability for the proposed indication, as stated above. There is no strong evidence to either support cariprazine marketing as maintenance/relapse prevention of schizophrenia or for the treatment of predominant negative symptoms of schizophrenia.

Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

1. *Given that about 70% of cariprazine and its metabolites are accounted for in the urine and faeces, can the tissue distribution and protein binding of the latter account for the remaining 30%?*

The less-than-complete recovery of cariprazine and its metabolites from urine and faeces (Study RGH-MD-01), is likely to be due to the fact that DDCAR as well as other metabolites were not at steady state at the time of evaluation. Based upon the assumed half life of the metabolites, it is estimated that excreta from the human metabolism study were collected at 73.5 to 79% of steady state for the major plasma metabolites of cariprazine (DDCAR, hydroxy cariprazine glucuronide, and hydroxy DDCAR glucuronide). As the total excretion was predominantly contributed by these metabolites, the expected theoretical total excretion at the time of sample collection would be approximately 76% of the daily dose ((73.5 + 79)/2). Comparing this value to the actual total excretion (70.4% or 60.9% of the daily dose for two patients or including data of all three patients, respectively) would result in recoveries of 92% (70.4 x 100/76) or 80% (60.9 x 100/76), respectively. This suggests that all major cariprazine metabolites have been captured in the human metabolism study.

2. *In the absence of a placebo arm, to exclude the effect of the actives regarding positive symptoms that is how was the contributory effect of either cariprazine or risperidone on the positive symptoms of schizophrenia, to the 'observed mild efficacy' on the negative symptoms delineated?*

The Delegate suggests that the evidence to support cariprazine in the treatment of predominant negative symptoms is not strong due to its design and what the Delegate perceives as modest results. The sponsor believes that Study RGH-188-005 is both well designed and uniquely demonstrates statistically significant and clinically meaningful efficacy in the treatment of predominant negative symptoms.

The RGH-188-005 trial was designed as a superiority study against risperidone, in a patient population with moderately severe, persistent, PNS. This study was rigorously designed in accordance with the EMA guidelines,[36] which are closely linked to recommendations put forward by Marder et al (2013)[37] and Nemeth et al (2017).[38]

Adult patients with stable schizophrenia and PNS were enrolled in the trial. Patients with co-morbidities (such as depression and EPS) and high levels of positive symptoms, were excluded to ensure any observed treatment effects could be attributed to predominant negative symptoms improvement and not to pseudospecific effects (that is improvements that were secondary to improvement in other factors).

The Delegate suggests that the study is somewhat incomplete as there was no placebo arm and also questioned the rationale of using risperidone as the comparator, given risperidone is not specifically used in the management of negative symptoms.

No placebo arm was included in this trial for two important reasons:

---

[36] EMA Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia, EMA/CHMP/40072/2010 Rev. 1, section 4.5.1

[37] Marder SR et al. Issues and perspectives in designing clinical trials for negative symptoms in schizophrenia. Schizophr Res 2013 Nov;150(2-3):328-33.

[38] Nemeth G et al. Cariprazine as monotherapy for the treatment of predominant negative symptoms in patients with schizophrenia: A randomized, double-blind, active-comparator controlled trial. Lancet 2017; 389: 1103-1113.

- randomisation of patients with schizophrenia to placebo for a long-term (26-week) study could result in an increased risk of relapse, raising a question of ethics and

- positive symptom exacerbation expected in the absence of active treatment,[39] would potentially confound study conduct and interpretation.

Risperidone was included as the active comparator in Study RGH-188-005 because out of only four second generation antipsychotic;[40] more effective than first generation antipsychotics in treating negative symptoms in a meta-analysis;[38,41] the other three products were not suitable. Clozapine is not used as a first line medication, but mainly for treatment of resistant patients. Olanzapine's metabolic profile is very different from that of cariprazine, which could unblind the study. Amisulpride would have confounded the study design due to two different dose ranges for acute schizophrenia and negative symptoms, and there would be the potential for unblinding due to different side effects profile (sedation).[39]

This study was designed to reduce the potential for confounding and misinterpretation of results. Furthermore, statistically significant effect sizes for cariprazine compared with an active control with proven antipsychotic efficacy not only confirm the efficacy of cariprazine but could even be expected to be greater if it were to be compared with a placebo.

The Delegate suggests that the studied population appears to be patients who at Baseline had mild to moderate negative symptoms. The negative symptoms at Baseline were, in fact, moderate, not mild. The highest possible score for PANSS Factor Score Negative Symptoms (FSNS) is 49 and the actual disease severity was 27.5 to 27.7 (so 28 for 7 items). This means that if a patient had scored on each negative symptom item, which is clinically not necessarily the case in negative symptom patients, the patient would have scored 4 for each of the 7 items. A score of 4 is considered moderate not mild. This is in line with the clinical judgement of the severity of negative symptoms as represented by the CGI-S of 4.1 to 4.2, which is moderately ill.

The Delegate suggests that the LS mean change from Baseline (CFB) values were only modest for both cariprazine and risperidone. However, Seqirus believes that the data in this study is convincing. The RGH-188-005 trial is the first large-scale study done in patients with schizophrenia and with PNS that has provided evidence of clinically significant improvement in predominant negative symptoms for an antipsychotic drug used as monotherapy. Cariprazine was statistically significantly better than risperidone in both the primary efficacy endpoint improving negative symptoms (CFB to Week 26 PANSS-FSNS p = 0.004) and the secondary endpoint improving patient functioning (CFB to Week 26 Personal and Social Performance scale (PSP) p < 0.001).

The LS mean CFB in the PANSS factor score for negative symptoms at Week 26 were -8.1 and -6.8 for cariprazine and risperidone (P = 0.002) in favour of cariprazine. The LS mean CFB in the PSP scores at Week 26 were 14.3 and 9.7 for cariprazine and risperidone, respectively. A PSP improvement of more than 10 points shifts the patient to a less severe PSP category, meaning the improvement is not only statistically significant but also clinically relevant for the patients on cariprazine.

Statistically significant differences in favour of cariprazine were seen in the number of patients who were PANSS responders (≥ 20% and ≥ 30% improvement) and who

---

[39] Marder SR et al. Methodological issues in negative symptom trials. Schizophr Bull 2011; 37(2): 250-4.
[40] Edgar CJ et al. Reliability, validity and ability to detect change of the PANSS negative symptom factor score in outpatients with schizophrenia on select antipsychotics and with prominent negative or disorganized thought symptoms. Psychiatry Res 2014; 218(1-2):210-24.
[41] Leucht S et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a metaanalysis. Lancet 2009; 373: 31–41.

additionally improved 'much' or 'very much' in their Clinical Global Impression-Investigators scale (CGI-I).

In the additional analyses, statistically significant differences in favour of cariprazine over risperidone were seen for CFB in mean CGI-S score, CGI-I, mean PANSS negative subscale score at Week 26 and in the number of patients who improved at least one category in the CGI-S and also who improved 'much' or 'very much' in the CGI-I.

Consequently, treatment with cariprazine demonstrated statistically significant improvement in predominant negative symptoms and that improvement was clinically meaningful, as shown by improvement in patient functioning. Given the considerable unmet medical need in this therapeutic area, it is important to bear in mind that any amount of change may be clinically relevant to patients without other treatment options.

3. *Does the double blind treatment for all active patients cease when the last randomised patient reached 26 weeks in the DB phase, if so was the cariprazine treatment no longer blinded after the last randomised patient reached 26 weeks in the DB phase?*

The Delegate has also asked us to address the duration of the double blind phase of the study. The sponsor can confirm that the double blind phase of the study had a variable duration of between 26 weeks (minimum) and 72 weeks (maximum). The last patient to enter DBP received 26 weeks of DB treatment (overall 46 weeks), in which time the first patient to enter DB reached 72 weeks of DB treatment (overall 96 weeks). After the last patient reached week 26 of DB treatment, all patients were discontinued and the study was terminated. In the DB phase the blinding was maintained until data base lock.

Advisory Committee considerations[42]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. *Modest demonstration of efficacy for the proposed indication*

The ACM was of the view that cariprazine efficacy data suggest modest improvement in addressing symptoms of schizophrenia, based on the observed changes in the Positive and Negative Syndrome Scale (PANSS) scores, it is not better than the existing antipsychotics currently registered for use in treatment of schizophrenia in adult patients in Australia.

2. *No strong evidence to either support cariprazine marketing as maintenance/relapse prevention of schizophrenia or for the treatment of predominant negative symptoms of schizophrenia.*

The ACM concurred with the Delegate that there is no strong evidence supporting the particular use of cariprazine for relapse prevention, maintenance or treatment of negative symptoms of schizophrenia.

---

[42] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

*3. **The recommended maximum daily dose is 6 mg that is. 6 mg/day, titrated from 1.5 mg/day to the patient's tolerability. The latter is in line with evidence from the submitted data and provides, a much more favourable benefit-risk balance for cariprazine in the proposed indication. The recommendation will also be in line with that of both the US and the EU regulatory authorities.***

Based on the available efficacy and safety data, the ACM concluded that the appropriate dose range for cariprazine is 1.5 to 6 mg once daily. Any perceived extra benefit at the higher dose of 9 mg daily, is accompanied by significant side effects profile of cariprazine.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Reagila is indicated for the treatment of schizophrenia in adult patients.*

All issues relating to the draft Product Information must be resolved to the satisfaction of the TGA.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Reagila (cariprazine hydrochloride) 1.5 mg, 3 mg, 4.5 mg and 6 mg, hard capsule, blister pack, indicated for:

> *Reagila is indicated for the treatment of schizophrenia in adult patients.*

Specific conditions of registration applying to these goods

- Reagila (cariprazine hydrochloride) is to be included in the Black Triangle Scheme. The PI and consumer medicines information for Reagila must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

- The cariprazine hydrochloride EU-RMP (version 1.7, dated 23 July2019, DLP 11 July 2019), with ASA (version 2.0, dated 26 August 2020), included with submission PM-2019-04790-1-1, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

Attachment 1. Product Information

The PI for Reagila approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration