

**5.02 CARIPRAZINE,  
Capsule 1.5 mg,  
Capsule 3 mg,  
Capsule 4.5 mg,  
Capsule 6 mg,  
Reagila<sup>®</sup>,  
Seqirus (Australia) Pty Ltd**

**1 Purpose of submission**

- 1.1 The submission requested the listing of cariprazine as an Authority Required (Streamlined) item on the Pharmaceutical Benefits Scheme (PBS) for the treatment of schizophrenia.
- 1.2 Listing was requested on the basis of a cost-minimisation analysis (CMA) versus aripiprazole and brexpiprazole. The components of the overall clinical claim addressed by the submission are presented in Table 1. Cariprazine has not previously been considered by the PBAC for the treatment of schizophrenia.

**Table 1: Key components of the clinical issue addressed by the submission**

Component	Description
Population	Adult patients with schizophrenia
Intervention	Cariprazine 1.5, 3, 4.5 or 6 mg per day
Comparator	Aripiprazole 10, 15, 20 or 30 mg per day / Brexpiprazole 1, 2, 3 or 4 mg per day
Outcomes	PANSS total score; time to relapse/imminent relapse; Adverse events (AEs); Discontinuations due to AEs; Serious AEs; Deaths <sup>1</sup>
Clinical claim	In patients with schizophrenia: <ul style="list-style-type: none"> <li>• Cariprazine is non-inferior in terms of effectiveness compared with aripiprazole</li> <li>• Cariprazine is non-inferior in terms of effectiveness compared with brexpiprazole</li> <li>• Cariprazine is non-inferior in terms of safety compared with aripiprazole</li> <li>• Cariprazine is non-inferior in terms of safety compared with brexpiprazole.</li> </ul>

Abbreviations: AE=adverse events; mg=milligram; PANSS= Positive and Negative Syndrome Scale (for schizophrenia);

Notes: These outcomes are reported for all included trials. Additional secondary efficacy and safety outcomes are reported for the direct comparison between cariprazine and aripiprazole (trial RGH-MD-04).

Source: Table 1.1.1 p29 of the submission

**2 Background**

**Registration status**

- 2.1 The submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration, the Clinical Evaluation Report, TGA Delegate’s Overview and the Advisory Committee on Medicines (ACM) minutes were available.
- 2.2 At the time of PBAC consideration the ACM had recommended the indication of: REAGILA<sup>®</sup> is indicated for the treatment of schizophrenia in adult patients.

2.3 The approved indication in the USA and EU, and a number of other individual countries, was consistent with the proposed TGA indication.

For more detail on PBAC's view, see section 7 PBAC outcome.

### 3 Requested listing

3.1 The proposed listing is outlined below.

Name, restriction, manner of administration, form	PBS item code	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
Cariprazine 1.5 mg capsule	NEW	1	30	5	\$ [REDACTED]	Reagila® Gedeon Richter Australia Pty Ltd
Cariprazine 3 mg capsule	NEW	1	30	5	\$ [REDACTED]	Reagila® Gedeon Richter Australia Pty Ltd
Cariprazine 4.5 mg capsule	NEW	1	30	5	\$ [REDACTED]	Reagila® Gedeon Richter Australia Pty Ltd
Cariprazine 6 mg capsule	NEW	1	30	5	\$ [REDACTED]	Reagila® Gedeon Richter Australia Pty Ltd

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<b>Category / Program:</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Episodicity:</b>	Chronic
<b>Severity:</b>	Acute and maintenance therapy
<b>Condition:</b>	Schizophrenia
<b>PBS Indication:</b>	Treatment of schizophrenia in adults
<b>Treatment phase:</b> e.g.: initial/ continuing	Initial and continuing
<b>Restriction:</b>	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required – Telephone, Electronic <input checked="" type="checkbox"/> Authority Required - Streamlined
<b>Treatment criteria:</b>	NR
<b>Clinical criteria:</b>	NR
<b>Population criteria:</b>	Adults
<b>Foreword:</b>	Shared Care Model: For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.
<b>Definitions:</b>	NR
<b>Prescriber Instructions:</b>	NR
<b>Administrative Advice:</b>	Shared Care Model: For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.
<b>Cautions:</b>	NR

Abbreviations: mg=milligram; no=number; NR=not reported; PBS=Pharmaceutical Benefits Scheme  
Source: compiled by the Commentary based on the submission; Table 1.4.1 p44 of the submission

- 3.2 The listing proposed for cariprazine on the PBS was consistent with that applied to the other antipsychotics.

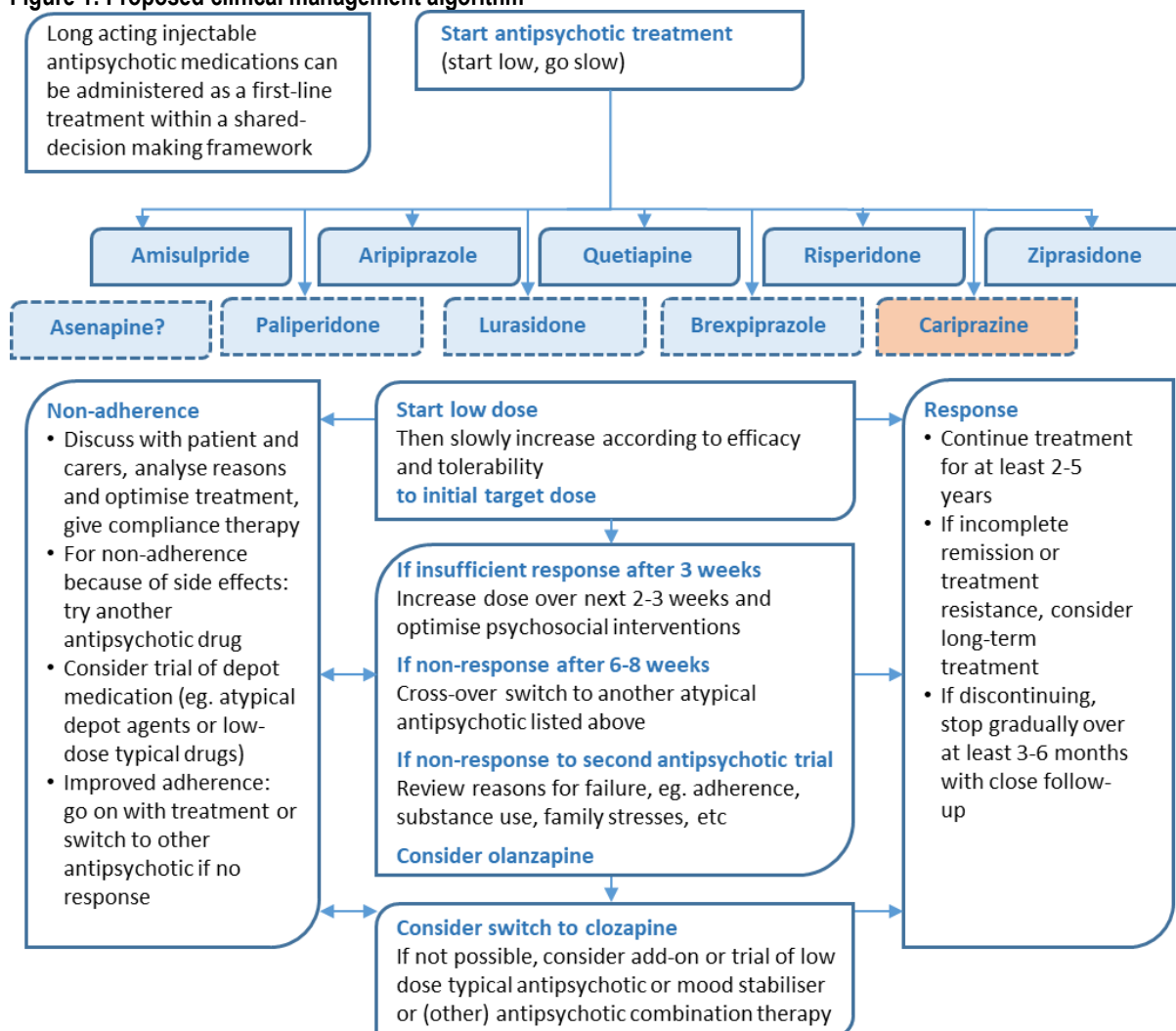
*For more detail on PBAC's view, see section 7 PBAC outcome.*

## 4 Population and disease

- 4.1 The submission stated that schizophrenia is a severe, lifelong, disabling psychiatric disorder involving a breakdown in the relationship between thought, emotion, and behaviour that has a major impact on patients, families and caregivers. It is a complex, multifactorial disorder of brain function with wide variation in symptoms and signs, and in the course of the illness. The submission described the symptoms of schizophrenia as categorised into three domains: positive symptoms, negative symptoms and cognitive symptoms.
- 4.2 Cariprazine is an orally active, atypical antipsychotic for use in adults with schizophrenia. It acts as a “dopamine multifunctional” agent, having potent partial agonist activity at dopamine D2/D3 receptors. The proposed place in therapy for cariprazine (see Figure 1) was consistent with the current PBS eligibility criteria for

aripiprazole and brexpiprazole, the proposed TGA indication and the trial eligibility criteria of the clinical evidence base presented in Section 2 of the submission.

Figure 1: Proposed clinical management algorithm



Source: Figure 1.2.1 p37 of the submission

Notes: The current algorithm includes atypical antipsychotics presented with blue background, and the proposed algorithm adds cariprazine (orange background) as an alternative treatment for acute and maintenance schizophrenia therapy. Atypical antipsychotics with dashed outlines are not included in the 2016 RANZCP Guidelines. Asenapine is included with a question mark as it is recommended that other antipsychotics with more extensive clinical data be considered ahead of it, and it may also be unsuitable for some patients based on its manner of administration.

For more detail on PBAC's view, see section 7 PBAC outcome.

## 5 Comparator

5.1 The submission nominated aripiprazole and brexpiprazole as the main comparators.

5.2 Aripiprazole, brexpiprazole and cariprazine are third generation, orally administered antipsychotics. The submission noted that aripiprazole is also available as a modified-release injectable form, appropriate for patients in whom long-acting injectable

therapy may represent the most suitable maintenance choice. The submission stated that cariprazine would not be a suitable replacement for oral aripiprazole in these patients.

- 5.3 Based on the current utilisation data, in 2019 approximately 17% of patients with schizophrenia initiating an oral atypical antipsychotic used aripiprazole (the second most commonly initiated treatment), and 6% used brexpiprazole. Olanzapine was the market leader, accounting for 37% of patients initiating treatment in 2019; this is despite some treatment guidelines, which recommend that olanzapine not be used as the first line treatment due to its metabolic side effects.
- 5.4 The submission noted the PBAC has accepted the equi-effectiveness and safety of a group of atypical antipsychotics, including aripiprazole, brexpiprazole, lurasidone, paliperidone and ziprasidone, which were listed on a cost-minimisation basis compared to olanzapine. As such, the submission claimed that cariprazine's non-inferiority to aripiprazole and brexpiprazole would establish its position within that group (relative to the other therapies). The submission noted olanzapine was not considered an alternative therapy due to its inferior safety in the first line setting (paragraph 5.10, Brexpiprazole Public summary document (PSD), March 2017).
- 5.5 The nomination of aripiprazole and brexpiprazole as main comparators may be appropriate according to Guidelines based therapy and on the basis that they are both oral, third generation antipsychotics. It may be reasonable that if the claim of non-inferiority to aripiprazole and brexpiprazole were accepted, it would establish an indirect equi-effectiveness of cariprazine to lurasidone, paliperidone and ziprasidone. However, utilisation data shows that olanzapine is the current market leader (by a factor of over 2:1 compared with aripiprazole). It is possible that cariprazine will also substitute for olanzapine, the most widely prescribed of the antipsychotics in this setting. The submission did not present evidence to inform a clinical comparison of cariprazine with olanzapine. The submission noted that it did not consider a comparison of cariprazine with second-generation antipsychotics (e.g. risperidone) to be appropriate given that they have a different mechanism of action and hence are not pharmacological analogues for cariprazine. During the evaluation, this was considered reasonable and by extension, this argument could apply to potential comparisons of cariprazine against any second-generation antipsychotics, including quetiapine.
- 5.6 The PBS-listed medicines olanzapine, paliperidone, ziprasidone, aripiprazole and lurasidone were recommended for listing on the basis that they delivered similar effectiveness and safety in the treatment of schizophrenia. Olanzapine, the first of the medicines in this group to be listed, was recommended on a cost-effectiveness basis compared to risperidone. Risperidone, amisulpride, asenapine and quetiapine were all recommended on a cost minimisation basis to each other as they all delivered similar effectiveness and safety (paragraph 5.9, Brexpiprazole PSD, March 2017). In the case of brexpiprazole, the PBAC concluded that the PBS-listed medicines paliperidone, ziprasidone and lurasidone could also have been considered

comparators, but that olanzapine should not be considered an alternative therapy given its inferior safety profile (paragraph 5.10, Brexpiprazole PSD, March 2017). Given that brexpiprazole is a nominated comparator for cariprazine, consideration could also be given to the potential for paliperidone, ziprasidone and lurasidone to be considered comparators for cariprazine, noting that they are not pharmacological analogues.

- 5.7 If treatment with cariprazine is substantially more costly than an alternative therapy or alternative therapies, the PBAC could only recommend listing of cariprazine if it is satisfied that cariprazine provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies (National Health Act 1953, Section 101(3B)). For the requested population, the following PBS-listed medicines may be considered alternative therapies because they could be replaced in practice: aripiprazole, brexpiprazole, lurasidone, paliperidone, ziprasidone and olanzapine. For the requested population, based on the equi-effective doses proposed in the submission, olanzapine is the only one of these therapies that is less costly than cariprazine, noting that the PBAC previously stated it should not be considered an alternative therapy for brexpiprazole due to its inferior safety profile (Table 15) (paragraph 5.10, Brexpiprazole PSD, March 2017).

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. The sponsor presented a written submission from a clinician which discussed how cariprazine would be used in practice, including dosing.

### ***Consumer comments***

- 6.2 The PBAC noted that no consumer comments were received for this item.

### ***Clinical trials***

- 6.3 The submission included a total of 17 trials (14 in the acute setting and three in the maintenance setting). The primary clinical evidence was based on one head-to-head randomised trial, RGH-MD-04, comparing cariprazine to aripiprazole in the acute setting. RGH-MD-04 was a double blind, parallel group, placebo and active-controlled trial in which aripiprazole was included as the positive control for the purpose of validating assay sensitivity. The submission noted that the trial was not powered for a direct comparison of cariprazine with aripiprazole; the comparison with aripiprazole was conducted as a post-hoc analysis. No trials presenting direct comparisons of cariprazine and brexpiprazole were identified in the submission.
- 6.4 The submission conducted an indirect treatment comparison (ITC) of cariprazine with aripiprazole and brexpiprazole, with placebo as the common arm. The ITC presented by the submission was based on the results of meta-analyses of the trials in the acute

setting. No ITC analysis was performed for trials in the maintenance setting due to differences in trial design.

6.5 Details of the included studies are provided in Table 2. There were no additional potentially relevant studies identified during the evaluation.

**Table 2: Trials and associated reports presented in the submission**

Trial identifier (ID)	Protocol title/Publication title	Publication citation
<b>Trials in adults with an acute exacerbation of schizophrenia</b>		
<b>Direct randomised trial (s) comparing cariprazine with aripiprazole</b>		
RGH-MD-04 <sup>1</sup>	A Double-Blind, Placebo and Active-Controlled Evaluation of the Safety and Efficacy of Cariprazine in the Acute Exacerbation of Schizophrenia. Durgam et al. Cariprazine in acute exacerbation of schizophrenia: a fixed-dose, phase 3, randomized, double-blind, placebo- and active-controlled trial A Double-Blind, Placebo and Active-Controlled Evaluation of the Safety and Efficacy of Cariprazine in the Acute Exacerbation of Schizophrenia.	April 2010  J Clin Psychiatry, 2015; 76(12): e1574-1582.  Clinicaltrials.gov NCT01104766; ICTRP No. 7450897
<b>Indirect comparison of cariprazine with aripiprazole and brexpiprazole in acute settings using placebo common reference</b>		
<b>Cariprazine</b>		
RGH-MD-03	A Double-Blind Placebo-Controlled Evaluation of the Safety and Efficacy of RGH-188 in the Acute Exacerbation of Schizophrenia. Durgam et al. Cariprazine in the treatment of schizophrenia: a proof-of concept trial. Study evaluating RGH-188 in the treatment of patients with schizophrenia. [No results posted]	August 2007  International Clinical Psychopharmacology, 2016;31(2):61-68 Clinicaltrials.gov NCT00404573
RGH-MD-05	A Double-Blind, Placebo and Active-Controlled Evaluation of the Safety and Efficacy of Cariprazine in the Acute Exacerbation of Schizophrenia. Kane et al. Efficacy and Safety of Cariprazine in Acute Exacerbation of Schizophrenia. Results from an International, Phase III Clinical Trial. A double-blind, placebo-controlled evaluation of the safety and efficacy of cariprazine in the acute exacerbation of schizophrenia.	April 2010  Journal of Clinical Psychopharmacology, 2015;35(4):367-373  Clinicaltrials.gov NCT01104779; ICTRP No. 8717948, 4673768
RGH-MD-16	Evaluation of the Safety and Efficacy of RGH-188 in the Acute Exacerbation of Schizophrenia.  Durgam et al. An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: A phase II, randomized clinical trial. Safety and efficacy of cariprazine (RGH-188) in the acute exacerbation of schizophrenia	June 2008  Schizophrenia Research, 2014;152:450-457  Clinicaltrials.gov NCT00694707

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Trial identifier (ID)	Protocol title/Publication title	Publication citation
<b>Aripiprazole</b>		
Kane (2002)	Kane et al. Efficacy and Safety of Aripiprazole and Haloperidol Versus Placebo in Patients with Schizophrenia and Schizoaffective Disorder.	J Clin Psychiatry, 2002; 63(9):763-771.
Potkin (2003)	Potkin et al. Aripiprazole, an Antipsychotic With a Novel Mechanism of Action, and Risperidone vs Placebo in Patients With Schizophrenia and Schizoaffective Disorder.	Arch Gen Psychiatry, 2003;60:681-690
Cutler (2006) CN138113	Cutler et al. The Efficacy and Safety of Lower Doses of Aripiprazole for the Treatment of Patients with Acute Exacerbation of Schizophrenia. Study of three doses of aripiprazole in patients with acute schizophrenia. [No results posted]	CNS Spectr, 2006; 11(9):691-702.  Clinicaltrials.gov NCT00080327; ICTRP No. 4596609
McEvoy (2007)	McEvoy et al. A randomized, double-blind, placebo-controlled, study of the efficacy and safety of aripiprazole 10, 15 or 20mg/day for the treatment of patients with acute exacerbations of schizophrenia.	J. Psych Res, 2007;41:895-905
<b>Brexiprazole</b>		
BEACON	Kane et al. A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. Efficacy study of OPC-34712 in adults with acute schizophrenia.	Schizophr Res, 2015; 164(1-3): 127-135.  Clinicaltrials.gov NCT01393613
VECTOR	Correll et al. Efficacy and safety of Brexpiprazole for the Treatment of Acute Schizophrenia: A 6-Week Randomized, Double-Blind, Placebo-Controlled Trial. Correll et al. Brexpiprazole for the treatment of acute schizophrenia: A randomized, controlled trial. Study of the effectiveness of three different doses of OPC-34712 in the treatment of adults with acute schizophrenia.	Am J Psychiatry, 2015; 172(9); 870-880.  Neuropsychopharmacology, 2014;39: S474  Clinicaltrials.gov NCT01396421; ICTRP No. 6501113
LIGHTHOUSE	An interventional, multi-center, randomized, double-blind, placebo-controlled, active reference, flexible dose study of brexpiprazole in adults with acute schizophrenia. Abstract FC71, 24th European Congress of Psychiatry. Brexpiprazole in patients with acute schizophrenia.	European Psychiatry, 33S, 2016;S72-S113.  Clinicaltrials.gov NCT01810380; ICTRP 5884084
STEP 203 <sup>1</sup>	A Phase 2, 6-Week, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Oral OPC-34712 Once Daily and Aripiprazole Once Daily for Treatment of Hospitalized Adult Patients with Acute Schizophrenia.	<a href="https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-012567-33">https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-012567-33</a>
	Study to evaluate the efficacy, safety, and tolerability of oral OPC-34712 and aripiprazole for treatment of acute schizophrenia	Clinicaltrials.gov NCT00905307; ICTRP No. 2478534, 6493997, 8717286

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Trial identifier (ID)	Protocol title/Publication title	Publication citation
<b>Maintenance trials in adults with schizophrenia</b>		
<b>Cariprazine</b>		
RGH-MD-06	<p>A Randomized, Double-blind, Placebo-Controlled, Parallel-Group Study of Cariprazine (RGH-188) in the Prevention of Relapse in Patients With Schizophrenia.</p> <p>Durgam et al. Long-term cariprazine treatment for the prevention of relapse in patients with schizophrenia: A randomised, double-blind, placebo-controlled trial.</p> <p>Durgam et al. Corrigendum to Long-term cariprazine treatment for the prevention of relapse in patients with schizophrenia: A randomized, double-blind, placebo-controlled trial. [Schizophr. Res. 176 (2016) 264-271].</p> <p>Correll et al. Long-Term Remission With Cariprazine Treatment in Patients With Schizophrenia: A Post Hoc Analysis of a Randomized, Double-Blind, Placebo-Controlled, Relapse Prevention Trial.</p> <p>A randomized, double-blind, placebo-controlled, parallel-group study of cariprazine (RGH-188) in the prevention of relapse in patients with schizophrenia.</p>	<p>June 2015</p> <p>Schizophrenia Research, 2016;176: 264-271.</p> <p>Schizophrenia Research, 2018;192: 493</p> <p>J Clin Psych, 2019; 80(2).</p> <p>Clinicaltrials.gov NCT01412060; ICTRP No. 5133438, 8719175</p>
<b>Aripiprazole</b>		
Pigott (2003)	Pigott et al. Aripiprazole for the Prevention of relapse in Stabilized Patients With Chronic Schizophrenia: A Placebo-Controlled 26-Week Study	J Clin Psychiatry 2003; 64(9):1048-1056.
<b>Brexpiprazole</b>		
EQUATOR	<p>Fleischhacker et al. Efficacy and safety of brexpiprazole (OPC-34712) as maintenance treatment in adults with schizophrenia: a randomised, double-blind, placebo-controlled study.</p> <p>Efficacy, Safety, and Tolerability of Brexpiprazole (OPC-34712) as Maintenance Treatment in Adults With Schizophrenia.</p>	<p>Int J Neuropharmacol, 2017 Jan 1;20(1):11-21</p> <p>Clinicaltrials.gov NCT01668797; ICTRP No. 6504056</p>
<b>Open-label extension studies</b>		
RGH-MD-11 (extension of RGH-MD-04 and RGH-MD-05)	<p>Evaluation of the Long-term Safety, Tolerability, and Pharmacokinetics of Cariprazine in Patients With Schizophrenia.</p> <p>Cutler et al. Evaluation of the long-term safety and tolerability of cariprazine in patients with schizophrenia: results from a 1-year open-label study.</p> <p>Evaluation of the long-term safety, tolerability, and pharmacokinetics of cariprazine in patients with schizophrenia.</p>	<p>September 2013</p> <p>CNS Spectrums, 2018;23: 39-50</p> <p>Clinicaltrials.gov NCT01104792; ICTRP: 8717945, 8270579</p>
RGH-MD-17 (extension of RGH-MD-16)	A Long-term, Open-label Extension Study of the Safety and Tolerability of RGH-188 (Cariprazine) in Patients with Schizophrenia.	May 2012

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Trial identifier (ID)	Protocol title/Publication title	Publication citation
	Durgam et al. Safety and tolerability of cariprazine in the long-term treatment of schizophrenia: results from a 48-week, single-arm, open-label extension study. A long-term, open-label extension study of the safety and tolerability of RGH-188 (cariprazine) in patients with schizophrenia.	Psychopharmacology (Berl), 2017; 234(2): 199-209.  Clinicaltrials.gov NCT00839852; ICTRP No. 8270313, 8717030

Source: Table 2.2.1 p54 of the submission

Note: The table only shows the main publications and associated reports for the included trials. The full list of list of publications/associated reports is provided in Table 2.2.1, pg54 of the submission.

1. RGH-MD-04, STEP-203 also included an aripiprazole positive control arm.

### 6.6 The key features of the included trials are presented in Table 3.

**Table 3: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
<b>Acute setting</b>					
<b>Cariprazine</b>					
RGH-MD-04 <sup>1</sup>	604	Phase III, R, DB 6 weeks	Low	Adults (18–60 years) with an acute exacerbation of schizophrenia.	Efficacy and safety
RGH-MD-05	439	Phase III, MC, R, DB 6 weeks	Low	Adults (18–60 years) with an acute exacerbation of schizophrenia	Safety and tolerability
RGH-MD-03	377	Phase II, MC, R, DB 6 weeks	Low	Adults (18–65 years) with an acute exacerbation of schizophrenia	Efficacy, safety and tolerability
RGH-MD-16	711	Phase II, MC, R, DB 6 weeks	Low	Adults (18–60 years) with an acute exacerbation of schizophrenia	Efficacy, safety and tolerability
RGH-MD-11	578	Phase III, MC, OL 48 week	N/A	Adults (18–60 years) with schizophrenia and those that had completed treatment in RGH-MD-04 and RGH-MD-05	Long term safety and tolerability
RGH-MD-17	92	Phase II, MC, OL 48 week	N/A	Adults (18–60 years) with schizophrenia that had completed study RGH-MD-16	Long term efficacy, safety and tolerability
<b>Aripiprazole</b>					
Kane (2002)	414	Phase III, MC, R, DB 4 week	Unclear	Adults (18–65 years) hospitalised for an acute relapse of schizophrenia or schizoaffective disorder	Efficacy, safety and tolerability
Potkin (2003)	404	Phase III, R, DB 4 weeks	Unclear	Adults (18–65 years) hospitalised for an acute relapse of schizophrenia or schizoaffective disorder	Efficacy, safety and tolerability
Cutler (2006)	367	MC, R, DB 6 week	Unclear	Adults (≥ 18 years) with an acute relapse of schizophrenia, and a documented worsening of symptoms in the previous 3 months and requiring inpatient hospitalisation	Efficacy, safety and tolerability
McEvoy (2007)	420	MC, R, DB 6 week	Unclear	Adults (≥ 18 years) with an acute exacerbation of schizophrenia requiring hospitalisation	Efficacy, safety and tolerability
<b>Brexpiprazole</b>					

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Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
<b>Acute setting</b>					
BEACON	674	Phase III, MC, R, DB 6 week	Low	Adults (18–65 years) who have been recently hospitalised or would benefit from hospitalisation for an acute relapse of schizophrenia	Efficacy, safety and tolerability
VECTOR	636	Phase III, MC, R, DB 6 week	Low	Adults (18–65 years) who have been recently hospitalised or would benefit from hospitalisation for an acute relapse of schizophrenia	Efficacy, safety and tolerability
LIGHTHOUSE	311	Phase III, MC, R, DB 6 week	Low	Adults (18–65 years) who would benefit from hospitalisation or continued hospitalisation for an acute relapse of schizophrenia.	Efficacy, safety and tolerability
STEP-203 <sup>1</sup>	765	Phase II, MC, R, DB 6 week	Unclear	Adults (18–65 years) who have been recently hospitalised or would benefit from hospitalisation for an acute relapse of schizophrenia.	Efficacy, safety and tolerability
<b>Maintenance setting</b>					
RGH-MD-06	200	Phase III, MC, R, DB 72 week	Low	Adults (18–60 years) with schizophrenia	Long term efficacy, safety and tolerability
Pigott (2003)	310	Phase III, MC, R, DB 26 week	Unclear	Adults (≥ 18 years) with stable schizophrenia	Efficacy, safety and tolerability
EQUATOR	202	Phase III, MC, R, DB 52 week	Low	Adults (18–65 years) with an acute exacerbation of schizophrenia requiring stabilisation or a history of relapse/exacerbation when they are not receiving anti-psychotic treatment.	Efficacy, safety and tolerability

Source: Prepared by the Commentary based on the submission

Abbreviations: DB = double-blind, MC = multi-centre; OL = open-label; R = randomised.

Notes: 1. The RGH-MD-04 and STEP-203 trials are also included in the master list of trials for cariprazine and brexpiprazole, respectively

### Acute setting trials

6.7 The submission noted that there were potential issues of transitivity between the trials that would influence the interpretation of their meta-analysed results and the results from the ITC:

- Two of the aripiprazole trials were of shorter duration compared with the cariprazine and brexpiprazole acute trials (4 weeks vs. 6 weeks). The submission claimed that this difference did not result in statistical heterogeneity. However, shorter exposure to aripiprazole may have reduced the potential benefit of the treatment (biasing against aripiprazole).
- The aripiprazole trials (Kane 2002 and Potkin 2003) included 30% of patients with schizoaffective disorder. The submission stated that patients with schizoaffective disorder may have responded differently to aripiprazole treatment. The submission did not present evidence to support any potential difference in response by patients with schizoaffective disorder.

- There were differences in the locations and time periods of the trials. The aripiprazole trials were conducted earlier than the cariprazine and brexpiprazole trials. The submission noted that this may have led to a smaller effect size in the cariprazine and brexpiprazole trials due to an increasing placebo response observed over time, resulting in smaller effect sizes in antipsychotics studied more recently. The mechanism by which placebo responses have been increasing over time is unclear.

#### Maintenance trials

- 6.8 The submission stated that although the trials in the maintenance setting were placebo controlled, there were potential important differences in the trial design that precluded formal indirect comparisons. All three maintenance trials evaluated the time to relapse as the primary outcome. However, the definitions of ‘relapse’ or ‘impending relapse’ differed across the trials.

#### ***Comparative effectiveness***

- 6.9 The primary outcome in the acute setting trials was the change in the Positive and Negative Syndrome Scale (for schizophrenia) (PANSS) total score. The methodology used for analyses of the primary efficacy outcome varied between the aripiprazole and brexpiprazole trials (ANCOVA LOCF vs. MMRM approach respectively). The cariprazine trial results were analysed using both approaches. The submission nominated a difference of 7 points in the change in PANSS as being the minimum clinically important difference (MCID). The ESC considered this was appropriate and consistent with evidence previously considered by the PBAC for brexpiprazole (Brexiprazole PSD, March 2017; Lurasidone PSD, March 2015; Paliperidone PSD, November 2007).
- 6.10 The primary efficacy outcome in the maintenance trials was time to relapse. The trials used different criteria to define ‘relapse’ and ‘impending relapse’, which differed based on the combination of objective rating scales and subjective clinical criteria applied in the definition of relapse. The criteria were mutually exclusive, such that a patient achieving any one was classified as having relapsed, with the exception of the increases in PANSS individual items and CGI-S score in the EQUATOR trial, which had to be achieved in combination. Although it seems that the intention of all three studies was to detect patients at a similar stage of relapse in their disease, this is unlikely to have been achieved in practice, due to the different criteria used in each study. The ESC considered that the submission’s assessment was reasonable. The differences in trial assessments of response/relapse would confound transitivity of the trials. Therefore, exclusion of the maintenance trials from the ITC was appropriate.

#### Acute setting results

- 6.11 The results showing change in PANSS total score from baseline to week 6 in the RGH-MD-04 trial are presented in Table 4. The results of the post-hoc analyses for cariprazine and aripiprazole in RGH-MD-04 showed statistically significant differences in favour of each treatment compared with placebo for the change in PANSS. The post-

hoc comparisons did not demonstrate a statistically or clinically significant difference between cariprazine (3 mg/day or 6 mg/day) and aripiprazole (10 mg/day) as the 95% confidence interval (CI) around the estimated mean difference in PANSS did not include the MCID of  $\geq 7$  points.

**Table 4: Summary of primary outcomes in RGH-MD-04**

	Cariprazine n/N (%)			Aripiprazole 10 mg/day n with event/N (%)			Absolute difference (95% CI)
	Baseline mean $\pm$ [SD]	Change from baseline LS mean (SE)	Difference vs placebo <sup>1</sup> LSMD (95% CI)	Baseline mean $\pm$ [SD]	Change from baseline LS mean (SE)	Difference vs placebo <sup>1</sup> LSMD (95% CI)	
<b>PANSS total score-MMRM</b>							
Cariprazine 3 mg/day	96.1 [8.7]	-20.2 (1.5)	-6.0 (-10.1, -1.9)	95.6 [9.0]	-21.2 (1.4)	-7.0 (-11.0, -2.9)	1.0 (-3.02, 5.02)
Cariprazine 6 mg/day	95.7 [9.4]	-23.0 (1.5)	-8.8 (-12.9, -4.7)	95.6 [9.0]	-21.2 (1.4)	-7.0 (-11.0, -2.9)	-1.8 (-5.82, 2.22)
<b>PANSS total score – LOCF</b>							
Cariprazine 3 mg/day	96.1 [8.7]	-16.4 (1.4)	-5.4 (-9.3, -1.4)	95.6 [9.0]	-18.8 (1.4)	-7.7 (-11.7, -3.8)	2.4 (-1.48, 6.28)
Cariprazine 6 mg/day	95.7 [9.4]	-18.9 (1.4)	-7.9 (-11.8, -4.0)	95.6 [9.0]	-18.8 (1.4)	-7.7 (-11.7, -3.8)	-0.1 (-3.98, 3.78)

Abbreviations: CI = confidence interval; LOCF = Last observation carried forward; LS = least squares; LSMD = Least squares mean difference; MMRM = Mixed-effects model for repeated measures; mg = milligram; PANSS = Positive and Negative Syndrome Scale (for schizophrenia); SE = standard error; SD=standard deviation;

Notes: 1. PANSS total score and CGI-S were analysed using MMRM and ANCOVA/LOCF methodologies; NSA-16 total score, CGI-I, PANSS positive score, PANSS negative score and NSA-16 total score were analysed using MMRM methodology; SQLS-R4 total score was analysed using ANCOVA/LOCF methodology (RGH-MD-04 CSR, Section 11.4.1).

Source: Table 2.5.1 p124 of the submission

- 6.12 The summary of the primary outcome (PANSS total score) in the acute studies in the ITC of cariprazine with aripiprazole and brexpiprazole is presented in Table 5. The three pivotal studies in patients with acute exacerbation of schizophrenia, RGH-MD-04, RGH-MD-05 and RGH-MD-16, showed consistent efficacy of cariprazine across the tested dose range of 1.5–9 mg/day, with statistically significant improvement in the PANSS total score compared to placebo. The submission stated that across the different doses, the 95% CIs were overlapping. The results of the RGH-MD-03 (proof of concept study) showed no statistically significant change in the PANSS total score from baseline to Week 6.
- 6.13 The decreases in PANSS total score following treatment with cariprazine were sustained in the two long-term safety follow-up studies, RGH-MD-11 and RGH-MD-17, suggesting that there was no worsening of schizophrenia symptoms during long-term cariprazine treatment. The submission presented these studies as representing treatment in the acute setting rather than maintenance. Given that the submission has interpreted this evidence as suggesting no longer-term worsening of schizophrenia symptoms, the evidence from these trials is more relevant to consideration of the use of cariprazine in the maintenance setting. Nonetheless, the absence of comparable endpoints on schizophrenia relapse or impending relapse

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mean that it was not possible to compare RGH-MD-11 and RGH-MD-17 with the other maintenance trials and they have been presented as relating to the acute setting.

**Table 5: Change in PANSS total score from baseline to 4 or 6 weeks in studies in acute exacerbations of schizophrenia – ITT population**

	N	Baseline mean ± [SD] or (SE)	Change from baseline LS mean (SE)	Difference vs placebo LSMD (95% CI)	p-value <sup>1</sup>
<b>Cariprazine</b>					
<b>RGH-MD-03 – MMRM</b>					
Placebo	126	94.1 [10.5]	-13.00 (1.89)	—	—
Cariprazine 1.5–4.5 mg/day	122	95.0 [10.7]	-17.99 (1.92)	-4.99 (-10.27, 0.28)	0.063
Cariprazine 6–12 mg/day	129	96.1 [11.4]	-16.83 (1.89)	-3.83 (-9.07, 1.40)	0.151
<b>RGH-MD-03 – LOCF</b>					
Placebo	126	94.1 [10.5]	-9.7 (1.6)*	—	—
Cariprazine 1.5–4.5 mg/day	122	95.0 [10.7]	-14.5 (1.6)*	-4.8 (-9.2, -0.4)	<b>0.0333<sup>2</sup></b>
Cariprazine 6–12 mg/day	129	96.1 [11.4]	-12.6 (1.6)*	-2.9 (-7.2, 1.5)	0.1947 <sup>2</sup>
<b>RGH-MD-04 – MMRM</b>					
Placebo	149	96.5 [9.1]	-14.3 (1.5)	—	—
Cariprazine 3 mg/day	151	96.1 [8.7]	-20.2 (1.5)	-6.0 (-10.1, -1.9)	<b>0.0044</b>
Cariprazine 6 mg/day	154	95.7 [9.4]	-23.0 (1.5)	-8.8 (-12.9, -4.7)	<b>&lt;0.0001</b>
Aripiprazole 10 mg/day	150	95.6 [9.0]	-21.2 (1.4)	-7.0 (-11.0, -2.9)	<b>0.0008</b>
<b>RGH-MD-04 – LOCF</b>					
Placebo	149	96.5 [9.1]	-11.0 (1.4)	—	—
Cariprazine 3 mg/day	151	96.1 [8.7]	-16.4 (1.4)	-5.4 (-9.3, -1.4)	<b>0.0078</b>
Cariprazine 6 mg/day	154	95.7 [9.4]	-18.9 (1.4)	-7.9 (-11.8, -4.0)	<b>&lt;0.0001</b>
Aripiprazole 10 mg/day	150	95.6 [9.0]	-18.8 (1.4)	-7.7 (-11.7, -3.8)	<b>0.0001</b>
<b>RGH-MD-05 – MMRM</b>					
Placebo	145	96.6 [9.3]	-16.0 (1.6)	—	—
Cariprazine 3–6 mg/day	147	96.3 [9.3]	-22.8 (1.6)	-6.8 (-11.3, -2.4)	<b>0.0029</b>
Cariprazine 6–9 mg/day	147	96.3 [9.0]	-25.9 (1.7)	-9.9 (-14.5, -5.3)	<b>&lt;0.0001</b>
<b>RGH-MD-05 – LOCF</b>					
Placebo	145	96.6 [9.3]	-12.3 (1.5)	—	—
Cariprazine 3–6 mg/day	147	96.3 [9.3]	-18.6 (1.5)	-6.3 (-10.3, -2.4)	<b>0.0016</b>
Cariprazine 6–9 mg/day	147	96.3 [9.0]	-20.2 (1.5)	-8.0 (-11.9, -4.0)	<b>&lt;0.0001</b>
<b>RGH-MD-16 – MMRM</b>					
Placebo	148	97.3 [9.22]	-13.29 (1.82)	—	—
Cariprazine 1.5 mg/day	140	97.1 [9.13]	-21.27 (1.77)	-7.97 (-12.94, -3.01)	<b>0.0017</b>
Cariprazine 3 mg/day	140	97.2 [8.66]	-21.45 (1.74)	-8.16 (-13.09, -3.22)	<b>0.0013</b>
Cariprazine 4.5 mg/day	145	96.7 [9.01]	-23.77 (1.74)	-10.48 (-15.41, -5.55)	<b>&lt;0.0001</b>
Risperidone 4 mg/day	138	98.1 [9.50]	-29.27 (1.74)	-15.98 (-20.91, -11.04)	<b>&lt;0.0001</b>
<b>RGH-MD-16 – LOCF</b>					
Placebo	148	97.3 [9.22]	-11.84 (1.54)	—	—
Cariprazine 1.5 mg/day	140	97.1 [9.13]	-19.38 (1.58)	-7.55 (-11.80, -3.29)	<b>0.0005</b>
Cariprazine 3 mg/day	140	97.2 [8.66]	-20.67 (1.59)	-8.83 (-13.09, -4.57)	<b>&lt;0.0001</b>
Cariprazine 4.5 mg/day	145	96.7 [9.01]	-22.25 (1.55)	-10.42 (-14.63, -6.20)	<b>&lt;0.0001</b>
Risperidone 4 mg/day	138	98.1 [9.50]	-26.94 (1.60)	-15.10 (-19.38, -10.82)	<b>&lt;0.0001</b>
<b>Aripiprazole</b>					
<b>Kane et al 2002<sup>3</sup></b>					
Placebo	106	100.2 (1.6)	-2.9 (2.36)	—	—
Aripiprazole 15 mg/day	102	98.5 (1.7)	-15.5 (2.40)	-12.6 (-18.9, -6.2)	<b>&lt;0.001</b>
Aripiprazole 30 mg/day	102	99.0 (1.9)	-11.4 (2.39)	-8.5 (-14.8, -2.1)	<b>0.009</b>
Haloperidol 10 mg/day <sup>5</sup>	104	99.3 (1.7)	-13.8	NR	<b>0.001</b>

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	N	Baseline mean ± [SD] or (SE)	Change from baseline LS mean (SE)	Difference vs placebo LSMD (95% CI)	p-value <sup>1</sup>
<b>Potkin et al 2003<sup>3</sup></b>					
Placebo	103	95.7, 94.3 [18.5]	-5.0 (2.17)		—
Aripiprazole 20 mg/day	101	94.4, 92.6 [19.5]	-14.5 (2.23)	-9.6 (-15.4, -3.8)	<b>0.001</b>
Aripiprazole 30 mg/day	101	92.6, 94.2 [18.5]	-13.9 (2.24)	-9 (-14.8, -3.1)	<b>0.003</b>
Risperidone 6 mg/day	99	94.9	-15.7	NR	<b>&lt;0.001</b>
<b>Cutler et al 2006<sup>4</sup></b>					
Placebo	88	90.9, 90.8 [13.3]	-5.3 (1.97)		—
Aripiprazole 2 mg/day	93	90.8, 90.7 [14.5]	-8.2 (1.90)	-2.9 (-8.29, 2.47)	0.289
Aripiprazole 5 mg/day	92	92.2, 92.0 [12.6]	-10.6 (1.93)	-5.2 (-10.7, 0.19)	0.058
Aripiprazole 10 mg/day	94	90.0 [11.9]	-11.3 (1.88)	-5.9 (-11.3, -0.58)	<b>0.030</b>
<b>McEvoy et al 2007<sup>4</sup></b>					
Placebo	108	92.3 (2.1)	-2.33 (2.35)	NR	—
Aripiprazole 10 mg/day	106	92.7 (1.9)	-15.04 (2.38)	-12.71 (-19.0, -6.4)	<b>≤0.001</b>
Aripiprazole 15 mg/day	106	93.2 (2.1)	-11.73 (2.38)	-9.40 (-15.7, -3.1)	<b>≤0.01</b>
Aripiprazole 20 mg/day	100	92.5 (2.1)	-14.44 (2.45)	-12.11 (-18.5, -5.7)	<b>≤0.001</b>
<b>Brexiprazole</b>					
<b>BEACON</b>					
Placebo	184	94.8 [13.0]	-13.53 (1.52)	—	—
Brexiprazole 1 mg/day	120	93.3 [12.8]	-16.90 (1.86)	-3.37 (-8.06, 1.32)	0.1588
Brexiprazole 2 mg/day	186	96.3 [12.8]	-16.61 (1.49)	-3.08 (-7.23, 1.07)	0.1448
Brexiprazole 4 mg/day	184	95.1 [12.5]	-20.00 (1.48)	-6.47 (-10.6, -2.35)	<b>0.0022</b>
<b>VECTOR</b>					
Placebo	184	95.9 [11.5]	-12.01 (1.60)	—	—
Brexiprazole 0.25 mg/day	90	93.4 [11.7]	-14.90 (2.23)	-2.89 (-8.27, 2.49)	0.3
Brexiprazole 2 mg/day	182	95.9 [13.7]	-20.73 (1.55)	-8.72 (-13.1, -4.37)	<b>&lt;0.0001</b>
Brexiprazole 4 mg/day	180	94.9 [12.2]	-19.65 (1.54)	-7.64 (-12.0, 3.30)	<b>0.0006</b>
<b>LIGHTHOUSE</b>					
Placebo	161	98.4 [10.3]	-15.9 (1.5)	—	—
Brexiprazole 2–4 mg/day	150	97.8 [10.3]	-20.0 (1.5)	-4.1 (-8.2, 0.1)	0.0560
<b>STEP-203</b>					
Placebo	93	97.5 [9.9]	-17.28 (2.19)	—	—
Brexiprazole 0.25 mg/day	41	97.3 [8.5]	-12.41 (3.41)	4.88 (-3.09, 12.85)	0.2288
Brexiprazole 0.5–1.5 mg/day	88	96.2 [10.0]	-21.98 (2.19)	-4.69 (-10.8, 1.39)	0.1299
Brexiprazole 2–3 mg/day	90	98.6 [10.5]	-19.00 (2.25)	-1.72 (-7.89, 4.46)	0.5841
Brexiprazole 4.5–5.5 mg/day	92	97.8 [11.0]	21.73 (2.19)	-4.45 (-10.5, 1.63)	0.1508
Aripiprazole 10–20 mg/day	50	97.1 [10.7]	20.97 (2.93)	-3.68 (-10.9, 3.51)	0.3142

Abbreviations: CI = confidence interval; ITT = intent/intention to treat; LOCF = last observation carried forward; LSMD = Least squares mean difference; MMRM = mixed-effects model for repeated measures; mg = milligram; PANSS = Positive and Negative Syndrome Scale (for schizophrenia); SE = standard error; SD=standard deviation.

Source: Table 2.5.3 p126 of the submission

Notes: One patient was enrolled twice in Study RGH-MD-05; only data from the first enrolment are included. All patients from Study Centres 504 and 043 in Study RGH-MD-05 were excluded due to a GCP violation

1. p-values for MMRM were based on a mixed-effects model for repeated measurements with treatment group, (pooled) study centre, visit, and treatment group by visit interaction as fixed effects, and baseline and baseline-by-treatment as covariates using an unstructured covariance matrix.

2. p-values for LOCF were based on an ANCOVA model for change from baseline, with treatment group and pooled study centre as factors and the baseline value as a covariate.

3. Trial endpoint = 4 weeks.

4. Trial endpoint = 6 weeks.

5. Active control, results not reported.

- 6.14 Overall, all three therapies (cariprazine, aripiprazole, brexpiprazole) showed a statistically significant treatment effect when compared with placebo. However, the effect size for the PANSS total score differed in the placebo arms across the acute trials. The submission noted that the heterogeneity of the placebo effect across the acute trials influenced the comparability of the primary outcome measure, which may in turn influence the results of the meta-analyses and interpretation of the ITCs.
- 6.15 The summary of the post-hoc direct comparison of secondary outcomes for cariprazine and aripiprazole from RGH-MD-04 is presented in Table 6. The submission noted that the pre-defined comparisons of the change from baseline versus placebo (presented as least squares mean difference (LSMD) with 95% CI) indicated statistically significant differences in favour of each cariprazine group and the aripiprazole group for the secondary outcome (Clinical Global Impression - Severity (CGI-S) and other patient-relevant outcomes. This includes the Clinical Global Impression - Improvement (CGI-I)), PANSS positive and negative subscales and total scores for the NSA-16 and SQLS-R4 instruments.

Table 6: Summary results and post-hoc direct comparison of change from baseline to Week 6 – RGH-MD-04: ITT population

	Cariprazine n/N (%)			Aripiprazole 10 mg/day n with event/N (%)			Absolute difference (95% CI)
	Baseline mean ± [SD]	Change from baseline LS mean (SE)	Difference vs placebo <sup>1</sup> LSMD (95% CI)	Baseline mean ± [SD]	Change from baseline LS mean (SE)	Difference vs placebo <sup>1</sup> LSMD (95% CI)	
<b>CGI-S – MMRM</b>							
Cari. 3 mg/day	4.9 [0.6]	-1.4 (0.1)	<b>-0.4</b> <b>(-0.6, -0.2)</b>	4.8 [0.6]	-1.4 (0.1)	<b>-0.4</b> <b>(-0.6, -0.2)</b>	0.0 (-0.28, 0.28)
Cari. 6 mg/day	4.8 [0.6]	-1.5 (0.1)	<b>-0.5</b> <b>(-0.7, -0.3)</b>	4.8 [0.6]	-1.4 (0.1)	<b>-0.4</b> <b>(-0.6, -0.2)</b>	-0.1 (-0.38, 0.18)
<b>CGI-S –LOCF</b>							
Cari. 3 mg/day	4.9 [0.6]	-1.4 (0.1)	<b>-0.4</b> <b>(-0.6, -0.2)</b>	4.8 [0.6]	-1.4 (0.1)	<b>-0.4</b> <b>(-0.6, -0.2)</b>	0.0 (-0.28, 0.28)
Cari. 6 mg/day	4.8 [0.6]	-1.5 (0.1)	<b>-0.5</b> <b>(-0.7, -0.3)</b>	4.8 [0.6]	-1.4 (0.1)	<b>-0.4</b> <b>(-0.6, -0.2)</b>	-0.1 (-0.38, 0.18)
<b>CGI-I</b>							
Cari. 3 mg/day	-	2.7 (0.1)	<b>-0.6</b> <b>(-0.9, -0.3)</b>	-	2.7 (0.1)	<b>-0.5</b> <b>(-0.8, -0.3)</b>	0.0 (-0.28, 0.28)
Cari. 6 mg/day	-	2.7 (0.1)	<b>-0.5</b> <b>(-0.8, -0.2)</b>	-	2.7 (0.1)	<b>-0.5</b> <b>(-0.8, -0.3)</b>	0.0 (-0.28, 0.28)
<b>PANSS positive subscale</b>							
Cari. 3 mg/day	25.3 [3.7]	-6.8 (0.5)	<b>-1.5</b> <b>(-2.8, -0.2)</b>	24.7 [3.5]	-7.2 (0.4)	<b>-1.9</b> <b>(-3.1, -0.6)</b>	0.4 (-0.86, 1.66)
Cari. 6 mg/day	24.6 [3.4]	-7.5 (0.5)	<b>-2.2</b> <b>(-3.5, -0.9)</b>	24.7 [3.5]	-7.2 (0.4)	<b>-1.9</b> <b>(-3.1, -0.6)</b>	-0.3 (-1.56, 0.96)
<b>PANSS negative subscale</b>							
Cari. 3 mg/day	24.0 [4.2]	-4.4 (0.4)	<b>-1.4</b> <b>(-2.4, -0.4)</b>	24.3 [4.5]	-4.2 (0.3)	<b>-1.2</b> <b>(-2.2, -0.2)</b>	-0.2 (-1.18, 0.78)
Cari. 6 mg/day	24.2 [4.2]	-4.7 (0.4)	<b>-1.7</b> <b>(-2.7, -0.7)</b>	24.3 [4.5]	-4.2 (0.3)	<b>-1.2</b> <b>(-2.2, -0.2)</b>	-0.5 (-1.48, 0.48)
<b>NSA-16 total score</b>							
Cari. 3 mg/day	52.9 [11.5]	-6.6 (0.8)	<b>-3.6</b> <b>(-5.8, -1.3)</b>	54.3 [11.1]	-7.2 (0.8)	<b>-4.2</b> <b>(-6.4, -2.0)</b>	0.6 (-1.62, 2.82)
Cari. 6 mg/day	54.4 [11.7]	-7.5 (0.8)	<b>-4.5</b> <b>(-6.7, -2.3)</b>	54.3 [11.1]	-7.2 (0.8)	<b>-4.2</b> <b>(-6.4, -2.0)</b>	-0.3 (-2.52, 1.92)
<b>SQLS-R4 total score</b>							
Cari. 3 mg/day	55.1 [21.3]	-9.9 (1.6)	<b>-6.8</b> <b>(-11.2, -2.4)</b>	58.5 [21.8]	-12.8 (1.6)	<b>-9.7</b> <b>(-14.0, -5.3)</b>	2.9 (-1.53, 7.33)
Cari. 6 mg/day	55.0 [22.6]	-11.5 (1.6)	<b>-8.3</b> <b>(-12.7, -4.0)</b>	58.5 [21.8]	-12.8 (1.6)	<b>-9.7</b> <b>(-14.0, -5.3)</b>	1.3 (-3.13, 5.73)

Abbreviations: Cari. = cariprazine; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; CI = confidence interval; ITT = intent/intention to treat; LOCF = last observation carried forward; LS = least squares; LSMD = least squares mean difference; MMRM = mixed-effects model for repeated measures; mg = milligram; NSA-16 = 16 item Negative Symptom Assessment; PANSS = Positive and Negative Syndrome Scale (for schizophrenia); SE = standard error; SD=standard deviation; SQLS-R4 = Schizophrenia Quality of Life Scale Revision 4

Source: Table 2.5.1 p124 of the submission.

Maintenance setting results

- 6.16 The results showing prevention of impending relapse reported in the maintenance studies are presented in Table 7, with corresponding Kaplan-Meier curves in Figure 2. The results from RGH-MD-06 showed that cariprazine use significantly delayed the time to relapse and resulted in a lower overall rate of relapse than placebo (24.8% vs 47.5%, respectively). A post-hoc analysis of patients who received cariprazine in the lower dose range of 3–6 mg/day confirmed that the significantly decreased time to, and rate of, relapse was maintained in those patients who continued to receive cariprazine 3–6 mg compared to patients who received placebo. At the end of the double-blind phase, the hazard ratios for relapse for cariprazine-treated patients compared with placebo were 0.45 (95% CI: 0.28, 0.73) in the 3–9 mg/day group and 0.40 (0.20, 0.82) in the 3–6 mg/day group, respectively (Cariprazine Clinical Overview, Module 2.5, p129 of the submission). The proportion of patients with relapse was consistent across the two cariprazine dose groups, suggesting that the effectiveness of cariprazine in preventing relapse is the same for the 3-6 mg/day and 3-9 mg/day dose groups (Figure 2).
- 6.17 The results from Pigott 200) showed fewer than 50% of patients in the aripiprazole arm had relapsed at the study endpoint; median time to relapse was therefore not reported. Patients receiving aripiprazole experienced a significantly longer time to relapse compared to those treated with placebo, and the relative risk of relapse with aripiprazole compared with placebo was 0.50 (95% CI = 0.35, 0.71;  $p < .001$ ). This showed that patients in the placebo group experienced a higher relapse rate and/or relapsed sooner than those in the aripiprazole group, with the curves separating around day 14 (Figure 2). The time to relapse following randomisation was significantly longer for aripiprazole than placebo ( $p < 0.001$ ).
- 6.18 Brexpiprazole 1–4 mg demonstrated superiority over placebo at preventing impending relapse with a hazard ratio of 0.338 (95% CI 0.174, 0.655;  $p = 0.0008$ ) and consequently, the trial was terminated early. A further final efficacy analysis (including 200 patients) was conducted after 53 events of impending relapse, where the hazard ratio for time to impending relapse for brexpiprazole versus placebo was 0.292 (95% CI 0.156, 0.548;  $p < 0.0001$ ). The proportion of patients in the brexpiprazole arm who met the criteria for impending relapse (13/96; 13.5%) was significantly lower than the proportion in the placebo arm (40/104; 38.5%),  $p < 0.0001$ .

Table 7: Results of time to (impending) relapse across the cariprazine, aripiprazole and brexpiprazole maintenance studies

Trial	Proposed medicine n/N event (%)	Proposed medicine Median TTE	Placebo n/N event (%)	Placebo Median TTE	Difference in median	p-value <sup>1</sup>	Hazard ratio <sup>2</sup> (95% CI)
<b>RGH-MD-06</b>	<b>Cariprazine 3–9 mg</b>						
Week 26–72 “time to first relapse”	25/101 (24.8)	Not reached	47/99 (47.5)	296 (157, -)	Not calculable <sup>3</sup>	0.0010	<b>0.45 (0.28, 0.73)</b>
	<b>Cariprazine 3–6 mg</b>						
	11/51 (21.6)	Not reached	25/51 (49.0)	192 (155, -)	Not calculable <sup>3</sup>	NR	<b>0.40 (0.20, 0.82)</b>
<b>Pigott (2003)</b>	<b>Aripiprazole</b>						
Week 26 “relapse” <sup>4</sup>	55/148 (37.4)	Not reached	90/149 (60.6)	Not reported	Not calculable <sup>3</sup>	<.001	0.50 <sup>5</sup> (0.35 -0.71)
<b>EQUATOR</b>	<b>Brexpiprazole</b>						
Week 52 “impending relapse”	13/96 (13.5)	Not reached	40/104 (38.5)	Not reached	Not calculable <sup>3</sup>	<.0001	<b>0.292 (0.156, 0.548)</b>

Abbreviations: CI=confidence interval; TTE = time to event

Source: Table 2.5.4 p129 of the submission

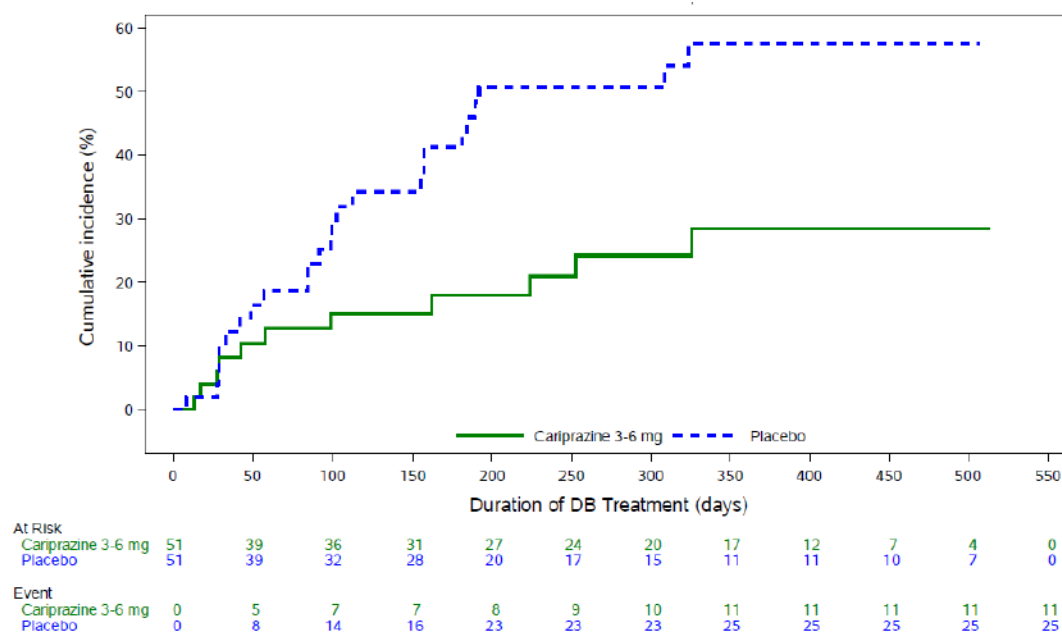
Notes:

1. p-value based on log-rank test.
2. Hazard ratios and relative risk were calculated using the Cox proportional hazards model.
3. Median TTE in the intervention arms was not reached.
4. Pigott (2003) reports percentage of patients ‘not experiencing relapse’; these values for ‘relapse’ were calculated.
5. Although this was reported as relative risk in the publication, it is assumed that it refers to the hazard ratio given that it is reported alongside the time to relapse Kaplan-Meier curves and that the relative risk of reported later as a secondary outcome in the publication to be 0.59 (0.45, 0.75).

Bold indicates statistically significant difference

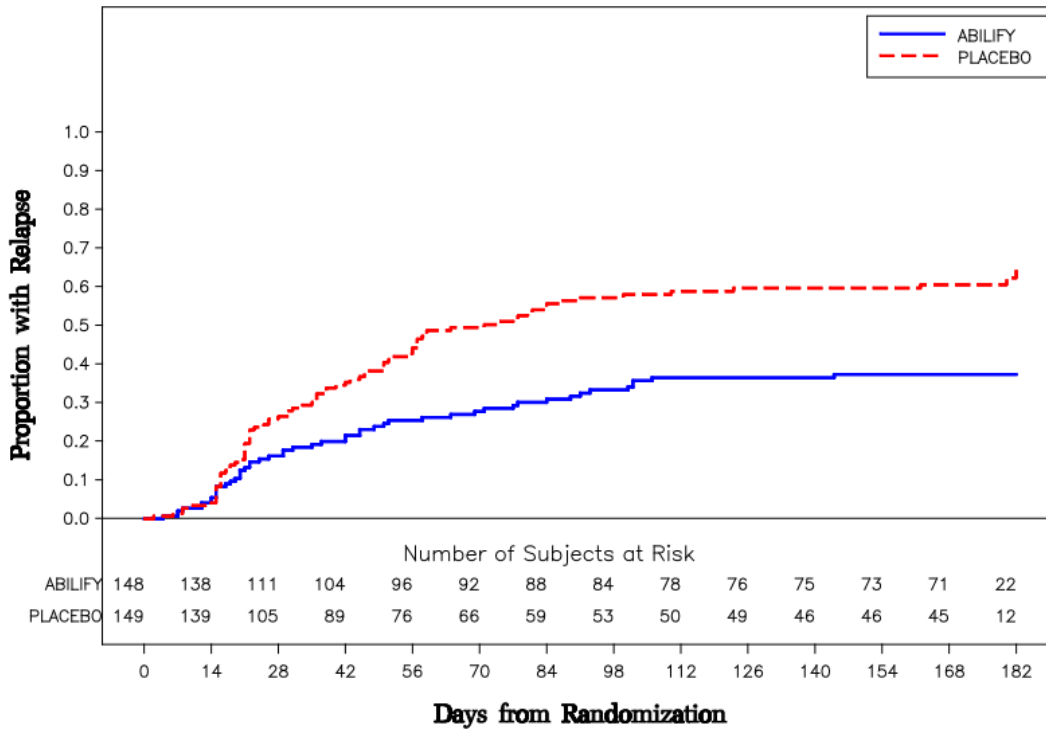
Figure 2: Kaplan-Meier curve of patients with (impending) relapse

KM plots of cumulative proportion of patients with relapse: RGH-MD-06

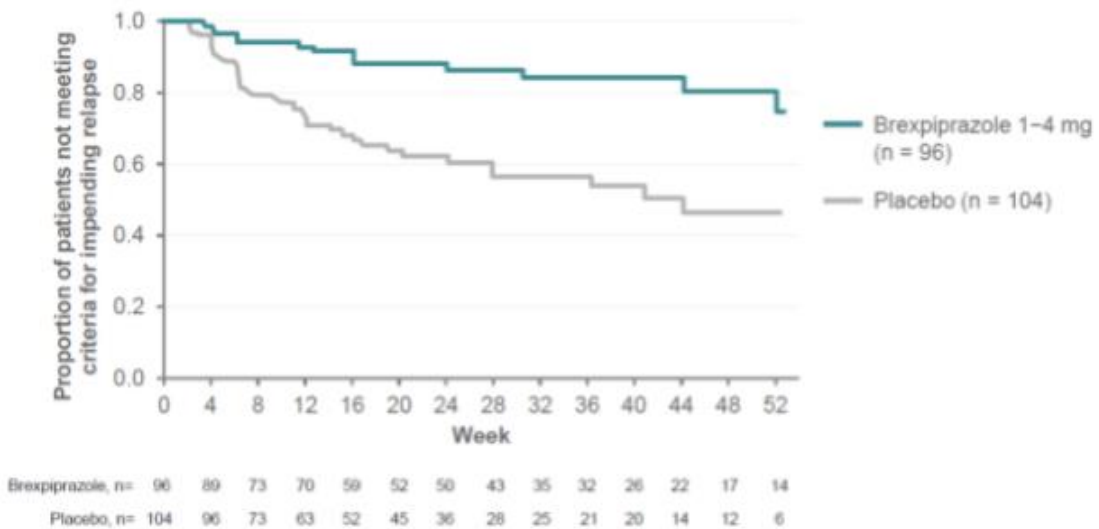


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KM of cumulative proportion of patients with “impending psychotic relapse” in aripiprazole maintenance trial (Pigott, 2003)



KM of cumulative proportion of patients not meeting criteria for “impending relapse” in brexpiprazole maintenance trial (EQUATOR)



Source: Figure 2.5.2 p130 of the submission, Figure 2.5.3 p131 of the submission, Figure 2.5.5 p132 of the submission  
Abbreviations: KM =Kaplan-Meier;

Meta-analysis of acute setting trials

- 6.19 The results of the meta-analyses showed the cariprazine, aripiprazole and brexpiprazole trials demonstrated statistically significant improvements in schizophrenia symptoms, as measured by PANSS total scores compared to placebo.
- 6.20 The submission concluded that the results of the meta-analyses confirmed the efficacy of cariprazine and the respective main comparators for the treatment of schizophrenia; most outcomes were similar between the intervention and placebo arms of the trials (Table 8).

**Table 8: Random effects meta-analysis of placebo-controlled cariprazine and main comparator trials – PANSS total score change from baseline vs placebo**

Active drug	Method	N trials	Pooled outcome (95% CI)	I <sup>2</sup> (%)	Q	df	p-value <sup>1</sup>
Cariprazine	MMRM	4	-7.275 (-9.375, -5.176)	0.00	1.40	3	0.7044
Cariprazine	ANCOVA – LOCF	4	-6.926 (-8.828, -5.024)	0.00	2.25	3	0.5222
Cariprazine	ANCOVA – LOCF (excluding RGH-MD-04)	3	-7.010 (-9.441, -4.579)	9.74	2.22	2	0.3303
Aripiprazole	ANCOVA – LOCF	6	-8.306 (-10.421, -6.192)	0.00	4.49	5	0.4818
Aripiprazole	ANCOVA – LOCF 4 or 6 weeks (excluding RGH-MD-04)	5	-8.497 (-11.145, -5.849)	8.93	4.39	4	0.3555
Aripiprazole	ANCOVA – LOCF 6 weeks	4	-7.614 (-10.399, -4.829)	14.81	3.51	3	0.3180
Aripiprazole	ANCOVA – LOCF 6 weeks (excluding RGH-MD-04, Kane (2002) and Potkin (2003))	3	-7.339 (-11.814, -2.864)	43.06	3.51	2	0.1727
Brexpiprazole	MMRM	4	-5.291 (-7.528, -3.053)	11.12	3.38	3	0.3373

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; df = degrees of freedom; LOCF = last observation carried forward; MMRM = Mixed-effects model for repeated measures; N = number

Source: Table 2.6.3 p147 of the submission

Note: 1. p-value refers to a test of difference across trials

ITC in the acute setting

- 6.21 The results of the ITC for the PANSS total score are presented in Table 9 and Table 10. The ITC compared cariprazine with aripiprazole and brexpiprazole via a common placebo arm. The ITC presented by the submission was based on the results of the meta-analyses of the acute trials. The submission noted that the trials differed in placebo response with the aripiprazole trials having the lowest reduction in PANSS total score from baseline (range of 2.3-5.3 vs. 9.7-16.0 and 12.01-17.28 in the cariprazine and brexpiprazole trials respectively). This difference may reflect underlying issues of transitivity across the trials. The submission noted that the difference in placebo response was likely to have biased the results of the ITC in favour

of the aripiprazole trials. The ESC considered that the submission’s conclusion on the potential for bias from differences in the placebo response seemed reasonable.

- 6.22 Based on the results of the ITC, the submission stated that cariprazine is non-inferior to aripiprazole and brexpiprazole with respect to efficacy; results of the analysis showed no statistically significant differences between cariprazine compared with aripiprazole and brexpiprazole in terms of the reduction in PANSS total score (Table 9 and Table 10). The submission stated that the 95% CI around the estimated effect size excluded a difference of 7 points in the PANSS total score in favour of aripiprazole (Table 9) and brexpiprazole (Table 10). The ESC considered that this conclusion seemed reasonable, noting the potential issues of transitivity across the trials (see paragraph 6.7).
- 6.23 Data from the RGH-MD-04 trial were excluded from the meta-analyses for the ITC versus cariprazine, as post-hoc direct comparisons were carried out.

**Table 9: Indirect comparisons of cariprazine versus aripiprazole using placebo as a common reference arm, excluding RGH-MD-04**

Treatment and duration		Change from baseline in PANSS total score		
		Treatment effect vs placebo Effect size (95% CI)		Cariprazine vs aripiprazole Effect size (95% CI)
Cariprazine	Aripiprazole	Cariprazine	Aripiprazole	
1.5–6 mg/day 6 weeks	10–30 mg/day 4 or 6 weeks	-7.01 (-9.44, -4.58)	-8.50 (-11.15, -5.85)	1.49 (-2.11, 5.08)
1.5–6 mg/day 6 weeks	10–20 mg/day 6 weeks	-7.01 (-9.44, -4.58)	-7.34 (-11.81, -2.86)	0.33 (-4.76, 5.42)

Abbreviations: CI = confidence interval; mg = milligram; PANSS = Positive and Negative Syndrome Scale (for schizophrenia)  
Source: Table 2.6.5 p154 of the submission

**Table 10: Indirect comparisons of cariprazine versus brexpiprazole using placebo as a common reference arm (change from baseline in PANSS total score)**

Treatment		Treatment effect vs placebo Effect size (95% CI)		Cariprazine vs aripiprazole Effect size (95% CI)
Cariprazine	Brexpiprazole	Cariprazine	Brexpiprazole	
1.5–6 mg/day MMRM 6 weeks	1–4 mg/day MMRM 6 weeks	-7.28 (-9.38, -5.18)	-5.29 (-7.53, -3.05)	-1.99 (-5.05, 1.08)

Abbreviations: CI = confidence interval; mg = milligram; LS = least squares; SE = standard error; Source: Table 2.6.7 p155 of the submission

The submission presented the results of a published network meta-analysis (Huhn et al 2019) comparing 32 antipsychotics in adults with acute symptoms of schizophrenia or related disorders (including schizoaffective disorder) using placebo-controlled and head-to-head RCTs. The results from Huhn 2019 showed an effect size for overall change in symptoms for cariprazine of -0.34 (95% CrI: -0.49 to -0.20), in between the effect sizes for aripiprazole at -0.41 (95% CrI: -0.50 to -0.32) and brexpiprazole at -0.26 (95% CrI: -0.39 to -0.12). There were no statistically significant differences in any of the pairwise comparisons between cariprazine and aripiprazole, nor cariprazine and brexpiprazole. The results of the network meta-analyses for adverse events (AEs) overlapped for cariprazine and the comparators, supporting the conclusion of a non-inferior safety profile across the three treatments.

ITC in the maintenance setting

6.24 The submission stated that no ITC analysis was performed for trials in the maintenance setting due to differences in trial design.

***Comparative harms***

Acute setting trials

6.25 A summary of the key AE data for cariprazine and aripiprazole from the RGH-MD-04 trial is presented in Table 11. The submission stated that for most of the AEs, the risk differences (RDs) were minimal and most relative risks (RRs) had wide 95% CIs that crossed 1, indicating no statistically significant difference in incidence and supporting a conclusion of non-inferior safety between cariprazine and aripiprazole. The ESC considered this was reasonable, noting that RGH-MD-04 was not powered for direct comparisons of events between cariprazine and aripiprazole.

Table 11: Summary of key adverse events in RGH-MD-04

	Cariprazine n with event/N (%)	Aripiprazole 10 mg/day n with event/N (%)	RD (95% CI)	RR (95% CI)
<b>TEAEs</b>				
Cariprazine 3 mg/day	95/155 (61.3)	100/152(65.8)	-0.04 (-0.15, 0.06)	0.93 (0.79, 1.10)
Cariprazine 6 mg/day	112/157(71.3)	-	-0.06 (-0.05, 0.16)	1.08 (0.93, 1.26)
<b>Discontinuations</b>				
Cariprazine 3 mg/day	151/55 (9.7)	14/152(9.2)	-0.00 (-0.06, 0.07)	1.05 (0.52, 2.10)
Cariprazine 6 mg/day	20/157 (12.7)	-	0.03 (-0.03, 0.10)	1.38 (0.72, 2.64)
<b>SAEs</b>				
Cariprazine 3 mg/day	2/155 (1.3)	4/152 (2.6)	-0.01 (-0.04, 0.02)	0.49 (0.09, 2.64)
Cariprazine 6 mg/day	5/157 (3.2)	-	0.01 (-0.03, 0.04)	1.21 (0.33, 4.42)
<b>Deaths</b>				
Cariprazine 3 mg/day	0/155	0/152	0	NE <sup>1</sup>
Cariprazine 6 mg/day	2 <sup>2</sup> /157 (1.3)	-	0.01 (-0.00, 0.03)	NE
<b>Insomnia</b>				
Cariprazine 3 mg/day	21/155 (13.5)	16/152 (10.5)	0.03 (-0.04, 0.10)	1.29 (0.70, 2.37)
Cariprazine 6 mg/day	22/157 (14.0)	-	0.03 (-0.04, 0.11)	1.33 (0.73, 2.43)
<b>Akathisia</b>				
Cariprazine 3 mg/day	11/155 (7.1)	11/152 (7.2)	-0.00 (-0.06, 0.06)	0.98 (0.44, 2.19)
Cariprazine 6 mg/day	23/157 (14.6)	-	<b>0.07 (0.01, 0.14)</b>	<b>2.02 (1.02, 4.01)</b>
<b>Headache</b>				
Cariprazine 3 mg/day	10/155 (6.5)	15/152 (9.9)	-0.03 (-0.10, 0.03)	0.65 (0.30, 1.41)
Cariprazine 6 mg/day	16/157 (10.2)	-	0.00 (-0.06, 0.07)	1.03 (0.52, 2.01)
<b>Anxiety</b>				
Cariprazine 3 mg/day	12/155 (7.7)	12/152 (7.9)	-0.00 (-0.06, 0.06)	0.98 (0.45, 2.11)
Cariprazine 6 mg/day	12/157 (7.6)	-	-0.00 (-0.06, 0.06)	0.97 (0.45, 2.09)
<b>Schizophrenia</b>				
Cariprazine 3 mg/day	3/155 (1.9)	8/152 (5.3)	-0.03 (-0.07, 0.08)	0.37 (0.10, 1.36)
Cariprazine 6 mg/day	4/157 (2.5)	-	-0.03 (-0.07, 0.02)	0.48, (0.15, 1.57)
<b>Nausea</b>				
Cariprazine 3 mg/day	3/155 (1.9)	11/152	<b>-0.05 (-0.10, -0.01)</b>	<b>0.27 (0.08, 0.94)</b>
Cariprazine 6 mg/day	5/157 (3.2)	-	-0.04 (-0.09, 0.10)	0.45 (0.16, 1.25)
<b>Agitation</b>				
Cariprazine 3 mg/day	5/155 (3.2)	5/152 (3.3)	-0.00 (-0.04, 0.04)	0.98 (0.29, 3.32)
Cariprazine 6 mg/day	11/157 (7.0)	-	0.04 (-0.01, 0.09)	2.13 (0.76, 5.99)

Abbreviations: mg = milligram; RD = risk difference; RR = relative risk; TEAE = treatment emergent adverse event; SAE = serious adverse events; SD = standard deviation

Source: Table 2.5.6 p133 of the submission

Notes: 1. Relative risk not estimable as denominator value = 0.

2. Neither of the deaths in the cariprazine 6 mg arm were considered to be related to treatment by the Investigator (RGH-MD-04 CSR, Section 12.3.1.1).

Bold indicates statistically significant difference.

6.26 The overall rates of treatment-emergent AEs (TEAEs) reported in the cariprazine trials were within the same range as the rates reported for aripiprazole. The submission stated that the majority of TEAEs with cariprazine were considered by the Investigator to be mild or moderate in severity, and there was no dose-response with regard to AE severity. The most frequent TEAEs were akathisia and extrapyramidal disorder.

*Cariprazine safety*

- 6.27 In both the acute and long-term placebo-controlled trials, the incidence of serious adverse events (SAEs) and adverse events leading to dropout (ADOs) was lower with cariprazine than with placebo. The most commonly reported SAEs and ADOs were associated with the underlying disease (worsening of schizophrenia or psychotic symptoms). In the pooled acute cariprazine trials, the incidence of AEs leading to treatment discontinuation was lower with cariprazine (9%) than placebo (12%).
- 6.28 The most common AE leading to study discontinuation in the cariprazine acute trials was exacerbation of schizophrenia, (5% for cariprazine vs 3% for placebo). In the pooled acute cariprazine trials, the incidence of SAEs was lower with cariprazine than placebo (5.5% and 8.7% respectively).
- 6.29 Across the cariprazine trials, only two deaths were reported, both in the RGH-MD-04 trial. Both deaths occurred during the double-blind treatment phase and both patients who died were in the cariprazine 6 mg/day treatment group. Neither of the deaths were considered by the Investigator to be related to the investigational product.
- 6.30 The AEs that occurred with an incidence of at least 5% and twice the rate of placebo in the cariprazine trials were extrapyramidal symptoms (EPS) and akathisia. None of the akathisia AEs reported in the cariprazine acute trials were SAEs, and most were considered mild or moderate in severity. The submission stated that the likely rate and severity of akathisia in clinical practice would be manageable for most cariprazine-treated patients following the recommendations for slow up-titration and use of the minimum effective dose.

*Aripiprazole safety*

- 6.31 The aripiprazole trials showed some variability in the incidence of TEAEs, which may be dose-related, as the study with the highest incidence of TEAEs at 91% (which exceeded the highest observed rates for cariprazine and brexpiprazole) used the highest doses of aripiprazole (20–30 mg; see Potkin 2003). Only one death was reported across the aripiprazole studies. The investigator judged the event as being unrelated to the study medication. In the aripiprazole acute trials, the observed incidence of akathisia ranged from 2.1–20%, thus in some trials exceeding the observed rates in the cariprazine trials.

*Brexpiprazole safety*

- 6.32 The submission reported that overall brexpiprazole was generally well tolerated in all studies. Across the brexpiprazole trials, one death was reported in a pooled publication, which appeared to attribute it to the BEACON trial.
- 6.33 Pooled analysis of the BEACON, VECTOR and STEP-203 trials demonstrated that the incidence of akathisia was similar in the brexpiprazole 2–4 mg and placebo groups, although rose markedly to 15% at doses above 4 mg/day. Discontinuation rates for

akathisia were < 1% in both short-term (0.1%) and long-term (0.4%) studies for brexpiprazole.

#### Maintenance setting trials

##### *Cariprazine safety*

- 6.34 In the cariprazine maintenance trial (RGH-MD-06), discontinuation due to AEs occurred more frequently in the run-in (dose titration) phase than in the stabilisation phase where patients maintained their dose of cariprazine (11.2% and 2.5%, respectively). The proportion of patients who completed the double-blind treatment period was similar for the cariprazine and placebo treatment groups. Due to the higher relapse rate observed in the placebo group relative to the cariprazine group, more patients in the cariprazine group were discontinued for reasons other than relapse (which may have included AEs).
- 6.35 The submission stated that observed rates of akathisia in the open-label phase of the cariprazine maintenance trial and open-label follow up studies were in keeping with the dose-response relationship for akathisia that is now well recognised. In the double-blind phase of the cariprazine maintenance trial, the reported incidence of akathisia in the cariprazine arm fell dramatically to 5.0% (from 19.2% in the open-label treatment phase) once dose titration was complete. This rate of akathisia compared favourably with the observed incidence in the placebo arm of 3.0% and was lower than the rates reported in the acute trials. The submission argued that these rates are a function of the trial design and target doses and are unlikely to be observed in clinical practice. This seemed reasonable noting that the submission addressed the potential for akathisia associated with cariprazine as part of its quality use of medicines (QUM) approach.

##### *Aripiprazole and Brexpiprazole safety*

- 6.36 The incidence of AEs with aripiprazole in the maintenance trials was consistent with the incidence of AEs reported in the acute trials except for that of Potkin 2003, which reported higher incidence of AE and discontinuations. During the maintenance phase of the long-term trial, the incidence of AEs with brexpiprazole was lower than for the acute trials and was comparable to that of placebo.

#### Meta-analysis (Safety)

- 6.37 The results of a meta-analysis of safety outcomes confirmed the safety of cariprazine and the main comparators for the treatment of schizophrenia; most outcomes were similar between the intervention and placebo arms of the trials. This seemed reasonable.
- 6.38 The meta-analyses of TEAEs in the cariprazine trials estimated a higher risk for the cariprazine arm compared to placebo, but the magnitude of the difference was small and there was no difference in discontinuations due to AEs or SAEs. The comparators had a similar risk of TEAEs and SAEs as placebo. Low to moderate heterogeneity was

observed mainly in the meta-analyses of discontinuations and in the meta-analyses of the brexpiprazole trials. This should be taken into account when interpreting the results of the subsequent ITC as the moderate heterogeneity indicated differences in safety profile across the included trials. The differences in the characteristics of the trials may affect the transitivity of the trials in the ITC presented by the submission.

### ITC (Safety)

6.39 Based on the results of the ITC of AEs the submission stated that cariprazine had non-inferior safety compared to aripiprazole and brexpiprazole; there were no statistically significant differences between cariprazine and aripiprazole in terms of TEAEs, or discontinuations due to AEs or SAEs (Table 12).

**Table 12: Random-effects meta-analyses of safety outcomes**

Active drug	Measurement	N trials	Pooled outcome (95% CI)	I <sup>2</sup> (%)	Q	df	p-value <sup>1</sup>
<b>Treatment emergent adverse events</b>							
Cariprazine	Pooled result, RR	4	1.086 (1.018, 1.159)	0.00	2.71	3	0.4389
	Pooled result, RD	4	0.058 (0.010, 0.106)	6.18	3.20	3	0.362
Cariprazine excluding RGH-MD-04	Pooled result, RR	3	1.114 (1.035, 1.199)	0.00	0.70	2	0.7063
	Pooled result, RD	3	0.079 (0.025, 0.133)	0.00	0.88	2	0.6439
Aripiprazole excluding RGH-MD-04	Pooled result, RR	3	1.065 (0.991, 1.145)	0.00	0.65	2	0.7231
	Pooled result, RD	3	0.052 (-0.004, 0.109)	0.00	0.48	2	0.786
Brexpiprazole	Pooled result, RR	3	0.991 (0.893, 1.098)	18.41	2.45	2	0.2936
	Pooled result, RD	3	-0.004 (-0.064, 0.055)	19.27	2.48	2	0.290
<b>Discontinuations due to adverse events</b>							
Cariprazine	Pooled result, RR	4	0.754 (0.535, 1.064)	23.94	3.94	3	0.268
	Pooled result, RD	4	-0.027 (-0.064, 0.010)	21.33	3.81	3	0.282
Cariprazine excluding RGH-MD-04	Pooled result, RR	3	0.666 (0.455, 0.975)	12.62	2.29	2	0.3184
	Pooled result, RD	3	-0.038 (-0.084, 0.007)	24.95	2.66	2	0.2638
Aripiprazole excluding RGH-MD-04	Pooled result, RR	5	0.629 (0.436, 0.907)	0.00	2.98	4	0.562
	Pooled result, RD	5	-0.028 (-0.064, 0.008)	26.48	5.44	4	0.245
Brexpiprazole	Pooled result, RR	4	0.641 (0.477, 0.860)	3.48	3.11	3	0.375
	Pooled result, RD	4	-0.036 (-0.073, 0.002)	38.05	4.84	3	0.284
<b>Serious adverse events</b>							
Cariprazine	Pooled result, RR	4	0.675 (0.403, 1.131)	0.00	2.14	3	0.543
	Pooled result, RD	4	-0.007 (-0.027, 0.012)	10.36	3.35	3	0.341
Cariprazine excluding RGH-MD-04	Pooled result, RR	3	0.601 (0.348, 1.039)	0.00	0.60	2	0.7418
	Pooled result, RD	3	-0.024 (-0.051, 0.002)	0.00	0.02	2	0.9919
Aripiprazole excluding RGH-MD-04	Pooled result, RR	5	0.972 (0.592, 1.597)	0.00	1.00	4	0.910
	Pooled result, RD	5	-0.001 (-0.024, 0.021)	0.00	0.93	4	0.920
Brexpiprazole	Pooled result, RR	4	0.688 (0.362, 1.306)	32.86	4.47	3	0.215
	Pooled result, RD	4	-0.012 (-0.033, 0.008)	16.15	3.58	3	0.311

Abbreviations: CI = confidence interval; RR = Relative Risk; RD = Risk Difference; N = number of trials; df = degrees of freedom.

Source: Table 2.6.4 p151 of the submission

Note: 1. p-value refers to a test of difference across trials

### Benefits/harms

6.40 A summary of the benefits and harms was not presented given the non-inferiority nature of the claim.

### **Clinical claim**

- 6.41 On the basis of post-hoc direct comparison of cariprazine and aripiprazole (RGH-MD-04 trial) and the ITC of cariprazine with aripiprazole and brexpiprazole via common placebo arm, the submission claimed that cariprazine was non-inferior in terms of effectiveness and safety compared to aripiprazole and brexpiprazole. The clinical claim was supported by the evidence presented, noting that the RGH-MD-04 trial, the only RCT comparing cariprazine with aripiprazole directly, included aripiprazole as the positive control for the purpose of validating assay sensitivity. In addition, while the results of the ITC did not include the MCID, they are likely to be confounded by issues of transitivity between the trials. The results of the post-hoc comparison of cariprazine with aripiprazole and the corresponding ITC was not used in the estimation of equi-effective doses.
- 6.42 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 6.43 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

### **Economic analysis**

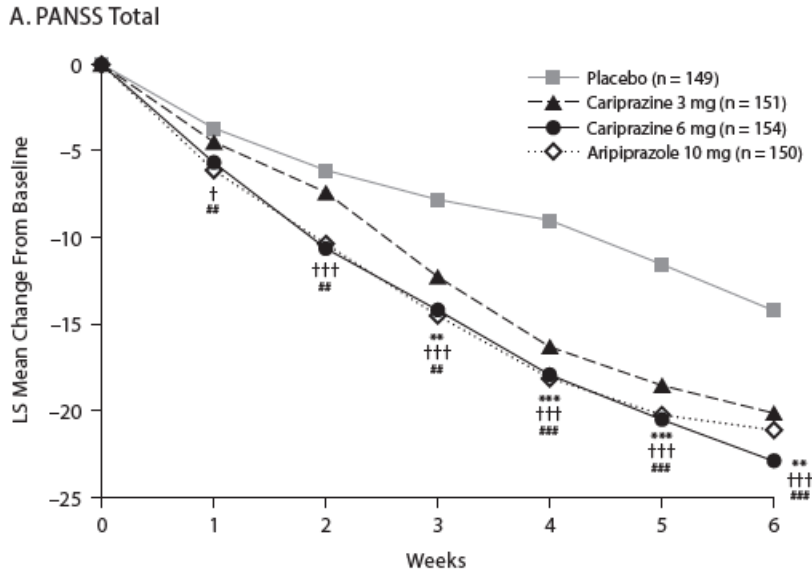
- 6.44 The submission presented a CMA comparing cariprazine to aripiprazole and brexpiprazole. The PBAC has previously considered the group of medicines that were listed on a cost-minimisation basis compared to olanzapine (paliperidone, ziprasidone, aripiprazole and lurasidone), as relevant comparators for brexpiprazole on the basis that, on balance, brexpiprazole has shown to be non-inferior to lurasidone. However, the PBAC was satisfied in 2017 that olanzapine should not be considered as an alternative therapy due to its inferior safety compared to the other medicines in the group (Brexpiprazole PSD, PBAC March 2017, paragraph 5.10). Given that brexpiprazole is a comparator for cariprazine, the PBAC considered that paliperidone, ziprasidone and lurasidone may also be alternative therapies for cariprazine. As shown in Table 14, based on the equi-effective doses proposed in the submission, none of these therapies are less expensive than cariprazine.
- 6.45 To estimate the equi-effective doses the submission considered that the most relevant comparison between cariprazine and the nominated comparators, aripiprazole and brexpiprazole, is at their steady state doses, as the intended use of these drugs is as indefinite chronic treatment. The PBAC considered that this was appropriate and in line with the PBAC Guidelines v5.0.
- 6.46 In the estimation of the equi-effective doses of cariprazine and aripiprazole, the submission relied on cariprazine utilisation data from Germany and aripiprazole PBS utilisation data from Australia, rather than data from the clinical trials presented in the submission. The approach relied on the distribution of prescriptions dispensed rather than the doses prescribed. The submission justified its approach in that:

- There were no direct randomised flexible dose trials where doses of both cariprazine and the comparator medicines were titrated against a response.
  - The dosing and titration schedules in the cariprazine trials are not reflective of the Australian recommended clinical practice, hence cannot be used to establish a steady state dose for cariprazine relevant to prescribing recommendations in Australia.
- 6.47 Based on the German prescription data for the period April 19-March 20, the distribution of prescriptions across the 1.5 mg, 3 mg, 4.5 mg and 6 mg cariprazine strengths was 41.2%, 32.3%, 14.9% and 11.6%. This was estimated to represent a dose of cariprazine of 2.96 mg ( $0.412 \times 1.5 + 0.323 \times 3 + 0.149 \times 4.5 + 0.116 \times 6$ ).
- 6.48 Based on PBS prescription data for 2019, the distribution of prescriptions across the 10 mg, 15 mg, 20 mg and 30 mg aripiprazole strengths was 47%, 19%, 19% and 15%. This was estimated to represent a dose of aripiprazole of 15.89 mg ( $0.47 \times 10 + 0.19 \times 15 + 0.19 \times 20 + 0.15 \times 30$ ).
- 6.49 Based on the above, the equi-effective doses were assumed in the submission to be 2.96 mg cariprazine and 15.89 mg aripiprazole. For consistency with the previously established PBAC relativities for brexpiprazole and aripiprazole (equi-effective doses of 3.58 mg and 19.06 mg), the equi-effective doses proposed in the submission were 3.55mg cariprazine ( $19.06 / 15.89 \times 2.96$ ), 19.06 mg aripiprazole and 3.58 mg brexpiprazole.
- 6.50 The PBAC noted that the use of data from which dose, but not effect, is measured is the least preferred form of evidence for estimating equi-effective dose according to the PBAC guidelines v5.0 and introduces a disconnect between the treatment utilisation underpinning the efficacy and safety claim of non-inferiority and that utilised for the statement of equi-effective doses. The PBAC further noted that the data used to infer the dose was the number of prescriptions dispensed rather than steady state dosing for patients. The pre-PBAC response stated that the steady state dose of cariprazine was estimated as 3.55 mg (not 2.96 mg). The PBAC noted there was no data to directly support the dose of 3.55 mg, rather this dose was calculated as described in the above paragraph.
- 6.51 In forming the equi-effective doses by comparing prescription data from Germany with those from Australia, the submission has assumed that utilisation of cariprazine in Australia will be the same as for Germany. This may not necessarily be the case. During the evaluation, the Sponsor was contacted to enquire as to whether prescription data on aripiprazole from Germany were available (as a means of circumventing issues of comparing data across countries). The Sponsor advised that those data could not be provided given that data on aripiprazole use in Germany includes its use in indications other than schizophrenia and in those under 18 (for which the treatment dose is lower). In addition to the concerns noted by the commentary, the ESC also considered that the German data provided for cariprazine may not be reliable as it is unclear to what extent cariprazine may have been

prescribed outside of the EMA approved indication of schizophrenia. The ESC also noted that based on the data provided the use of cariprazine in Germany is increasing and so may include a relatively large proportion of new patients who are not receiving steady state doses.

- 6.52 The pre-PBAC response stated that there were only two reported cases of off-label use of cariprazine during the Periodic Safety Update Report period. The pre-PBAC response noted the data for aripiprazole similarly included data for initiating and switching patients in whom up-titration would be required.
- 6.53 The ESC noted that cariprazine was registered in a number of countries and considered that there may be other prescription data available, which could be used to compare use of cariprazine and aripiprazole in the same country. The Pre-Sub-Committee-Response (PSCR) stated that of all the European markets, Germany has had cariprazine available for the longest time and therefore has the most extensive historic utilisation data available.
- 6.54 The ESC noted that the submission had relied on Level 4 evidence (market prescription data) to determine the equi-effective doses, rather than the Level 2 evidence available in the submission (head-to-head trial with fixed doses, Study RGH-MD-04). The ESC noted that the data available from RGH-MD-04 suggested that 6 mg of cariprazine resulted in equivalent outcomes to 10 mg aripiprazole based on the change in PANSS total scores (see Figure 3), and considered that this may represent more appropriate equi-effective doses than those proposed in the submission. The ESC noted that there was an increase in efficacy up to 6 mg of cariprazine, and that the recommended maximum dose is 6 mg due to increased AEs at higher doses. The ESC considered that if AEs are limited below 6 mg, it is possible that clinicians would attempt to achieve the optimum effect by using the maximum safe dose of 6 mg. The ESC acknowledged that the trial included a single fixed dose of aripiprazole.
- 6.55 The pre-PBAC response stated that the study RGH-MD-04 does not provide the evidence required to determine the equi-effective doses, as it is a fixed dose trial that included a single 10 mg dose of aripiprazole and does not allow for estimation or comparison of steady state dose. It also rejected the ESC's suggestion that based on this trial, the maximum recommended dose of cariprazine (6 mg) may be a more appropriate equi-effective dose to the minimum starting dose of aripiprazole (10 mg). The pre-PBAC response stated that these equi-effective doses were clinically implausible and inconsistent with the demonstrated non-inferior efficacy of cariprazine 3 mg to aripiprazole 10 mg in the study.

Figure 3: Primary and Secondary Efficacy data from RGH-MD-04: Change from Baseline at each Study Week  
 Figure 1. Primary and Secondary Efficacy: Change From Baseline at Each Study Week (ITT, MMRM)<sup>a</sup>



Source: Cariprazine in Acute Exacerbation of Schizophrenia: A Fixed-Dose, Phase 3, Randomized, Double-Blind, Placebo- and Active-Controlled Trial, Durgam et.al; Figure 1, page 5

6.56 A summary of the information available to inform the equi-effective doses of cariprazine and aripiprazole is presented in Table 13.

**Table 13: Possible dose relativities for cariprazine and aripiprazole**

Possible Relativity	Source	Issues
3.55 mg cariprazine = 19.06 mg aripiprazole (1 mg cariprazine = 5.37 mg aripiprazole)	Submission based on comparison of in-market data.	Level 4 evidence. Decouples statement of therapeutic relativity from dose. Unclear applicability of German prescribing practices to Australia Potential dilution of in-market dose by use in other indications.
3 mg cariprazine = 10 mg aripiprazole (1 mg cariprazine = 3.33 mg aripiprazole)	Implied based on trial RGH-MD-04, CSR Figure 11.4.1.1-1	Level 2 evidence. Trial not powdered for comparison of drugs. Aripiprazole dose fixed at starting dose, cariprazine dose is at second step in titration.
6 mg cariprazine = 10 mg aripiprazole (1 mg cariprazine = 1.67 mg aripiprazole)	Implied based on trial RGH-MD-04, CSR Figure 11.4.1.1-1	Level 2 evidence. Trial not powdered for comparison of drugs. Aripiprazole dose fixed at starting dose, cariprazine dose is at maximum dose.
1.5 mg cariprazine = 10 mg aripiprazole (1 mg cariprazine = 6.67 mg aripiprazole)	Theoretical comparison of starting doses.	No comparative evidence provided.
6 mg cariprazine = 30 mg aripiprazole (1 mg cariprazine = 5 mg aripiprazole)	Theoretical comparison of maximum doses.	No comparative evidence provided.
3 mg cariprazine = 15 mg aripiprazole (1 mg cariprazine = 5 mg aripiprazole)	Theoretical comparison of DDD.	No comparative evidence provided.

Source: Compiled during preparation of the ESC Advice.

<sup>b</sup>DDD = defined daily dose

6.57 The pre-PBAC response considered the equi-effective doses estimates in the submission (3.55 mg/day cariprazine and 19.06 mg/day aripiprazole) were supported by:

- The weighted average doses across the treatment arms that fell within recommended ranges and were included in the meta-analyses and indirect comparisons. These were stated to be 3.90 mg of cariprazine and 18.54 mg of aripiprazole.
- An indirect comparisons of the cariprazine RGH-MD-04 trial versus the aripiprazole McEvoy 2007 trial using aripiprazole 10 mg as a common arm. The pre-PBAC response stated that the results support non-inferior efficacy of cariprazine 3 mg/day compared to aripiprazole 15 mg/day, as the 95% CI excluded the MCID of 7 points in the PANSS total score in favour of aripiprazole. The PBAC noted that in McEvoy 2007 a larger numerical difference in PANSS total score from baseline to week 6 was reported for the 10 mg/day group compared with the 15 mg/day group (-15.04 and -11.73, respectively), and thus the presented indirect comparison also potentially supports equi-effective dose of 3 mg/day cariprazine and 10 mg/day aripiprazole.

- 6.58 The PBAC noted the flat dose response for aripiprazole made estimating the equi-effective doses for cariprazine and aripiprazole from the available evidence difficult. The PBAC recalled when recommending the listing of brexpiprazole, that equi-effective doses were determined for brexpiprazole and lurasidone, the nominated secondary comparator, rather than for brexpiprazole and aripiprazole, the nominated primary comparator. The PBAC further recalled the equi-effective doses were based on doses used in long-term maintenance trials (Brexpiprazole PSD, PBAC March 2017, paragraph 6.33). Thus, the PBAC considered it appropriate for equi-effective doses for cariprazine and brexpiprazole to be determined based on doses used in long-term maintenance trials.
- 6.59 The PBAC noted the brexpiprazole maintenance trial included in this submission was the same trial as included in the March 2017 brexpiprazole submission (EQUATOR/331-10-232). Thus, the PBAC considered the dose of brexpiprazole should be 3.58 mg/day.
- 6.60 The PBAC noted in the cariprazine maintenance trial (RGH-MD-6) the dose for the long term maintenance period was determined during the 8 week flexible dose run-in period. The PBAC noted the average dose in this trial (6.39 mg/day) exceeded the maximum recommended dose (6 mg/day) with more than half of the patients (54.8%) treated with a dose of 9 mg/day.
- 6.61 The PBAC noted 2 additional open-label flexible dose cariprazine trials were included in the submission. Trial RGH-MD-11 was a 53 week open label flexible dose study that enrolled either new patients or patients who completed one of the lead-in studies: RGH-MD-04 or RGH-MD-05. The cariprazine average daily dose was 5.66 mg. The PBAC acknowledged the submission's arguments that the steady-state dose was potentially overestimated due to (i) permitting dose of 3, 6 and 9 mg/day but not 1.5 and 4.5 mg/day and (ii) including the 9 mg/day dose which is greater than the maximum recommended dose. In this trial, 28.7% of patients were treated with the 9 mg/day dose. Assuming these patients were treated with a dose of 6 mg/day, the average daily dose would be 5.35 mg.
- 6.62 Trial RGH-MD-17 was a 53 week open-label, flexible dose safety and tolerability extension study for outpatients who had completed study RGH-MD-16. The final average daily dose was 3.97 mg. The PBAC considered that the steady-state dose was potentially underestimated as patients were not permitted to up-titrate to 6 mg/day. Further, almost 70% of patients were treated with 4.5 mg/day, the maximum dose permitted in the trial, and it is likely that a proportion of these patients would have up-titrated to a dose of 6 mg/day if allowed. If all patients treated with a dose of 4.5 mg/day were titrated up to 6 mg/day, the average daily dose would have been approximately 5 mg.
- 6.63 Overall, the PBAC considered based on Trial RGH-MD-11 and Trial RGH-MD-17 the cariprazine average daily dose is likely to be greater than 3.97 mg but less than 5.35 mg. The PBAC considered the revised estimated dose from Trial RGH-MD-17 (5

mg/day) to be reasonable for determining the equi-effective dose. The PBAC therefore considered it reasonable for the cost-minimisation analysis to be based on equi-effective doses of 5 mg/day cariprazine and 3.58 mg/day brexpiprazole.

- 6.64 The submission did not include additional costs and/or cost offsets as part of the CMA on the basis that there were no differences in the prescribing, administration or safety profiles of cariprazine and its main comparators that would be expected to result in differential costs of administration, monitoring or managing AEs respectively. The ESC considered the submission's approach was reasonable.
- 6.65 The submission cost-minimised cariprazine to aripiprazole due to its lowest cost and in accordance with Section 101(3B) of the National Health Act. The pricing of aripiprazole used in the CMA was calculated using the AEMP of the aripiprazole dose strength (20 mg = \$ [REDACTED]) closest to the estimated equi-effective dose for aripiprazole (19.06 mg): \$ [REDACTED] (DPMQ = \$ [REDACTED]). The PSCR noted that the aripiprazole price per mg decreases with increasing strength (\$ [REDACTED], \$ [REDACTED], \$ [REDACTED] and \$ [REDACTED] for aripiprazole 10, 15, 20 and 30 mg strengths, respectively) and that use of the price per mg for the 20 mg strength is a more conservative assumption than applying the weighted average price per mg, since there is higher utilisation of the lower strengths of aripiprazole.
- 6.66 Based on the equi-effective doses of cariprazine 3.55 mg = aripiprazole 19.06 mg as proposed in the submission, the submission estimated a cost of \$ [REDACTED] (AEMP) and \$ [REDACTED] (DPMQ). Applying that cost, the submission calculated the cost-minimised pricing for each strength of cariprazine, with the distribution of prices across the four strengths of cariprazine capsules being arbitrary.
- 6.67 The price of cariprazine as estimated by the submission is presented alongside the price comparison of the five atypical antipsychotics considered non-inferior by the PBAC (Table 14) using the same approach used in Table 1 of the Brexpiprazole PSD, March 2017. Based on the equi-effective doses proposed in the submission, cariprazine appears to be the least expensive amongst these six drugs based on their equi-effective dose to olanzapine. This approach assumed a proportional price to that of the AEMP corresponding to the antipsychotic strength that was closest to the equi-effective dose (equivalent to 15.032 mg olanzapine; price (AEMP) for 30 days = \$21.84), as per the Therapeutic Relativity Sheet. Olanzapine was not included in the price comparison of atypical antipsychotics because the PBAC has previously considered olanzapine as not an appropriate alternative therapy due to its inferior safety profile compared to the drugs in the group (Brexpiprazole PSD, PBAC March 2017, paragraph 5.10).

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**Table 14: Price comparison of atypical antipsychotics considered non-inferior by the PBAC and Cariprazine**

Drug	Aripiprazole	Brexpiprazole	Lurasidone	Paliperidone	Ziprasidone	Cariprazine <sup>1</sup>
ATC Group	NO5AX	NO5AX	NO5AE	NO5AX	NO5AE	NO5AX
Basis of recommendation	Cost-minimised to olanzapine	Cost-minimised to lurasidone	Cost-minimised to ziprasidone	Cost-minimised to olanzapine	Cost-minimised to olanzapine	Cost-minimised to aripiprazole
EED vs olanzapine <sup>2</sup>	21.3 mg	Indirect 4.00 mg <sup>3</sup>	Indirect 88.17 mg <sup>4</sup>	11.4 mg	125.75 mg	3.97 mg <sup>5</sup>
AEMP June 2020 Closest dose to EED	\$111.49 for 20 mg, 30	\$122.10 for 4 mg, 30	\$123.94 for 80 mg, 30	\$160.31 for 9 mg, 28	\$124.20 per 60 mg, 60	\$ [REDACTED] per 4.5 mg, 30
AEMP for EED for 30 days <sup>6</sup>	\$118.74	\$122.10	\$136.33 (\$136.60) <sup>7</sup>	\$217.56	\$130.15	\$ [REDACTED]

Abbreviations: EED = equi-effective dose; AEMP = approved ex-manufacturer price; mg = milligram

Source: Table 3.4.2, p178 of the submission.

Note: 1 Estimates for cariprazine was calculated during the evaluation

2 Per Therapeutic Relativity Sheet, equivalent to olanzapine 15.032 mg.

3 Based on equi-effective doses of 3.58 mg brexpiprazole and 78.9 mg lurasidone.

4 Based on equi-effective doses of 80 mg lurasidone and 114.1 mg ziprasidone. Table 1 in the Brexpiprazole PSD, March 2017 dose rounds this number down to 88 mg.

5 Based on equi-effective doses of 19.06 mg aripiprazole and 3.55 mg cariprazine

6 Calculated as proportional to the AEMP of the dose closest to the EED, with the exception of brexpiprazole, which has flat pricing and was therefore assumed to have the same price as all other strengths.

7 Calculated during the evaluation using 88.17 mg as presented by the submission.

### Drug cost/patient/month

6.68 The cost per patient per month based on the equi-effective doses proposed in the submission is presented in Table 16. There are differences in the mean dose for the CMA and financial estimates for each drug, which can be attributed to the differences in the source of data upon which the mean doses were derived (see notes to Table 15).

**Table 15: Drug cost per patient for the proposed drug (cariprazine) and comparator drug (aripiprazole)**

	Cariprazine		Aripiprazole	
	CMA	Financial estimates	CMA	Financial estimates
Mean dose	3.55 mg/day <sup>a</sup>	2.87 mg/day <sup>b</sup>	19.06 mg/day <sup>a</sup>	15.68 mg/day <sup>b</sup>
Cost/patient/month	\$ [REDACTED] <sup>c</sup>	\$ [REDACTED] <sup>d</sup>	\$ [REDACTED] <sup>f</sup>	\$ [REDACTED] <sup>g</sup>

Abbreviations: CMA = cost-minimisation analysis; mg = milligram.

Source: Table 4.2.9, p187; Excel file 'Cariprazine UCM', worksheet '4a.Scripts – affected'; Excel file 'Economic model workbook' sheets 'Aripiprazole utilization', 'Cariprazine utilization' of the submission.

Note: \* estimated during the evaluation.

<sup>a</sup>Equi-effective dose of drugs presented in the submission

<sup>b</sup> Calculated as the weighted mean dose of drug using the dose strength presented in the submission and the proportion of use of drug in Year 1, 2021.

<sup>c</sup> Price per equi-effective dose of drug presented by the submission

<sup>d</sup> Calculated as the average weighted price of drug using the price per dose strength and proportion of use of drug in Year 1, 2021

### Estimated PBS usage & financial implications

6.69 This submission was not considered by DUSC.

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6.70 The submission used a market share approach to estimate the market size and financial implications of listing cariprazine on the PBS. This approach was reasonable. A summary of key inputs used in the financial estimates is provided in Table 16.

**Table 16: Key inputs for financial estimates**

Parameter	Value applied	Source	Comment
<b>Eligible population</b>			
Relative proportion of aripiprazole and brexpiprazole dispensed in 2019 for patients initiating a new treatment or switching from one atypical antipsychotic to another.	Aripiprazole = 76% Brexpiprazole = 24%	Analyses of 10% PBS sample	Estimates were appropriately derived from the proportion of atypical antipsychotic schizophrenia treatment starts for naïve initiations, switches and delayed switches for aripiprazole and brexpiprazole.
<b>Treatment utilisation</b>			
Uptake rate	Year 1: 220% Year 2: 110% Year 3: 110% Year 4: 110% Year 5: 110%	Observed and projected uptake of brexpiprazole in the first five years after PBS listing. The submission assumed the uptake rate for brexpiprazole, plus 10% additional uptake by reasoning that cariprazine has efficacy for negative symptoms, would apply.	The PBAC noted that no justification was provided for the numerical value 10% as the additional uptake for cariprazine. It appears that the submission has doubled the uptake rate for cariprazine in Year 1.
Proportion of cariprazine scripts replacing oral aripiprazole and brexpiprazole	Oral aripiprazole: 58.1% each year Brexpiprazole: 41.9% each year	PBS utilisation data for patients initiating a new treatment or switching from one atypical antipsychotic to another for aripiprazole and brexpiprazole.	It is likely that the listing of cariprazine will not only result in replacement of aripiprazole and brexpiprazole but also their displacement to a later line.
Scripts dispensed	Year 1: [REDACTED] <sup>1</sup> Year 2: [REDACTED] <sup>2</sup> Year 3: [REDACTED] <sup>3</sup> Year 4: [REDACTED] <sup>4</sup> Year 5: [REDACTED]	This was calculated as a product of the number of brexpiprazole scripts dispensed and projected to be dispensed in the first five years after listing and the estimated uptake rate of cariprazine.	This was appropriate.
<b>Costs</b>			
Cariprazine (DPMQ)	1.5 mg = \$ [REDACTED] 3 mg = \$ [REDACTED] 4.5 mg = \$ [REDACTED] 6 mg = \$ [REDACTED]	Requested price was estimated by cost-minimising cariprazine to aripiprazole.	The PBAC did not accept the equi-effective doses proposed in the submission.
Oral Aripiprazole (DPMQ)	10 mg = \$81.41 15 mg = \$110.50 20 mg = \$132.88 30 mg = \$160.40	8717T 8718W 8719X 8720Y	This was appropriate.
Brexpiprazole (DPMQ)	1 mg = \$144.86 2 mg = \$144.86 3 mg = \$144.86 4 mg = \$144.86	11189X 11188W 11190Y 11184P	This was appropriate.
Patient co-payment	PBS co-payment = \$13.82 RPBS co-payment = \$5.37	Weighted average of all PBS services. Weighted average of all RPBS services.	Estimates were appropriately sourced and calculated based on utilisation of aripiprazole.
MBS costs	None used	NA	This appears reasonable as the submission claimed no additional

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Parameter	Value applied	Source	Comment
			MBS services would be required because cariprazine has a similar safety profile, as its main comparators, aripiprazole and brexpiprazole, and the frequency of consultation for cariprazine will remain the same as for aripiprazole and brexpiprazole.

Abbreviations: mg = milligram; NA = not applicable; PBS = Pharmaceutical Benefit Scheme; RPBS = Repatriation Schedule of Pharmaceutical Benefits.

Source: Table 3.4.1, p177; Table 3.4.4, p 179; Table 4.2.6, p186; text page 186 and Economic workbook 'Cariprazine UCM', worksheet '2d. Scripts – market' of the submission.

The redacted values correspond to the following ranges:

<sup>1</sup>500 to <5,000

<sup>2</sup>20,000 to <30,000

<sup>3</sup>40,000 to <50,000

<sup>4</sup>50,000 to <60,000

<sup>5</sup>70,000 to <80,000

6.71 The submission provided detailed information in applying the market share approach. The Commentary noted the following issues of concern with the steps taken by the submission in applying the market share approach:

- The submission claimed that cariprazine would primarily replace its closest pharmacological analogues, aripiprazole and brexpiprazole. The submission examined the impact of potential replacement of the five non-inferior drugs as previously considered by the PBAC (aripiprazole, brexpiprazole, lurasidone, paliperidone and ziprasidone) in sensitivity analyses (Table 18). The submission's assumption that substitution would result in only replacement of cariprazine for its pharmacological analogues may not be appropriate. It is likely that it will also result in displacement of these treatments (and possibly lurasidone, paliperidone and ziprasidone) to later line use.
- The submission estimated the future market size of cariprazine based on the projected rate of growth and number of scripts of oral aripiprazole and brexpiprazole over the six years following PBS listing. The approach taken by the submission to calculate the projected growth of the comparators appeared reasonable; however, since prescription data are available from 2017, it would have been more appropriate for the submission to estimate the linear projections of brexpiprazole using the same approach as for aripiprazole, based on data from 2017 to 2019, for consistency. The PBAC considered that by using monthly data from 2019, when the utilisation and growth rate of brexpiprazole had increased, the submission may have overestimated the projections for 2020 to 2025.
- The market share of cariprazine was estimated using brexpiprazole. The PBAC noted the submission claimed cariprazine uptake would exceed brexpiprazole by 10% (no justification was provided for this assumption) because of its

proven efficacy in treatment of negative symptoms. The submission further assumed that cariprazine would be listed in July 2021 relative to brexpiprazole that was listed in October, thus the relative uptake for the first year for cariprazine is doubled to correspond to two quarters. Despite the PBAC Guidelines v5.0 stating that sponsors should present a full six years of financial data, the submission presented data for Year 1 that was not based on a full 12 months but reflected part of a calendar year. The submission also doubled its assumed 10% additional uptake of brexpiprazole for Year 1 (Table 16). Based on the justification provided by the submission and the additional 10% uptake applied for Year 2 to Year 5, it is expected that correspondingly, there will be an additional 10% uptake in Year 1 and not 20% additional uptake. Assuming 10% additional uptake in Year 1 will result in 500 to <5,000 cariprazine scripts compared to the estimated 500 to <5,000 scripts.

- The submission assumed substitution of each strength of the comparator by the most likely strength of cariprazine based on similarity to the cariprazine dose equivalent (based on the equi-effective doses). The submission further assumed that substitution for brexpiprazole 2 mg, which represents approximately 40% of brexpiprazole utilisation, is split between the 1.5 mg and 3 mg strengths of cariprazine based on the differences in the specific dosing and manner of administration recommendations for brexpiprazole compared to cariprazine. The split between the two cariprazine strengths, 1.5 mg and 3 mg, for brexpiprazole 2 mg was not consistent for all the years and the submission did not provide any justification for this. The submission varied this assumption in a sensitivity analysis (Table 17).
- The resulting numbers and proportions of each strength of cariprazine dispensed on the PBS/RPBS varied over the first five years of listing cariprazine. The average weighted price of cariprazine will change when the submission's estimated proportion of scripts used in Australia over the first five years of listing are applied as weights: \$ [REDACTED] (AEMP) in 2021 to \$ [REDACTED] (AEMP) in 2025.

6.72 The ESC noted that there was an increase in efficacy up to 6 mg of cariprazine, and that the recommended maximum dose is 6 mg due to increased AEs at higher doses. The ESC considered that if AEs are limited below 6 mg, it is possible that clinicians would attempt to achieve the optimum effect by using the maximum safe dose of 6 mg. This PBAC noted that this could lead to a higher cost to the Government than was estimated by the submission, as the submission assumed that the lower strengths would be used more than the higher strengths.

6.73 The pre-PBAC response disagreed with the ESC that clinicians would attempt to achieve the optimum effect by using the maximum safe dose of 6 mg, stating that the dosing recommendations are to use the lowest effective dose and real-world utilisation patterns shows limited use of the 6 mg dose.

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- 6.74 The ESC considered that cariprazine may have clinical benefits over aripiprazole and brexpiprazole, including a slightly favourable AE profile, which may lead to an increase in the market share, however the ESC acknowledged that this would be difficult to forecast.
- 6.75 A summary of the estimated use and financial implications for listing cariprazine on the PBS is presented in Table 17. The submission assumed that cariprazine would be listed in July 2021. The PBAC noted the submission presented information for part of the first year of listing (2021) that corresponds with information for only four full years of listing. The Commentary was not able to extend the submission's methods of calculating use in that fourth year to estimate use in years 5 and 6 due to the structure of the analysis in the Excel file 'Cariprazine UCM' presented by the submission.

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Table 17: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of scripts dispensed <sup>a</sup>	█ <sup>1</sup>	█ <sup>2</sup>	█ <sup>3</sup>	█ <sup>4</sup>	█ <sup>5</sup>	Not provided
<b>Estimated financial implications of cariprazine</b>						
Cost to PBS/RPBS less copayments	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>	Not provided
<b>Estimated financial implications for aripiprazole and brexpiprazole</b>						
Cost to PBS/RPBS less copayments	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	Not provided
<b>Net financial implications</b>						
Net cost to PBS/RPBS	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	Not provided
<b>Sensitivity analysis</b>						
Market share						
Low: 90% of brexpiprazole	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	Not provided
High: 130% of brexpiprazole	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	Not provided
Cariprazine substitution dose						
For doses where range is warranted: Equal distribution of lower and higher	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	Not provided
Lower dose selected	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	Not provided
Higher dose selected	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>	\$█ <sup>6</sup>	Not provided
Replacement of other atypical antipsychotics						
70% uptake from main comparators) 50% of lurasidone 80 mg replaced by cariprazine 4.5 mg	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	Not provided
25% of lurasidone 80 mg replaced by cariprazine 4.5 mg	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	Not provided
60% uptake from main comparators 50% of lurasidone 80 mg replaced by cariprazine 4.5 mg	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	Not provided
80% uptake from main comparators 50% of lurasidone 80 mg replaced by cariprazine 4.5 mg	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	Not provided
25% of lurasidone 80 mg replaced by cariprazine 4.5 mg	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	-\$█ <sup>6</sup>	Not provided

Abbreviations: mg = milligram; PBS = Pharmaceutical Benefit Scheme; RPBS = Repatriation Schedule of Pharmaceutical Benefits.

Source: Table 4.2.9, Table 4.2.13, Table 4.3.5, Table 4.4.1 and Table 4.6.3 of the submission.

<sup>a</sup> Assuming scripts per year as estimated by the submission.

The redacted values correspond to the following ranges:

<sup>1</sup>500 to <5,000

<sup>2</sup>20,000 to <30,000

<sup>3</sup>40,000 to <50,000

<sup>4</sup>50,000 to <60,000

<sup>5</sup>70,000 to <80,000

<sup>6</sup>\$0 to <\$10 million

- 6.76 The total cost to the PBS/RPBS of listing cariprazine was estimated to be net cost saving in Year 5, and a total of net cost saving in the first 5 years of listing. The submission noted that the listing of cariprazine would result in a cumulative reduction in expenditure of \$0 to <\$10M over the first five years of listing to the PBS/RPBS. This reduction arose mainly from cariprazine replacing brexpiprazole, which is more expensive. However, it relies on the assumption that cariprazine use replaces rather than displaces aripiprazole and brexpiprazole use; estimated reductions may not materialise to the extent that is presented, as there is likely to be use of these therapies as later line treatment.
- 6.77 The ESC noted that the PSCR maintained that cariprazine would replace rather than displace aripiprazole and brexpiprazole. The ESC considered that this was reasonable, as prescribers would be more likely to prescribe a drug with a different mechanism of action if cariprazine proved ineffective, rather than aripiprazole or brexpiprazole.
- 6.78 The submission stated that there would be no implications for the wider health budget, as the listing of cariprazine is not expected to be accompanied by any change in MBS services (including specialist consultation, which is expected to remain the same) or prescription processing. This appeared reasonable given that cariprazine and its main comparators, aripiprazole and brexpiprazole have the same mode of administration and similar safety profile.
- 6.79 The submission noted that uncertainty around the cariprazine substitution doses and different substitution proportions of the five drugs considered non-inferior by the PBAC has a relatively minor and minimal impact on the financial estimates respectively (Table 18).
- 6.80 The PBAC considered that the cost savings to the Government may not materialise if prescribers use the higher strengths of cariprazine rather than the lower strengths as predicted by the submission (as discussed in paragraph 6.60).

### **Quality Use of Medicines**

- 6.81 The submission acknowledged the occurrence of akathisia with cariprazine administration and the need to ensure quality use of medicines (QUM) thereof. The submission presented a summary of recommendations provided in both the proposed PI and consumer medicines information to address akathisia. The submission proposed prescriber education activities to support QUM for cariprazine.

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## 7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required (STREAMLINED) listing of cariprazine (Reagila®) for the treatment of schizophrenia. The PBAC considered that the claims of non-inferior effectiveness and safety to aripiprazole and brexpiprazole were reasonable. The PBAC considered for the purposes of Section 101(3B) of the *National Health Act 1953*, additional alternative therapies include paliperidone, ziprasidone and lurasidone. The PBAC's recommendation for listing was therefore, among other matters, based on its assessment that the cost of cariprazine should be no greater than the lowest price alternative therapy. The PBAC considered the cost-minimisation analysis should be based on the following equi-effective doses: cariprazine 5 mg per day and brexpiprazole 3.58 mg per day.
- 7.2 The PBAC considered that there was a low to moderate clinical need for cariprazine, noting that there are a number of alternative antipsychotics available on the PBS.
- 7.3 The PBAC accepted aripiprazole and brexpiprazole as appropriate comparators, and considered that paliperidone, ziprasidone and lurasidone were also relevant alternative therapies. The PBAC considered that olanzapine was not an appropriate alternative therapy due to its inferior safety profile. The PBAC also considered that second-generation antipsychotics (e.g. risperidone and quetiapine) were not appropriate alternative therapies.
- 7.4 The PBAC noted the primary evidence presented in the submission was a randomised placebo-controlled trial which included an aripiprazole arm as an active control (Study RGH-MD-04). The PBAC noted the trial was not powered for a direct comparison of cariprazine and aripiprazole, and the comparison was conducted post-hoc. The PBAC noted the reduction in PANSS total score at week 6 versus placebo was not statistically significantly different for the cariprazine 3 mg/day and aripiprazole 10mg/day treatment groups, or for the cariprazine 6mg/day and aripiprazole 10mg/day treatment groups.
- 7.5 The PBAC noted indirect treatment comparisons for cariprazine versus aripiprazole and cariprazine versus brexpiprazole, using placebo as the common comparator, were presented as supportive evidence. The PBAC noted both the primary and supportive comparisons were in the acute treatment setting. The PBAC further noted the indirect treatment comparisons were potentially impacted by transitivity issues across the studies. However, overall the PBAC was satisfied that cariprazine is non-inferior in terms of efficacy and safety compared to aripiprazole and brexpiprazole.
- 7.6 The PBAC noted the equi-effective doses assumed in the submission were based on German prescription data for cariprazine and Australian PBS prescription data for aripiprazole. The PBAC shared the ESC's concern about the methodology used by the submission to calculate the equi-effective doses, noting that using data from which dose, but not effect, is measured is the least preferred form of evidence according to the PBAC Guidelines v5.0. The PBAC further noted that the data used to infer the doses

was the number of prescriptions dispensed rather than steady state dosing for patients, and that different data sources were used for the cariprazine and aripiprazole doses. The PBAC considered the analysis presented in the submission was an unreliable basis for determining the equi-effective doses.

- 7.7 As outlined in paragraphs 6.58-6.63 above, the PBAC considered it would be reasonable for the cost-minimisation analysis to be based on equi-effective doses of 5 mg/day cariprazine and 3.58 mg/day brexpiprazole.
- 7.8 The PBAC considered for the purposes of Section 101(3B) of the *National Health Act 1953*, the alternative therapies were aripiprazole, brexpiprazole, paliperidone, ziprasidone and lurasidone, and recommended that the cost of cariprazine should be no greater than the lowest price alternative therapy.
- 7.9 The PBAC considered that there was uncertainty about the projected usage of cariprazine due to potentially overestimated prescription growth rates of brexpiprazole and uncertainty about the most commonly prescribed strength of cariprazine. Consistent with the cost-minimisation basis of the listing, the PBAC expected the listing of cariprazine to be approximately cost neutral.
- 7.10 The PBAC recommended that cariprazine should be treated as interchangeable on an individual patient basis with aripiprazole, brexpiprazole, paliperidone, lurasidone, ziprasidone.
- 7.11 The PBAC advised that cariprazine is suitable for prescribing by nurse practitioners in a shared care model.
- 7.12 The PBAC recommended that the Early Supply Rule should not apply.
- 7.13 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because cariprazine is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over aripiprazole and brexpiprazole, or not expected to address a high and urgent unmet clinical need given the presence of alternative therapies, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.
- 7.14 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## **8 Recommended listing**

- 8.1 Add new medicinal product:

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MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
CARIPRAZINE					
cariprazine 1.5 mg capsule, 30	NEW	1	30	5	Reagila
cariprazine 3 mg capsule, 30	NEW	1	30	5	Reagila
cariprazine 4.5 mg capsule, 30	NEW	1	30	5	Reagila
cariprazine 6 mg capsule, 30	NEW	1	30	5	Reagila
<b>Restriction Summary 4246 / Treatment of Concept: 4246</b>					
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)					
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners - SCM					
<b>Restriction type :</b> <input checked="" type="checkbox"/> Authority Required – Streamlined [4246]					
<b>Condition:</b> Schizophrenia					
<b>Indication:</b> Schizophrenia					
<b>Administrative Advice:</b> <b>Shared Care Model:</b> For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.					

***This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.***

## 9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## 10 Sponsor's Comment

The sponsor had no comment.