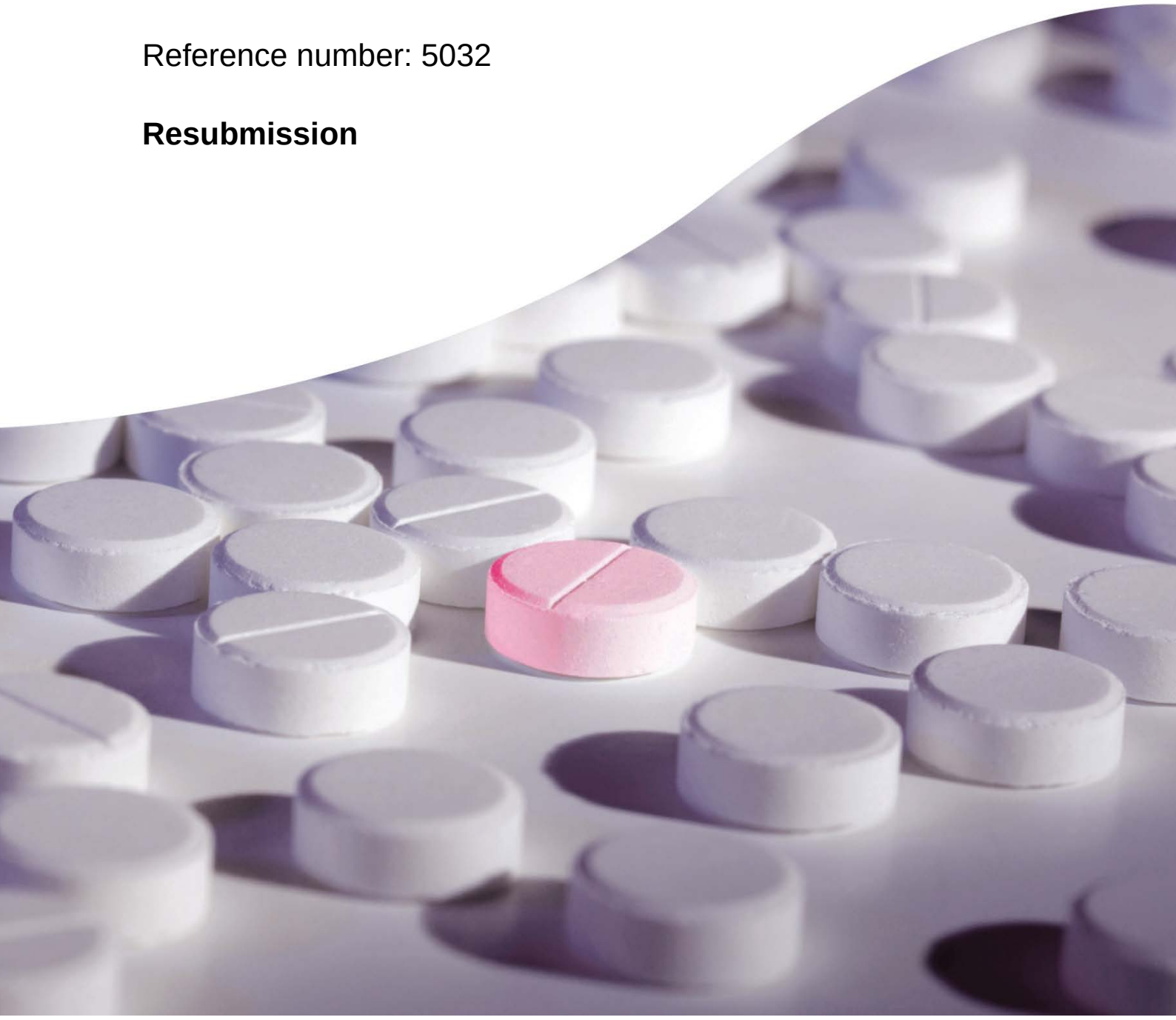
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG Secretariat Assessment Report

Cariprazine (Reagila®)
1.5 mg, 3 mg, 4.5 mg, 6 mg hard capsules

Reference number: 5032

Resubmission



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

Please direct any queries to AWTTC:

All Wales Therapeutics & Toxicology Centre (AWTTC)
The Routledge Academic Centre
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 218 26900

This report should be cited as:
All Wales Therapeutics & Toxicology Centre. AWMSG Secretariat Assessment Report. Cariprazine (Reagila®) 1.5 mg, 3 mg, 4.5 mg, 6 mg hard capsules. Reference number: 5032. March 2022.

This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

AWMSG Secretariat Assessment Report
Cariprazine (Reagila®▼) 1.5 mg, 3 mg, 4.5 mg, 6 mg hard capsules

1.0 Key facts

Assessment details	Resubmission of cariprazine (Reagila®▼) for the treatment of schizophrenia in adults. ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. The applicant company suggests that AWMSG considers cariprazine for use as a second-line therapy in people with schizophrenia where predominantly negative symptoms have been identified.
Current clinical practice	Schizophrenia in adults is usually treated with oral antipsychotic medicines and psychosocial interventions. The National Institute for Health and Care Excellence guideline on the management of schizophrenia in adults states that the choice of antipsychotic should be made by the service user and healthcare professional together. There is no standard treatment for negative symptoms of schizophrenia.
Clinical effectiveness	Results of two phase III studies, a phase IIb study and a 97-week phase III study showed that cariprazine improved symptoms of acute schizophrenia and increased the time to relapse compared with placebo. Results from a phase IIIb study comparing cariprazine and risperidone to treat predominant negative symptoms of schizophrenia showed that both agents improved negative symptoms, with a statistically significantly greater improvement seen with cariprazine.
Cost-effectiveness	A cost-utility analysis compares cariprazine with risperidone in the second-line treatment of predominant negative symptoms of schizophrenia in adults. The company base case suggests that cariprazine is [commercial in confidence figure removed] more costly and produces an additional [commercial in confidence figure removed] quality-adjusted life-years (QALYs) gained resulting in an incremental cost-effectiveness ratio (ICER) of [commercial in confidence figure removed].

	Based on sensitivity and scenario analyses provided by the company, AWTTC considers the most plausible ICER range to be between cariprazine being dominant and [commercial in confidence figure removed] per QALY gained. The cost-utility analysis uses risperidone as the only comparator. Considering that aripiprazole, olanzapine, quetiapine and amisulpride would also be used in routine practice, this will bias the results given that comparator treatment options are not identical.
Budget impact	The company estimates that 75 patients are eligible to receive treatment with cariprazine in Wales in Year 1, increasing to 231 patients in Year 5. The company base case suggests an additional cost of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. The base case also predicts NHS resource savings valued at [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. These result from reduced cost of hospitalisation and adverse events. Sensitivity analysis changing uptake rates by 20% resulted in cost differences between [commercial in confidence figures removed] in Year 1 and between [commercial in confidence figures removed] in Year 5. The budget impact analysis uses a different comparator to the cost-effectiveness analysis.
Additional factors to consider	Cariprazine (Reagila®) is approved for restricted use through national commissioning in Scotland and by local decision in England.

This assessment report is based on evidence submitted by Recordati Pharmaceuticals Ltd and an evidence search conducted by AWTTC on 13 December 2021[1].

2.0 Background

2.1 Condition and clinical practice

Schizophrenia is a severe, long-term, mental health condition that causes a range of different psychological symptoms[2]. The course of schizophrenia varies considerably[3]. Most people gradually recover from the first episode, but relapses are common[4]. Symptoms are usually categorised into three types: cognitive, such as problems with memory and attention; positive, such as delusions and hallucination; and negative, such as lack of drive and social withdrawal. Positive symptoms tend to ease with time, but negative symptoms may increase and become more severe. Negative symptoms can be either ‘secondary’ or ‘primary’. Secondary symptoms are thought to occur as a consequence of positive symptoms, depression or side effects of

antipsychotics. However, primary negative symptoms remain during periods of clinical stability (predominant negative symptoms). Up to one quarter of people with schizophrenia have outstanding and persistent primary negative symptoms, and up to two-thirds of people with chronic schizophrenia might experience negative symptoms at any given time. People with schizophrenia often have great difficulties in integrating in society and, for example, may not be able to continue with work or studies[4].

The National Institute for Health and Care Excellence (NICE) recommends offering oral antipsychotic medicines to treat schizophrenia[3]. The choice of antipsychotic medicine should be made by the person with schizophrenia and their healthcare professional together, taking the views of a carer, if the person agrees[3].

Despite the common use of continuing antipsychotic medication in clinical practice, relapse rates remain relatively high[5]. One third or more of people starting antipsychotic medication for the first time will have a relapse within the first year to 18 months, and around 80% within five years. Commonly accepted predictors of relapse include a greater severity of negative symptoms at baseline[5]. There is no standard treatment for negative symptoms of schizophrenia[4].

2.2 Medicine

Cariprazine (Reagila®) is an atypical oral antipsychotic that acts as a partial agonist of dopamine D2 and D3 receptors which is thought to be important in modulating mood and cognition[4,6]. It shows preferential binding to D3 receptors and partial agonist activity at serotonin 5-HT1A receptors[4,7]. The European Medicines Agency (EMA) approved cariprazine for the treatment of schizophrenia in adults in July 2017[4].

Cariprazine is taken once daily, at the same time each day[7]. The recommended starting dose is 1.5 mg; if needed, the dose can be increased slowly in 1.5 mg increments to a maximum dose of 6 mg/day[7]. Because of the long half-life of cariprazine and its active metabolites, changes in dose will not be fully reflected in plasma for several weeks. Patients should be monitored for adverse reactions and treatment response for several weeks after starting cariprazine and after each dosage change[7].

The All Wales Medicines Strategy Group (AWMSG) has previously appraised cariprazine for this indication and issued a non-recommendation in July 2020 because the case for clinical effectiveness and cost-effectiveness was not proven within the subpopulation highlighted by the company[8]. The company had focused its previous submission on a subpopulation of patients only.

In this resubmission the company has provided evidence for the whole licensed population as well as the subpopulation in which cariprazine may be particularly advantageous. The submitting company has suggested AWMSG consider cariprazine for use as a second-line therapy in adults with schizophrenia where predominant negative symptoms (PNS) have been identified[1]. This is in line with the recommendation from the Scottish Medicines Consortium, which restricted the use of cariprazine to second-line therapy in patients where predominantly negative symptoms have been identified as an important feature[9]. The company has also included real world outcome data[1].

2.3 Comparators

- The company has provided clinical and cost-effectiveness evidence for risperidone as the main comparator[1].

2.4 Guidance and related advice

- European Psychiatric Association (2021) EPA Guidance on treatment of negative symptoms in schizophrenia[10]
- The Maudsley Prescribing Guidelines in Psychiatry (2021)[11]
- British Association for Psychopharmacology (2020) Evidence-based guidelines for the pharmacological management of schizophrenia: updated recommendations[5]
- NICE (2014) Clinical guideline 178: Psychosis and schizophrenia in adults: prevention and management[3]
- Scottish Intercollegiate Guidelines Network (SIGN) (2013) Guideline 131: Management of schizophrenia[12]

AWMSG has previously recommended the use of the following medicines for the treatment, or maintenance treatment, of schizophrenia in adults: paliperidone palmitate (Xeplion®)[13]; quetiapine (Seroquel XL®)[14]; aripiprazole monohydrate (Abilify Maintena®)[15] and olanzapine (ZypAdhera®)[16]; and lurasidone (Latuda®) for use in adults and adolescents aged 13 years and older[17].

Brexpiprazole (Rexulti®) for the treatment of schizophrenia in adults is not recommended for use in Wales because of nonsubmission to AWMSG[18].

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, cariprazine (Reagila®) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

3.0 Clinical effectiveness

The company's submission includes a phase IIb study (RGH-MD-16) and two phase III studies (RGH-MD-04 and RGH-MD-05) of the efficacy and safety of cariprazine in the treatment of acute episodes of schizophrenia, as well as a long-term phase III relapse prevention study (RGH-MD-06)[1]. It also includes data from a phase IIIb study (RGH-188-005) that compares the efficacy and safety of cariprazine with risperidone in patients with schizophrenia and predominant negative symptoms (PNS). The company has included results of a literature search, which identified four meta-analyses of antipsychotics[1,] and data from a real-world study[1].

3.1 Studies RGH-MD-16, RGH-MD-04 and RGH-MD-05

Each of these three randomized, double-blind studies enrolled adult patients (aged 18–60 years) with schizophrenia diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR) criteria[19-21].

To be included in a study, patients had to have:

- had the diagnosis of schizophrenia for at least one year with a current exacerbation lasting under two weeks; and
- a record of at least one psychotic episode needing hospitalization or change of medication or treatment in the previous year[19-21].

In each study patients underwent a washout period of seven days, followed by six weeks of treatment and two weeks of safety follow-up[19-21]. Cariprazine was started at a dose of 1.5 mg/day and increased to reach the target dose by Day 2, 3 or 4. All studies measured the change from baseline to Week 6 in Positive and Negative Syndrome Scale (PANSS) as the primary efficacy endpoint. Change in Clinical Global Impression Severity (CGI-S) scale was a secondary endpoint[19-21].

Study RGH-MD-16 randomized patients to treatment with either placebo (n = 151); cariprazine 1.5 mg/day (n = 145); cariprazine 3.0 mg/day (n = 146); cariprazine 4.5 mg/day (n = 147); or risperidone 2.0 mg/day increased to 4.0 mg/day on Day 3 (n = 140)[20].

Study RGH-MD-04 randomized patients to treatment with either placebo (n = 153); cariprazine 3 mg/day (n = 155); cariprazine 6 mg/day (n = 157); or aripiprazole 10 mg/day (n = 152)[19].

Study RGH-MD-05 randomized patients to treatment with either placebo (n = 147); cariprazine 3–6 mg/day (n = 151); or cariprazine 6–9 mg/day (n = 148)[21].

Study completion was 64% of patients in study RGH-MD-16, 67% in study RGH-MD-04 and 58% in study RGH-MD-05. The main results are shown in Tables 1, 2 and 3. In all three studies, cariprazine significantly improved patients' symptoms of an acute exacerbation of schizophrenia. PANSS total score change from baseline to Week 6 was statistically significantly superior in all cariprazine treatment arms compared with placebo[19-21]. For all three studies, sensitivity analyses were performed and confirmed the robustness of the results[19-21].

Table 1. Main results of study RGH-MD-016[4]

	Cariprazine 1.5 mg (n=140)	Cariprazine 3 mg (n=140)	Cariprazine 4.5 mg (n=145)	Placebo (n=148)	Risperidone 4 mg (n=138)
Primary endpoint: PANSS-T change from baseline to Week 6 in ITT population					
Mean change (SE)	−17.3 (1.7)	−18.7 (1.8)	−20.2 (1.6)	−9.5 (1.6)	−25.3 (1.7)
LS mean treatment difference against placebo	−7.5	−8.8	−10.4		−15.0
95% CI	−11.8 to −3.3	−13.1 to −4.6	−14.6 to −6.2		−19.4 to −10.8
P value	0.0005	<0.0001	<0.0001		<0.0001
Secondary outcome: CGI-S change from baseline to Week 6 in ITT population					
Mean change (SE)	−0.9 (0.1)	−1.1 (0.1)	−1.2 (0.1)	−0.6 (0.1)	−1.4 (0.1)
LS mean treatment difference against placebo	−0.4	−0.5	−0.6		−0.8
95% CI	−0.6 to −0.1	−0.7 to −0.2	−0.9 to −0.4		−1.1 to −0.6
P value	0.004	0.003	<0.0001		<0.0001
CGI-S: Clinical Global Impression Severity scale; CI: confidence intervals; ITT: intention-to-treat; LS: least squares; PANSS-T: Positive and Negative Syndrome Scale - total score; SE: standard error					

Table 2. Main results of study RGH-MD-04[4,19]

	Cariprazine 3 mg (n=151)	Cariprazine 6 mg (n=154)	Placebo (n=149)	Aripiprazole 10 mg (n=150)
Primary endpoint: PANSS-T change from baseline to Week 6 in ITT population				
Mean change (SE)	−20.2 (1.5)	−23.0 (1.5)	−14.3 (1.5)	−21.2 (1.4)
LS mean treatment difference against placebo	−6.0	−8.8		−7.0
95% CI	−10.1 to −1.9	−12.9 to −4.7		−11.0 to −2.9
P value	0.0044	<0.0001		0.0008
Secondary endpoint: CGI-S change from baseline to Week 6 in ITT population				
Mean change (SE)	−1.4 (0.1)	−1.5 (0.1)	−1.0 (0.1)	−1.4 (0.1)

	Cariprazine 3 mg (n=151)	Cariprazine 6 mg (n=154)	Placebo (n=149)	Aripiprazole 10 mg (n=150)
LS mean treatment difference against placebo	−0.4	−0.5		−0.4
95% CI	−0.6 to −0.2	−0.7 to −0.3		−0.6 to −0.2
P value	0.0004	<0.0001		0.0001
CGI-S: Clinical Global Impression Severity scale; CI: confidence intervals; ITT: intention-to-treat; LS: least squares; PANSS-T: Positive and Negative Syndrome Scale - total score; SE: standard error				

Table 3. Main results of study RGH-MD-05[4,21]

	Cariprazine 3–6 mg (n=147)	Cariprazine 6–9 mg (n=147)	Placebo (n=145)
Primary endpoint: PANSS-T change from baseline to Week 6 in ITT population			
Mean change (SE)	−22.8 (1.6)	−25.9 (1.7)	−16.0 (1.6)
LS mean treatment difference against placebo	−6.8	−9.9	
95%CI	−11.3 to −2.4	−14.5 to −5.3	
P value	0.0029	<0.0001	
Secondary endpoint: CGI-S change from baseline to Week 6 in ITT population			
Mean change (SE)	−1.4 (0.1)	−1.6 (0.1)	−1.0 (0.1)
LS mean treatment difference against placebo	−0.3	−0.5	
95% CI	−0.6 to −0.1	−0.8 to −0.3	
P value	0.0115	<0.0001	
CGI-S: Clinical Global Impression Severity scale; CI: confidence intervals; ITT: intention-to-treat; LS: least squares; PANSS-T: Positive and Negative Syndrome Scale - total score; SE: standard error			

Post-hoc analyses of studies MD-16 and MD-04 were conducted in subgroups of acutely exacerbated patients in the intention-to-treat population who were identified with moderate-to-severe negative symptoms using PANSS-based criteria at baseline[22]. The analyses included 79 patients treated with placebo; 94 patients treated with cariprazine 1.5–3.0 mg/day; 66 patients treated with cariprazine 4.5–6.0 mg/day; and 44 patients treated with aripiprazole. Overall, results showed that treatment with cariprazine led to significantly greater improvements in negative symptoms in patients with acutely exacerbated schizophrenia compared with the placebo subgroups only[19,20,22]. In addition, higher cariprazine doses (4.5 mg/day to 6.0 mg/day) were significantly more effective than aripiprazole in improving negative symptoms[22].

3.2 Study RGH-MD-06

This 97-week double-blind study assessed the efficacy, safety and tolerability of long-term treatment with cariprazine for preventing symptomatic relapse in patients with schizophrenia[23]. Patients were enrolled if they had a diagnosis of schizophrenia for at least one year and a current psychotic episode lasting less than four weeks. After an open-label, run-in phase (8 weeks) and stabilization phase (12 weeks)

patients were randomized to receive either cariprazine (3 mg/day, 6 mg/day or 9 mg/day; n = 101) or placebo (n = 99) from Weeks 26 to 72[23].

Results showed that time to relapse was significantly longer for cariprazine-treated patients than placebo-treated patients[23]. Overall, relapse occurred in 24.8% of patients treated with cariprazine and 47.5% of patients treated with placebo[23].

A post-hoc analysis of this study evaluated whether cariprazine could maintain symptomatic remission (defined as scores of 3 or more on eight items from subscales of the PANSS)[24]. At randomization, 169 of 200 patients met symptomatic remission criteria. During double-blind treatment, 60.5% of patients treated with cariprazine sustained remission up until the final visit, compared with 34.9% of placebo-treated patients[24]. Cariprazine was associated with a statistically significant and clinically meaningful longer time to loss of sustained remission than placebo [24].

3.3 Study RGH-188-005

This double-blind, phase IIIb study evaluated the safety and efficacy of cariprazine compared with risperidone in the treatment of PNS in adults (aged 18–65 years) with long-term (> 2 years), stable schizophrenia diagnosed by DSM-IV-TR criteria and PNS for at least six months[25]. Presence of PNS was defined as: a Positive and Negative Syndrome Scale-factor score for negative symptoms (PANSS-FSNS) of 24 or more, and a score of four or more on at least three of the core negative PANSS items (blunted affect, passive or apathetic social withdrawal, lack of spontaneity, and flow of conversation). Patients were excluded if they had another DSM-IV-TR disorder or other condition that could have interfered with the study; if they had previously not responded to risperidone to treat a psychotic episode; or if they had taken risperidone within six weeks of screening[25].

The study had a four-week run-in period during which each patient's current antipsychotic treatment was down-titrated and then stopped[25]. This was followed by a 26-week treatment period, and a two-week safety follow-up period. Patients were randomly assigned to receive cariprazine (n = 230) or risperidone (n = 231). Cariprazine doses started at 1.5 mg/day increasing to a target dose of 4.5 mg/day from Day 14; risperidone doses started at 2 mg/day increasing to 4 mg/day at Day 14. During the 24-week continuation phase, the target dose was maintained except in cases of poor tolerability or impending psychotic deterioration, when the dose of cariprazine or risperidone could range from 3 mg to 6 mg daily[25].

The primary endpoint was change from baseline to Week 26 in the PANSS-FSNS conducted in the modified intention-to-treat (mITT) population which included all randomised patients who had at least one dose of study medicine and had at least one post-baseline PANSS-FSNS assessment[25]. Results showed that cariprazine treatment led to a greater least squares mean change from baseline to Week 26 in PANSS-FSNS compared with risperidone treatment (See Table 4). The corresponding effect size was 0.31.

There was also a statistically significant improvement in the key secondary outcome, Personal and Social Performance scale (PSP; Table 4)[25]. The PSP is an assessment of a patient's functioning in four main areas: socially useful activities, personal and social relationships, self-care, and disturbing and aggressive behaviours[26]. Additional efficacy measures assessed included: Clinical Global Impressions-Severity (CGI S), Clinical Global Impressions-Improvement (CGI-I) and PANSS negative subscale.

These supported the primary analysis which reported greater efficacy of cariprazine over risperidone[25].

Responder analysis demonstrated that a total of 157 cariprazine-treated patients (69.2%) achieved decreases of at least 20% in PANSS-FSNS compared with 133 risperidone-treated patients (58.1%; p = 0.002)[25]. Post-hoc analysis using at least 30% decrease also showed greater improvements for cariprazine (49.8%) than risperidone (36.2%; p = 0.003)[4].

Additional analyses showed small and non-significant changes for positive, depressive and extrapyramidal symptoms. This suggests an effect of cariprazine on primary negative symptoms.

Table 4: Primary and key secondary endpoints from Study RGH-188-005

	Cariprazine (n=227)	Risperidone (n=229)	LS mean difference, (95%CI); p value
Primary endpoint: change in PANSS-FSNS in mITT population			
Mean baseline PANSS-FSNS	27.7	27.5	
LS mean difference from baseline to week 26	−8.9	−7.4	−1.5 (−2.4, −0.5) p=0.002
Secondary outcome: change in PSP total score in mITT population			
Mean baseline PSP total score	48.8	48.1	
LS mean difference from baseline to week 26	14.3	9.7	4.6 (2.7, 6.6) p<0.0001
CI: confidence intervals; LS: least squares; mITT: modified intention-to-treat; PANSS-FSNS: Positive and Negative Syndrome Scale-factor score for negative symptoms; PSP: Personal and Social Performance. On the PANSS-FSNS, a higher score indicates worse severity; on the Personal and Social Performance scale, a higher score indicates better functioning.			

3.4 Meta-analyses

The company highlighted the results of three meta-analyses on the efficacy of antipsychotic medicines in treating schizophrenia[27-29]. Two meta-analyses in acute schizophrenia showed cariprazine was comparable to most other second-generation antipsychotics; with no significant differences among the different antipsychotic medicines used[27,28]. One meta-analysis focused on metabolic function in patients with schizophrenia and showed cariprazine to have little effect on weight[29].

There are no comparative data for cariprazine and other second-generation antipsychotics in patients with schizophrenia and PNS. The company highlighted a published pair-wise meta-analysis done within this subpopulation[30]. With regard to PNS amisulpride was significantly better than placebo, however amisulpride also showed significant improvement in depressive symptoms. In terms of direct comparisons between antipsychotics cariprazine was superior to risperidone and based on one small study (n = 35) olanzapine was significantly better than haloperidol. All of the included studies had limitations in study design and outcome measurement, such as using different tools to assess negative symptoms. Therefore,

it is difficult to compare cariprazine with other second-generation antipsychotic medicines for treating schizophrenia with PNS[30].

3.5 Comparative safety

Across all clinical studies the most frequent treatment-emergent adverse events included akathisia (14.8%) or extrapyramidal disorder (7.3%), headache (12.5%) and insomnia (13.9%). The most frequent serious adverse events and adverse events leading to premature discontinuation were: worsening of schizophrenia, psychotic symptoms followed by akathisia. Several adverse events, including akathisia or restlessness, creatine phosphokinase elevation, insomnia, anxiety and blurred vision were dose-dependent[4]. Most events were mild to moderate in severity[7].

In study RGH-MD-16, cariprazine showed a potentially more favourable weight gain profile than risperidone, and was not associated with an increase in prolactin levels[20]. More patients treated with cariprazine or risperidone had treatment-emergent EPS (parkinsonism) and akathisia than those patients treated with placebo; the cumulative incidence curve suggested that risperidone-treated patients experienced more EPS-related adverse events than patients treated with cariprazine[20].

In study RGH-MD-04, the only treatment-related adverse event that occurred at a rate of 5% or more was akathisia; the rate of akathisia in the cariprazine 6 mg treatment group was twice the rate seen in the placebo group[19]. Higher percentages of patients with a more than 7% change in their weight were seen in the cariprazine 3 mg (6%) and 6 mg (5%) and aripiprazole (6%) treatment groups compared with the placebo group (3%)[19].

In study RGH-188-005 the overall safety profiles for cariprazine and risperidone were similar, with comparable incidences of adverse events, treatment-related adverse events, serious adverse events and adverse events leading to discontinuation of treatment[25]. The most common adverse events in both treatment groups were insomnia, akathisia, schizophrenia, headache and anxiety[25].

The long-term safety profile of cariprazine in the 97-week study RGH-MD-06 was consistent with the safety profile seen in previous cariprazine studies[23]. In a 16-week observational study, the tolerability profile of cariprazine was similar to that seen in clinical studies; 12.9% of patients experienced akathisia, and 10.3% of patients experienced anxiety[31].

3.6 Real-world experience

A panel of clinicians and researchers from several countries in the EU met to discuss their real-world experience with cariprazine[32]. The panel members agreed that cariprazine had important clinical and pharmacological advantages over other antipsychotic medicines, mainly its superior efficacy in treating the negative symptoms of schizophrenia. The final panel recommendations were that cariprazine is ideal for the treatment of patients with a first episode of psychosis, those with predominant negative symptoms (maintenance or acute phase) or those who had significant side effects with other antipsychotic medicines [32].

A 16-week open-label, observational study was conducted in Latvia to evaluate the effectiveness and safety of cariprazine in 116 adults with schizophrenia and negative symptoms for whom treatment with other antipsychotics had not worked[31]. Around 83% of patients completed the study. Results showed improvement in schizophrenia

symptoms rated on a seven-point scale called the short assessment of negative domains (SAND). Change in symptom control from baseline to the end of the study was statistically significant (−7.3; $p < 0.001$), with the most improvement in negative symptoms (−6.3; $p < 0.001$). Treatment-emergent adverse events were experienced by 40% of patients[31].

3.7 AWTTC critique

- Cariprazine is licensed for the treatment of schizophrenia in adults[7].The short-term efficacy of cariprazine in acute exacerbation of schizophrenia was primarily measured as improvement in PANSS total score and supported by CGI-S scores for the dose range of 1.5–6 mg/day. Results were comparable to that of aripiprazole and slightly smaller than that of risperidone (both fixed-dose at lower therapeutic end, active controls)[19-21]. Maintenance of effect has been shown with relapse-prevention in study RGH-MD-06[4].
- The company has suggested AWMSG consider cariprazine for a subpopulation with predominantly negative symptoms. The EMA states that despite available treatments there is a substantial unmet medical need, especially for the treatment of negative symptoms and currently no standard treatment has been established[4].
- The key evidence for the subpopulation comes from study RGH-188-005 and the EMA stated in principle this was appropriately designed to demonstrate efficacy in patients with predominantly negative symptoms. The results showed improvement in negative symptoms of schizophrenia after 26 weeks of cariprazine treatment was statistically significantly greater than the improvement seen after 26 weeks of risperidone treatment ($p = 0.002$) [4]. The estimated mean differences did not reach the significant difference −2.25 that had been used in the sample size calculation; however, statistically significant results were achieved with a lower difference. This was further supported by the key secondary outcome (PSP) which showed statistically significant improved functionality in favour of cariprazine[25].
- The EMA stated that it was difficult to interpret the clinical relevance of the primary outcome (PANSS-FSNS) reported in study RGH-188-005. It is uncertain because there is no guidance or consensus to support a threshold for clinical relevance[4]. However, the results of the responder analysis and that of the post-hoc analysis (based on a decrease of at least 30%) support the clinical relevance of study RGH-188-005 and favour cariprazine treatment. Despite some limitations in study RGH-188-005, the EMA concluded an effect on negative symptoms had been demonstrated and these were relevant for the overall conclusion on clinical efficacy for cariprazine.
- In the absence of direct comparative evidence of cariprazine and treatment options other than risperidone the company highlighted meta-analyses to support the position outlined to them by clinical experts in Wales, that no single atypical is the preferred treatment option for patients with PNS. It is difficult to draw any conclusions from these analyses given the heterogeneity across the studies.
- AWTTC-sought clinical expert opinion confirms that there is no preferred treatment for patients with PNS in Wales. They anticipate cariprazine would be used as an option where negative symptoms predominate and other treatments have failed or as an additional choice for patients with metabolic risks who require an antipsychotic that does not worsen these physical risks.
- Cariprazine is available in NHS Scotland through national commissioning; it is recommended for restricted use as second-line therapy in patients where

predominantly negative symptoms have been identified as an important feature[9]. Cariprazine is also available to patients in England through local approval.

- The incidence of akathisia was higher for cariprazine compared with risperidone and aripiprazole in the studies[4]. The EMA suggested that this might affect adherence, but could likely be handled in clinical practice with anti-extrapyramidal symptoms medication[4]. Generally, the adverse events reported in cariprazine-treated patients were consistent with those reported after treatment with other approved second-generation antipsychotics[4].

4.0 Cost-effectiveness

4.1 Context

The company's submission includes a cost-utility analysis (CUA) comparing cariprazine oral hard capsules (1.5 mg, 3 mg, 4.5 mg and 6 mg once daily) with risperidone tablets (maximum of 16 mg daily), for the second-line treatment of patients with predominant negative symptoms (PNS) of schizophrenia[1].
The CUA is a Markov model, comprising one-week cycles in the first six weeks followed by 12-week cycles thereafter. The model adopts a 54-week time horizon and an NHS Wales/Personal and Social Services perspective. Costs and outcomes are discounted at a rate of 3.5% where the time horizon exceeds one year. The model was adapted from a previously published model [33], and is characterised by eight health states (plus death) based on aggregated thresholds of the negative, positive and cognitive factor scores of the Positive and Negative Symptom Scale (PANSS)[34]: mild symptoms, moderate symptoms (with negative or positive and negative symptom dominance), severe symptoms (with negative, negative and cognitive, positive and cognitive or positive symptom dominance) and extremely severe symptoms.

Patients enter the model aged 40 years (with 57.5% being male based on RGH-188-005) in either the "severe with negative symptom dominance" or the "severe with negative and cognitive symptom dominance" states, and receive either cariprazine or risperidone at flexible doses as part of up titration of dosage as observed in the pivotal study[25].

The transition probabilities between health states are derived from the RGH-188-005 clinical study[25]. Observed PANSS data were assigned to individual health states based on aggregated criteria described in literature[34]. Transition probabilities for the one-week cycles were based on the first four weeks of follow-up, whereas 12-week cycle probabilities were obtained from cases where the interval between two PANSS assessments was between 11 and 13 weeks. Transitions between some health states were not observed in the study and therefore not included in the model.

The model accounts for adverse events based on incidence in the RGH-188-005 clinical study, including dyskinesia, pseudo-Parkinsonism, akathisia, orthostatic hypotension, sedation and clinically significant weight gain[25]. Rates for both treatment arms are applied per cycle with ranges sampled from beta distributions informed by the study data.

Patients can switch to other second-generation antipsychotics due to intolerability, lack of efficacy or personal decision in both model arms. Discontinuation (switching)

rates were assumed to be equal across states and were taken from published evidence[35] for risperidone and also applied to cariprazine. Population mortality based on National Life Tables is included in the model but no adjustment for schizophrenia-related mortality was applied[36].

Treatment acquisition costs for cariprazine 4.5 mg once daily were supplied by the company. Comparator costs were based on the NHS drug tariff price for a 4 mg target dose of risperidone[37]. Following discontinuation of the initial treatment, costs of subsequent second-generation antipsychotics were based on a weighted average of the principal treatment options (including quetiapine, olanzapine, aripiprazole, amisulpride, lurasidone, clozapine, paliperidone and risperidone) as reported in prescribing data from NHS Wales Prescription cost analysis[38]. No administration costs were included as the medications are taken orally.

Healthcare resource use was obtained from a large multi-national (including UK) study reporting the naturalistic follow-up of patients with schizophrenia over two years[39]. Resource use estimates were applied to the model population using a two-part generalised linear mixed model fitted to gamma distributions to arrive at healthcare resource use per health state. Resource use considered in the model included: GP visits; psychiatrist, psychologist and other specialist visits; day clinics and inpatient days, costed using Personal Social Services Research Unit (PSSRU) unit costs[40]. Adverse event incidence was based on events in study RGH-188-005[24] with resource use taken from Nemeth et al. (2019)[33] and costed using published unit costs[40]. No residential care costs were included in the base case.

No utility data were collected in the pivotal study[25]. Utility values were assigned to PANSS health states using utilities generated by Lenert et al.[34], employing an online standard gamble approach with 620 members of the public. The mean utility rating for each state and the disutility for adverse events were estimated by re-weighting responses so that calculated mean values reflected the age and racial proportions of the 1998 United States census. Utility decrements for adverse events were obtained from published literature[34,41].

Deterministic and probabilistic sensitivity analyses were conducted to test the influence of the uncertainty of individual parameters on the model results. Scenario analysis explored the cost-differences between cariprazine and risperidone taking into account different time horizons, duration of treatment effect, hospitalisation costs, and cost of residential care.

4.2 Results

The results of the base case are detailed in Table 5. When compared with risperidone, cariprazine is [commercial in confidence figure removed] more costly and produces an additional [commercial in confidence figure removed] quality-adjusted life-years (QALYs). The slight cost differences and incremental QALY gains are predominantly driven by the higher acquisition costs of cariprazine, partially offset by fewer hospitalisations and higher likelihood of patients transitioning to or remaining in the health state of mild symptoms in the cariprazine arm.

Table 5. Results of the base case analysis

	Cariprazine	Risperidone	Difference
Medicine acquisition costs*	¶¶	¶¶	¶¶
Administration costs	¶¶	¶¶	¶¶
Healthcare costs (including hospitalisations and adverse events)	¶¶	¶¶	¶¶
Total costs	¶¶	¶¶	¶¶
Total life years	¶¶	¶¶	¶¶
Total QALYs	¶¶	¶¶	¶¶
ICER (£/QALY gained)	¶¶		

¶¶: commercial in confidence figure removed
*Acquisition costs include costs of cariprazine and risperidone as second-line treatments and costs of a basket of treatments in third-line upon discontinuation of second-line treatment.
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

In deterministic sensitivity analyses, the incremental cost-effectiveness ratio (ICER) for cariprazine ranged from dominant to [commercial in confidence figure removed], with assumptions around health state utilities and hospitalisation days (as the key cost driver) impacting most on cost-effectiveness results. The results of scenario analysis are assessed in order of plausibility in Table 6.

Probabilistic sensitivity analyses indicate that cariprazine has an 87% and 94% probability of being cost effective at willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained, respectively.

Table 6. Results of scenario analyses

Scenarios	ICER	Plausibility
Time horizon of 5 years	**£1,367**	This scenario is plausible considering that schizophrenia is a long-term condition.
Time horizon of 10 years	**£1,555**	This scenario is plausible considering that schizophrenia is a long-term condition.
Residential care costs included	**Cariprazine dominant**	This scenario is plausible considering that some patients especially in the more severe states will require residential care.
Hospitalisation costs reduced by 50% in all health states	¶¶	This scenario is less plausible than the base case which is based on data from a large multicentre observational study[39].
Hospitalisation costs reduced by 100% in all health states	¶¶	This scenario is less plausible than the base case which is based on data from a large multicentre observational study [39]. It is plausible and backed up by evidence to assume increased hospitalisation with increased symptom severity.
Adverse events excluded	**£1,993**	This scenario is implausible considering that cariprazine and risperidone do not have identical adverse event profiles.
All health state and adverse events costs removed	¶¶	It is implausible to assume that increased efficacy in negative symptom control would not affect healthcare resource use.
Excluding discontinuation due to lack of efficacy	¶¶	It is implausible to assume that patients would not discontinue treatment if it was not effective.
ICER: incremental cost-effectiveness ratio ¶¶: commercial in confidence figure removed		

4.3.AWTTC critique

The submission is characterised by strengths and limitations.

Strengths:

- The submission gives a detailed, transparent account of the methods and data sources used in the analysis.
- Reasonable justifications are provided for the assumptions applied in the model.
- The company has made an effort to use the best available data.

Limitations:

- The submission only includes a comparison with risperidone. The major comparator treatments that would be displaced in Wales include: risperidone, aripiprazole, olanzapine, quetiapine and amisulpride. The company states that no evidence exists for differences in outcomes between risperidone and other second-generation antipsychotics[27]. Thus, risperidone data are taken as representative for all available treatment options in Wales. No information is therefore available on the cost-effectiveness of cariprazine in relation to the other available comparators. Considering clinical practice in Wales and the

company's suggestion that olanzapine and quetiapine account for over 70% of total second-generation antipsychotics prescriptions in Wales, using risperidone as a single comparator will lead to bias since outcomes and costs of other treatment options cannot be assumed to be equivalent. However, the company states that olanzapine and quetiapine are more costly compared to risperidone which would increase cost-effectiveness of cariprazine. Furthermore, they suggest that neither olanzapine, risperidone, amisulpride nor clozapine have been demonstrated to be superior over the other three[30].

- The model includes eight health states (plus death) based on severity and dominance (negative, positive, cognitive) of symptoms. Transitions between these health states are based on data from the pivotal study[25]. However, not all transitions were observed during the study (for example, transitions to and from the extremely severe symptom state). Unobserved transitions were omitted in the model which could impact on the applicability of the results to routine clinical practice. The company's justification for this omission is that basing these transitions on clinical opinion would introduce too much bias.
- No utility data were collected in the pivotal study[25]. Utilities were therefore derived from a published study that assigned utility values to PANSS health states based on a standard gamble experiment including 620 members of the public which were re-weighted to represent the 1998 United States population[34]. While this appears to be the best available and most relevant utility data for the patient population and model, the lack of standardised, current UK-based, EQ-5D derived utilities will introduce bias of unknown proportion.
- The company calculates the cost of 28 days of once daily risperidone 4 mg tablets as £3.30 based on data extracted from the Welsh prescriptions database between August 2020 and July 2021. In comparison, the list price is £3.40 for 60 risperidone 4 mg tablets[42]. While this, in effect, overestimates the cost of risperidone, the impact on the ICER is small (£1,958 per QALY gained).
- Discontinuation and switching rates were taken from literature for risperidone[35] and assumed to be equal for cariprazine and across all health states. Considering that adverse event profiles for the two treatment options are not equal, this simplification will introduce bias.
- No disease-specific mortality was taken into account in the model. Considering that people with schizophrenia were reported to be two and a half times more likely to die prematurely compared with the general population[43], this may cause bias. However, the company argues that any impact of disease specific mortality over the short 54-week time horizon in the base case should be negligible.
- Considering the complexity of the disease and possible health states, simplifications and clustering had to be applied which required substantial data manipulation. While this was undertaken in the pursuit of the most relevant data, the amount of manipulation required may introduce bias and uncertainty.
- The pivotal study was conducted in 66 study centres in 11 European countries: Bulgaria, Croatia, Czech Republic, France, Hungary, Poland, Romania, Serbia, Spain, Russia and Ukraine[25]. No patients were recruited in the United Kingdom. Based on a cohort of 22,497 patients with schizophrenia[44], patient characteristics in the UK are similar to those in study RGH-188-005. However, depending on differences in healthcare systems and population, the results may not be generalisable to the Welsh population.

- The economic evaluation extrapolates the 24-week follow-up data to 54 weeks, assuming constant transition between states, which may introduce bias.
- Healthcare resource use data (including data on frequency of hospitalisations) were based on data collected between 1998 and 2002[39]. Therefore, the dated data source does not take into account changes in mental health care within the last 20 years and might not reflect current clinical practice and recommendations. The company argues that these are the only available data that report resource use data specifically for the eight Mohr-Lenert health states required for the model. Furthermore, the company states that the appropriateness of the data to the current healthcare context and the higher probability of hospitalisation in patients with PNS was confirmed by clinical experts and published evidence[45]. Considering that hospitalisation costs were identified as the key cost driver in the model, this could introduce considerable bias.

4.4 Review of published evidence on cost-effectiveness

A literature review conducted by AWTTC identified three economic evaluations comparing cariprazine to risperidone in the subpopulation of interest, of which one was a journal article[33] and two were conference abstracts with limited information available[46,47]. All of these have authors who are affiliated with the applicant company and relate to the same clinical study and Markov model as this submission. The CUAs reported in these papers focus on Hungary and Nordic countries, and report incremental QALY gains associated with the use of cariprazine compared to risperidone. These differ from the QALY gain reported in the company's submission, as a result of adopting different time horizons and different healthcare settings. The ICER in Hungary was €28,897 and €22,685 based on a 2-year and 5-year time horizon, respectively, due to higher cariprazine acquisition cost.

5.0 Budget impact

5.1 Context and methods

The company estimates an annual prevalence of schizophrenia in Wales of 25,855 people in Year 1, increasing to 26,318 in Year 5. This estimate is based on a prevalence of 1% reported in the EMA's European public assessment report[4], applied to the Welsh population and accounting for an annual population growth of 0.45% and the number of people reaching adulthood. Clinical expert opinion sought in Wales has suggested that prevalence is dependent upon genetics and social deprivation and may be up to 1.4%. The number of new people with schizophrenia is assumed to be 388 people in Year 1, increasing to 395 people in Year 5 based on an incidence rate of 15.2 in 100,000[48] applied to the Welsh population[49] and accounting for an annual population growth of 0.45%[49].

Taking into account prevalence, incidence and mortality[50], this results in 26,033 people with schizophrenia in Year 1, increasing to 26,499 in Year 5. Of these people, 100% are assumed to be treated with medication and 20% will have PNS of schizophrenia[51]. A discontinuation rate of 32.9% is taken into account and an uptake rate of 2.15% is assumed in Year 1, increasing to 6.5% in Year 5. This results in an estimated 75 people receiving cariprazine in Year 1, increasing to 231 people in Year 5. The annual cost of cariprazine is set to £1,048, with a yearly cost of existing

second-generation antipsychotics assumed as £102.91. The company performed basic sensitivity analysis altering uptake rates by 20%.

5.2 Results

The budget impact is presented in Table 7. The company estimates that introducing cariprazine would lead to an overall cost of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. This estimate incorporates cost differences resulting from the displacement of currently available second-generation antipsychotics. Sensitivity analysis changing uptake rates by 20% resulted in cost differences between [commercial in confidence figures removed] in Year 1 and between [commercial in confidence figures removed] in Year 5.

Table 7. Company-reported costs associated with use of cariprazine for the treatment of predominant negative symptoms of schizophrenia in adults

	Year 1	Year 2	Year 3	Year 4	Year 5
Subpopulation of eligible patients (indication under consideration)	5,207	5,230	5,253	5,276	5,300
Uptake of new medicine (%)	2.15%	2.80%	3.70%	4.90%	6.50%
Number of patients receiving new medicine allowing for discontinuations	75	98	130	173	231
Medicine acquisition costs in a market without new medicine	£375,063	£376,729	£378,402	£380,083	£381,771
Medicines acquisition costs in a market with new medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition cost	¶¶	¶¶	¶¶	¶¶	¶¶
Net supportive medicines costs	£0	£0	£0	£0	£0
Net medicine acquisition costs (savings/costs) - including supportive medicines where applicable	¶¶	¶¶	¶¶	¶¶	¶¶
¶¶: commercial in confidence figure removed					

The company estimated that net resource implications arising from the introduction of cariprazine will lead to a saving of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. This is a consequence of reduced hospitalisation and adverse events costs. These

resource-type savings are included for potential planning purposes but may not be realised in practice.

5.3 AWTTC critique

- The submission gives an account of the methods and data sources used to estimate budget impact. However, considerable uncertainty surrounding data inputs remains.
- The displaced medicine is a complex mixture of second-generation antipsychotics on the market with market shares, dosages and percentages of generic versus branded products assumed and estimated. This will introduce bias as the real cost of the displaced basket of medicines is unclear. Furthermore, this comparator is different to the comparator used in the pharmacoeconomic evaluation (risperidone only).
- In the absence of Welsh schizophrenia prevalence data, the number of eligible patients was extrapolated from English data[52]. It is uncertain how accurately this extrapolation reflects the situation in Wales.
- The annual incidence rate of 15.2 per 100,000 people is based on a systematic review which included publications from between 1965 and 2002[48]. The fact that these publications are dated and the central 80% of estimates varied over a fivefold range between 7.7 and 43.0 per 100,000 population could introduce considerable bias.

References

1. Recordati Pharmaceuticals Ltd Form B: Detailed appraisal submission. Cariprazine (Reagila®). Nov 2021.
2. NHS. Schizophrenia. Nov 2019. Available at: https://www.nhs.uk/conditions/schizophrenia/. Accessed Dec 2021.
3. National Institute for Health and Care Excellence. NICE Guideline. CG178. Psychosis and schizophrenia in adults: prevention and management. . Feb 2014. Available at: https://www.nice.org.uk/guidance/cg178. Accessed Dec 2021.
4. European Medicines Agency. Assessment Report: Reagila®. Procedure No.: EMEA/H/C/002770. Sep 2017. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/reagila. Accessed Dec 2021.
5. Barnes T, Drake R, Paton C et al. Evidence-based guidelines for the pharmacological treatment of schizophrenia: updated recommendations from the British Association for Psychopharmacology. *Journal of Psychopharmacology.* 2020;34(1):3-78.
6. Cho DI, Zheng M, and Kim KM. Current perspectives on the selective regulation of dopamine D_2 and D_3 receptors. *Archives of Pharmacal Research.* 2010;33(10):1521-1538.
7. Recordati Pharmaceuticals Limited. Reagila®. Summary of Product Characteristics. Aug 2018. Available at: https://www.medicines.org.uk/emc/product/9401/smpc. Accessed Dec 2021.
8. All Wales Medicines Strategy Group. Final Appraisal Recommendation - 0520. Cariprazine (Reagila®) 1.5 mg, 3 mg, 4.5 mg and 6 mg hard capsule. Jul 2020. Available at: https://awttc.nhs.wales/accessing-medicines/medicine-recommendations/cariprazine-reagila/. Accessed Jan 2022.
9. Scottish Medicines Consortium. SMC 2317. Cariprazine (Reagila®) 1.5 mg, 3 mg, 4.5 mg, 6 mg hard capsules. Apr 2019. Available at: https://www.scottishmedicines.org.uk/medicines-advice/cariprazine-reagila-full-submission-smc2137/. Accessed Dec 2021.
10. Galderisi S, Kaiser S, Bitter I et al. EPA guidance on treatment of negative symptoms in schizophrenia. *European Psychiatry.* 2021;61(1):1-15.
11. Taylor DM, Barnes TRE, and Young AH. The Maudsley Prescribing Guidelines in Psychiatry; 14th Edition. Jul 2021. Accessed Nov 2021.
12. Scottish Intercollegiate Guidelines Network. SIGN guideline . Management of schizophrenia. Mar 2013. Available at: https://www.sign.ac.uk/our-guidelines/management-of-schizophrenia/. Accessed Dec 2021.
13. All Wales Medicines Strategy Group. Final Appraisal Recommendation - 2512. Paliperidone palmitate (Xeplion®) 50 mg, 75 mg, 100 mg, 150 mg prolonged-release suspension for injection. Nov 2012. Available at: https://awmsg.nhs.wales/medicines-appraisals-and-guidance/medicines-appraisals/paliperidone-palmitate-xeplion/. Accessed Dec 2021.
14. All Wales Medicines Strategy Group. Final Appraisal Recommendation - 1509. Quetiapine (Seroquel XL®) prolonged-release tablet. Sep 2009. Available at: https://awmsg.nhs.wales/medicines-appraisals-and-guidance/medicines-appraisals/quetiapine-seroquel-xl/. Accessed Dec 2021.
15. All Wales Medicines Strategy Group. Final Appraisal Recommendation - 2214. Aripiprazole monohydrate (Abilify Maintena®) 400 mg powder and solvent for prolonged-release suspension for injection. Aug 2014. Available at:

https://awmsg.nhs.wales/medicines-appraisals-and-guidance/medicines-appraisals/aripiprazole-monohydrate-abilify-maintena/. Accessed Dec 2021.
16. All Wales Medicines Strategy Group. Final Appraisal Recommendation - 1516. Olanzapine (ZypAdhera®) 210 mg, 300 mg, 405 mg powder and solvent for prolonged-release suspension for injection. Jul 2017. Available at: https://awmsg.nhs.wales/medicines-appraisals-and-guidance/medicines-appraisals/olanzapine-zypadhera/. Accessed Dec 2021.
17. All Wales Medicines Strategy Group. Final Appraisal Recommendation - 0421. Lurasidone (Latuda®) 18.5 mg, 37 mg, 74 mg film-coated tablet. Mar 2015. Available at: https://awmsg.nhs.wales/medicines-appraisals-and-guidance/medicines-appraisals/lurasidone-latuda1/. Accessed Dec 2021.
18. All Wales Medicines Strategy Group. Statement of Advice. Brexpiprazole (Rexulti®) 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg film-coated tablet. Reference number: 1372. Dec 2018. Available at: http://www.awmsg.org/awmsgonline/app/appraisalinfo/1372. Accessed Jan 2022.
19. Durgam S, Cutler AJ, Lu K et al. Cariprazine in acute exacerbation of schizophrenia: a fixed-dose, phase 3, randomized, double-blind, placebo- and active-controlled trial. *Journal of Clinical Psychiatry.* 2015;76(12):1574-1582.
20. Durgam S, Starace A, Li D et al. An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophernia: a phase II, randomized clinical trial. *Schizophrenia Research.* 2014;152:450-457.
21. Kane JM, Zukin S, Wang Y et al. Efficacy and safety of cariprazine in acute exacerbation of schizophrenia. *Journal of Clinical Psychopharmacology.* 2015;35(4):367-373.
22. Earley W, Guo H, Daniel D et al. Efficacy of cariprazine on negative symptoms in patients with acute schizophrenia: a post hoc analysis of pooled data. *Schizophrenia Research.* 2019;204:282-288.
23. Durgam S, Earley W, Li R et al. Long-term cariprazine treatment for the prevention of relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled trial. *Schizophrenia Research.* 2016;176:264-271.
24. Correll CU, Potkin SG, Zhong Y 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. *Journal of Clinical Psychiatry.* 2019;80(2):18m12495.
25. Nemeth G, Laszlovszky I, Czobor P et al. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. *Lancet.* 2017;389:1103-1113.
26. Morosini PL, Magliano L, Brambilia L et al. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatrica Scandinavica.* 2000;101(4):323-329.
27. Leucht S, Arbter D, Engel RR et al. How effective are second-generation antipsychotic drugs? A meta-analysis of placebo-controlled trials. *Molecular Psychiatry.* 2009;14(4):429-447.
28. Huhn M, Nikolakopoulou A, Schneider-Thoma J et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: A systematic review and network meta-analysis. *Lancet.* 2019;394:939-951.
29. Pillinger T, McCutcheon RA, Vano L et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors

of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *The Lancet. Psychiatry.* 2020;7(1):64-77.
30. Krause M, Zhu Y, Huhn M et al. Antipsychotic drugs for patients with schizophrenia and predominant or prominent negative symptoms: a systematic review and meta-analysis. *European Archives of Psychiatry and Clinical Neuroscience* 2018;268(7):625-639.
31. Rancans E, Dombi ZB, Matrai P et al. The effectiveness and safety of cariprazine in schizophrenia patients with negative symptoms and insufficient effectiveness of previous antipsychotic therapy: an observational study. *International Clinical Psychopharmacology.* 2021;36(3):154-161.
32. Fagiolini A, Alcala JA, Aubel T et al. Treating schizophrenia with cariprazine: from clinical research to clinical practice. Real world experiences and recommendations from an International Panel. *Annals of General Psychiatry.* 2020;19(3):55.
33. Nemeth B, Bendes R, Nagy B et al. Cost-utility analysis of cariprazine compared to risperidone among patients with negative symptoms of schizophrenia. *Health Policy and Technology.* 2019;8(1):84-91.
34. Lenert LA, Sturley AP, Rapaport MH et al. Public preferences for health states with schizophrenia and a mapping function to estimate utilities from positive and negative symptom scale scores. *Schizophrenia Research.* 2004;71(1):155-165.
35. Lieberman JA, Stroup TS, McEvoy JP et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *The New England Journal of Medicine.* 2005;353(12):1209-1223.
36. Office for National Statistics. National life tables: Wales 2016-2018. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetableswalesreferencetables. Accessed Jan 2022.
37. NHS Business Services Authority. NHS electronic drug tariff 2019. Part VIII. . 2019. Available at: https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff/drug-tariff-part-viii. Accessed Jan 2022.
38. NHS Wales Shared Services Partnership. Primary care services prescription cost analysis. 2019. Available at: http://www.primarycareservices.wales.nhs.uk/prescription-cost-analysis. Accessed Jan 2022.
39. Millier A, Horvath M, Ma F et al. Healthcare resource use in schizophrenia, EuroSC findings. *Journal of Market Access and Health Policy.* 2017;5(1).
40. Personal Social Services Research Unit. Unit costs of health and social care, 2018. 2018. Available at: https://www.pssru.ac.uk/project-pages/unit-costs/. Accessed Jan 2022.
41. Millier A, Amri I, Boyer L et al. Utility decrements associated with side effects in schizophrenia. *Journal of Medical Economics.* 2014;17(12):853-861.
42. Monthly Index of Medical Specialities. Risperidone. 2022. Available at: http://www.mims.co.uk/. Accessed Jan 2022.
43. Laursen TM. Life expectancy among persons with schizophrenia or bipolar affective disorders. *Schizophrenia Research.* 2011;131(1-3):101-104.
44. Hayes JF, Marston L, Walters K et al. Mortality gap for people with bipolar disorder and schizophrenia: UK-based cohort study 2000-2014. *The British Journal of Psychiatry.* 2017;211(3):175-181.

45. Patel R, Jayatilleke N, Broadbent M et al. Negative symptoms in schizophrenia: a study in a large clinical sample of patients using a novel automated method. *BMJ Open.* 2015;5(9):e007619.
46. Nemeth B, Bendes R, Nagy B et al. Cost-utility analysis of cariprazine compared to risperidone among patients with negative symptoms of schizophrenia in selected Nordic countries. *Value in Health.* 2018;21(Suppl 3):S281.
47. Nemeth B, Bendes R, Nagy B et al. Cost-utility analysis of cariprazine compared to risperidone among patients with negative symptoms of schizophrenia in selected central and eastern European countries. *Value in Health.* 2018;21(Suppl 3):S281-282.
48. McGrath J, Saha S, Chant D et al. Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiologic Reviews.* 2008;30(1):67-76.
49. StatsWales. National level population estimates by year, age and UK country. Available at: https://statswales.gov.wales/Catalogue/Population-and-Migration/Population/Estimates/nationallevelpopulationestimates-by-year-age-ukcountry. Accessed Jan 2022.
50. Bushe CJ, Taylor M, and Haukka J. Mortality in schizophrenia: a measurable clinical endpoint. *Journal of Psychopharmacology.* 2010;24(11. Suppl. 4):17-25.
51. Kirkpatrick B, Fenton WS, Carpenter WC et al. The NIMH-MATRICS consensus statement on negative symptoms. *Schizophrenia Bulletin.* 2006;32(2):214-219.
52. McManus S, Bebbington P, Jenkins R et al. Mental health and wellbeing in England: Adult Psychiatric Morbidity Survey 2014. 2016. Available at: https://webarchive.nationalarchives.gov.uk/20180328140249/http://digital.nhs.uk/catalogue/PUB21748. Accessed Jan 2022.