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

Recordati Pharmaceuticals Ltd

5 April 2019

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

cariprazine (Reagila®) is accepted for restricted use within NHSScotland.

Indication under review: the treatment of schizophrenia in adult patients.

SMC restriction: for use as a second-line therapy in patients where predominantly negative symptoms have been identified as an important feature.

In patients with stable schizophrenia with predominantly negative symptoms, cariprazine improved negative symptoms more than another second-generation antipsychotic.

Chairman
Scottish Medicines Consortium

Indication

The treatment of schizophrenia in adult patients.¹

Dosing Information

Cariprazine is for oral use, to be taken once daily at the same time of the day with or without food. The recommended starting dose of cariprazine is 1.5mg once daily. Thereafter the dose can be increased slowly in 1.5mg increments to a maximum dose of 6mg/day, if needed. The lowest effective dose should be maintained according to the clinical judgement of the treating physician. Because of the long half-life of cariprazine and its active metabolites, changes in dose will not be fully reflected in plasma for several weeks. Patients should be monitored for adverse reactions and treatment response for several weeks after starting cariprazine and after each dosage change.¹

Product availability date

September 2018

Summary of evidence on comparative efficacy

Cariprazine is an atypical antipsychotic and a dopamine D3 and D2 receptor partial agonist with preferential binding to D3 receptors. The dopamine D3 receptor is considered to play an important role in modulating mood and cognition. In addition cariprazine has affinity for the serotonin 5-HT1A receptor which may contribute clinical benefit for the treatment of patients with predominant negative symptoms in schizophrenia.^{1,2} The submitting company has requested that SMC considers cariprazine when positioned for use as second-line therapy in patients with schizophrenia, where predominant negative symptoms (PNS) have been identified as an important feature.

The evidence to support the efficacy and safety of cariprazine in patients with schizophrenia with PNS comes from the RGH-188-005 study. This was a randomised, double-blind, phase IIIb study comparing the efficacy, safety and tolerability of cariprazine and risperidone in adults (aged 18 to 65 years) with schizophrenia and PNS.^{2,3} Eligible patients were required to have a diagnosis of schizophrenia (according to Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision [DSM-IV-TR] and confirmed by the Structured Clinical Interview for DSM-IV-TR, Clinical Trials Version) with onset ≥ 2 years before screening and have stable PNS for ≥ 6 months: this required no psychiatric hospital admissions, acute exacerbations or imprisonments. To be classed as having PNS patients required: a Positive and Negative Syndrome Scale-factor score for negative symptoms (PANSS-FSNS) ≥ 24 , this scale is based on items N1 (blunted affect), N2 (emotional withdrawal), N3 (poor rapport), N4 (passive or apathetic social withdrawal), N6 (lack of spontaneity and flow of conversation), G7 (motor retardation), and G16 (active social avoidance) of PANSS with each item on a scale of 1 to 7 (1 indicating absence of symptoms, 7 indicating severe symptoms); a score of ≥ 4 on at least two of three core negative PANSS items (blunted

affect, lack of spontaneity and flow of conversation, passive or apathetic social withdrawal) at screening and during the run-in period, and PANSS factor score for positive symptoms (PANSS-FSPS) ≤ 19 . Patients with other psychiatric, neurological or behavioural disorders that could have interfered with the study were excluded.^{2,3}

The study consisted of a 4-week run-in period, a 26-week double-blind treatment period (consisting of a 2-week study treatment up-titration phase and a 24-week study treatment continuation phase) and a 2-week safety follow-up period. Patients could continue with up to two anti-psychotic medicines at stable doses from screening throughout the 4-week run-in period but the dose(s) were reduced from day 0 to day 14 when they were discontinued (this could be extended by 14 days to reduce withdrawal effects and deterioration). Patients were randomised equally to once daily oral cariprazine (n=230) or risperidone (n=231) which were titrated to target doses of 4.5mg/day and 4mg/day respectively from day 14. From day 21 until the end of the double-blind treatment phase, the dose of cariprazine and risperidone could range from 3 to 6mg/day. During this period doses could be decreased or increased due to tolerability problems or condition deterioration, patients who had their dose modified could be changed back to the target dose.^{2,3}

The primary outcome was the change from baseline to week 26 or early termination 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. The primary analysis was performed using a mixed-effects model for repeated measures (MMRM) method for handling missing data.^{2,3} Cariprazine improved negative symptoms associated with schizophrenia by a statistically significant greater extent than risperidone. There was also a statistically significant improvement in the key secondary outcome, Personal and Social Performance (PSP) which provides important evidence of improved patient functioning and recovery. See detailed results in Table 1 below.^{2,3}

Table 1. Primary and key secondary outcome of the RGH-188-005 study at week 26 in the modified intention-to-treat population using a mixed-effects model for repeated measures.^{2,3}

	cariprazine (n=227)	risperidone (n=229)
Mean baseline PANSS-factor score for negative symptoms	27.7	27.5
Mean change from baseline to week 26, least squares mean	-8.9	-7.4
Mean difference, (95% CI), p-value	-1.5 (-2.4 to -0.5) p=0.002	
Mean baseline PSP total score	48.8	48.1
Mean change from baseline to week 26, least squares mean	14.3	9.7

Mean difference, (95% CI), p-value	4.6 (2.7 to 6.6) p<0.001
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PANSS=Positive and Negative Syndrome Scale, CI=confidence interval, PSP=Personal and Social Performance scale

Sensitivity analyses of the primary outcome using observed data and the last observation carried forward method for dealing with missing data were supportive of the primary analysis.³

Additional efficacy analysis of Clinical Global Impressions-Severity, Clinical Global Impressions-Improvement and PANSS negative subscale (this included items N1 [blunted affect], N2 [emotional withdrawal], N3 [poor rapport], N4 [passive or apathetic social withdrawal], N5 [difficulty in abstract thinking], N6 [lack of spontaneity and flow of conversation], and N7 [stereotyped thinking]) supported the primary analysis and reported favourable efficacy for cariprazine over risperidone.^{2,3} A responder analysis was conducted based on criteria requiring a decrease of at least 20% in PANSS FSNS. The results indicated an advantage for treatment with cariprazine over risperidone (69% versus 58%). A post hoc more stringent responder analysis based on a decrease of at least 30% also favoured treatment with cariprazine over risperidone (50% and 36%). The responder analyses provide support for the clinical relevance of the study result.^{3,4}

An additional analysis was performed to assess whether changes were specific to improvements in negative symptoms and not secondary to other improvements (pseudospecificity). This found that differences from baseline were small for changes in PANSS-FSPS, Calgary Depression Scale for Schizophrenia total score and Simpson-Angus Scale items 1 to 8 and were similar for both cariprazine and risperidone. These results indicate that improvements in negative symptoms were not secondary to improvements in other domains of schizophrenia (positive or depressive symptoms or extrapyramidal effects) supporting a primary effect on negative symptoms.^{2,3}

Exploratory post hoc analyses of two 6-week studies in patients with acute schizophrenia (MD-16 and MD-04) using small subgroups of patients with PNS found greater improvements in PANSS-FSNS with cariprazine compared with placebo.^{5,6}

A 97-week, phase III withdrawal study (MD-06) evaluated the efficacy, safety, and tolerability of cariprazine for relapse prevention in adults with schizophrenia. It included a 20-week open-label period, during which patients were treated with cariprazine 3 to 9mg/day. Stable patients were then randomised to continued cariprazine (3 to 9mg/day, n=101) or placebo (n=99) for up to 72 weeks in the double-blind treatment withdrawal phase. Time to relapse was significantly longer for patients randomised to cariprazine (median not reached) than for patients randomised to placebo (median 296 days), p=0.001. The relapse rates were 25% and 47% for patients treated with cariprazine and placebo respectively, hazard ratio 0.45 (95% confidence interval: 0.28 to 0.73).^{3,7,8} A post hoc analysis excluding patients receiving greater than the maximum licensed dose of cariprazine was consistent with the primary analysis. The European Medicines Agency (EMA) concluded this study did not provide evidence of efficacy on improving negative symptoms,³ but that it does support a maintenance of efficacy in relapse prevention over a longer term.

Summary of evidence on comparative safety

In general the adverse event (AE) profile of cariprazine is comparable to the AE profile of risperidone and other atypical antipsychotics.³ In study RGH-188-005, any AE related to study medicine was reported in 53% and 57% of patients in the cariprazine (n=230) and risperidone (n=230) groups respectively. Serious AEs were reported in 3% of patients in both treatment groups and 10% and 12% of patients in the cariprazine and risperidone groups discontinued treatment because of an AE.²

During the double-blind phase of the RGH-188-005 study, the most frequently reported AEs in the cariprazine (n=230) and risperidone (n=230) groups respectively were: extrapyramidal symptoms-related AEs (including akathisia and restlessness) (14% versus 13%), akathisia (8.3% versus 5.2%), insomnia (9.1% versus 10%), schizophrenia (includes schizophrenia aggravated, schizophrenia exacerbated, and schizophrenia relapse) (6.5% versus 4.3%), headache (5.7% versus 10%), anxiety (5.7% versus 4.8%), somnolence (3.9% versus 5.7%) and nausea (3.9% versus 2.6%).²

Treatment-emergent parkinsonism was assessed using the Simpson-Angus Scale (SAS). Patients were considered to have treatment-emergent parkinsonism if they had a SAS score ≤ 3 at baseline and >3 at any double-blind assessment; this was reported for 6.5% and 9.6% of patients treated with cariprazine and risperidone respectively.²

Summary of clinical effectiveness issues

Schizophrenia is a life-long condition with an aetiology thought to result from excessive dopaminergic activity. The condition is associated with three categories of symptoms: positive, including hallucinations and delusion; cognitive, including memory and attention problems; and negative, including demotivation, social withdrawal, inability to feel pleasure and blunted affect. Positive symptoms may improve over time, however negative symptoms may worsen and become more debilitating. Negative symptoms are strongly linked with long-term morbidity, poor psychosocial functioning, increased likelihood of unemployment and meaningful social and economic costs. Secondary negative symptoms may develop from depression, positive symptoms or side-effects of antipsychotic treatments. Patients with PNS may be difficult to treat and existing antipsychotics are limited in effectiveness.^{2, 3} Clinical guidance does not make specific antipsychotic treatment recommendations for the management of schizophrenia with PNS.^{9, 10} There is some evidence to support the modest efficacy of amisulpride, clozapine, olanzapine, and risperidone on negative symptoms.³ Amisulpride is the only antipsychotic with a licensed indication that specifically mentions PNS but patients with PNS are included in the broader licensed indication for cariprazine.³

The submitting company has requested that SMC considers cariprazine when positioned for use as second-line therapy in patients with schizophrenia, where PNS have been identified as an important feature.

In the key study RGH-188-005 patients with stable schizophrenia with PNS, there was a statistically significant greater improvement in negative symptoms from baseline to week 26 in the cariprazine group compared with the risperidone group. The key secondary outcome on Personal and Social Performance was statistically significant in favour of cariprazine and provides important evidence of improved patient functioning and recovery.^{2,3}

Despite the attrition rate being greater (23% versus 10% for cariprazine and risperidone respectively) and the treatment difference being less (1.5 versus 2.25) than was assumed for the sample size calculation, the result for the primary outcome was statistically significant.³ The clinical relevance of this result is uncertain as there is no guidance or consensus to support a threshold for clinical relevance.³ However, responder analyses based on 20% and 30% decreases in PANSS FSNS both favoured cariprazine over risperidone and are supportive.

The change from baseline in PANSS general psychopathology score in both the cariprazine and risperidone groups of study RGH-118-005 were not statistically significant, but were considered by the EMA to be numerically large enough to influence the overall assessment of negative symptoms and possibly contribute to pseudospecificity.³ Cognition impairment and anxiety were assessed using PANSS and not additionally assessed using specific rating tools which are more robust for these symptoms. The results of study RGH-188-005 may have been confounded by a lack of sensitivity for these symptoms.³ The study did not include patients with current psychiatric hospital admission which may limit the generalisability of the study results to these patients.

The dose of risperidone used in the RGH-188-005 did not reflect the upper end of the licensed dosing range. The target dose in the study was 4mg daily with a maximum of 6mg daily; the British National Formulary (BNF) and Summary of Product Characteristics advise that the usual dose is 4 to 6mg daily, however doses above 10mg daily should only be used if benefit is considered to outweigh risk and the maximum recommended dose is 16mg daily.^{11, 12}

There are no comparative data for cariprazine with other antipsychotics in patients with schizophrenia and PNS. The submitting company highlighted a published pair-wise meta-analysis in patients with schizophrenia and PNS.¹³ The meta-analysis included 9 studies (n=2,115 patients) of 6 to 26 weeks in duration, and the primary outcome was change from baseline in negative symptoms of schizophrenia based on validated assessment tools such as PANSS-negative subscale, the Scale for the Assessment of Negative Symptoms (SANS), and the Brief Negative Symptom Scale (BNSS). Secondary outcomes (change from baseline in depressive and positive symptoms) assessed the potential for pseudospecificity. Amisulpride was superior to placebo for the primary outcome (based on 4 studies, n=590 patients) but was also superior for depressive symptoms indicating a lack of specificity for negative symptoms. Olanzapine was superior to haloperidol (based on 1 study, n=35 patients), and cariprazine was superior to risperidone (based on 1 study,

RGH-188-005, n=456 patients) for the primary outcome with no evidence of a difference for depressive symptoms or positive symptoms in either study. For the comparisons of placebo with olanzapine (1 study, n=104 patients), and amisulpride with olanzapine (1 study, n=140 patients) there was no evidence of a difference between study treatments for negative, depressive or positive symptoms. The results are limited by heterogeneity in defining schizophrenia with PNS, study duration, populations and instruments used to assess negative symptoms.¹³ In patients with schizophrenia with PNS definite conclusions cannot be made on the relative efficacy of cariprazine to other second generation antipsychotics such as amisulpride and olanzapine.

The availability of cariprazine would provide a treatment option for the management of schizophrenia in patients with PNS, an area where there is a current lack of available evidence to support treatment choice.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis to evaluate cariprazine versus risperidone for the treatment of patients with schizophrenia with PNS. The time horizon for the analysis was one year, although this varied up to 10 years in scenario analyses. Although schizophrenia is likely to last for the patient's remaining lifetime upon diagnosis, SMC has considered time horizons of similar duration for this condition in the past.

A Markov state transition model was used which included 8 possible health states ranging from 1 (mild symptoms) to 8 (extremely severe symptoms) reflecting the Mohr-Lenert classification system. The model categorised patients by their type of symptoms according to the PANSS scores in each domain (positive, negative, cognitive) which were mapped onto the the Mohr-Lenert classification system.. Patients started off in the model in either state 4 (severe with negative symptoms dominance) or state 6 (severe with negative and cognitive symptoms) and could remain in those states or move to any of the other 6 states. It is noted that while included in the model structure, no patients entered states 7 (severe with positive symptoms dominance) or 8. Death was incorporated into the model, although no differences in mortality were assumed between treatments.

Clinical efficacy data were taken from the RGH-188-005 study, with treatment discontinuation data taken from an alternative study of risperidone patients and applied to both arms in the model^{14, 15}. Treatment efficacy was assumed for 1 year in the base case although this was varied in scenario analyses up to 5 years. As the clinical data from RGH-188-005 provide results for the primary outcome in terms of mean least squares, comparing the clinical efficacy data with the transition probabilities used in the economic evaluation is difficult, as it is unclear what the state distribution would be at each follow-up point in the study.

In the analysis, patients received cariprazine 4.5mg once daily or risperidone 4mg once daily. Dose modifications were not considered. Discontinuations were permitted and it was assumed that

discontinuation due to lack of efficacy was possible in any health state. Scenario analyses exclude discontinuations due to lack of efficacy, but those due to specific adverse events, lack of tolerability more generally, patient decision, or other causes were still possible. Treatment switching to other second generation anti-psychotics (namely amisulpride, aripiprazole, olanzapine, quetiapine and risperidone) was permitted following discontinuation. The medicines costs incurred upon switching were a weighted average of the costs of these treatments. Other resource use costs related to GP, psychiatrist, psychologist, or other specialist visits, day clinic visits and hospitalisation days. It is not clear that this covers all relevant costs for these patients, including residential and social care costs, given that the perspective for the analysis is the NHS and Social Care in Scotland. Resource use estimates came from a European study looking at resource use in schizophrenia in three countries, including the UK and were assigned to the health states of the model described above. ¹⁶

Utility data for the 8 health states were taken from a standard gamble exercise conducted in the USA¹⁹. Disutilities relating to adverse events were partially sourced from the same standard gamble exercise where available or derived from EQ-5D data collected during the European study from which resource use information was also taken. Utility values for the poorest (severe – negative and cognitive) to best (mild) states in the model ranged from 0.53 to 0.88 respectively. Although no attempt was made to calibrate the utility values given the different methods used to elicit them, values used are in line with similar studies that are possible alternatives from within the wider evidence base.

Table 2. Base case results

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Cariprazine	7,502	0.748	71.89	0.023	3,110
Risperidone	7,430	0.725			

QALY=Quality-adjusted life year, ICER=Incremental cost-effectiveness ratio

One way and scenario sensitivity analyses were also undertaken. The one way sensitivity analysis found that the model was particularly sensitive to hospitalisation costs, adverse events in the risperidone arm, the utility associated with the mildest health state and the probability of switching for health state 2. Probabilities were varied in a scenario analysis, but this considered only one set of alternative values adjusted based on expert elicitation methods and also covering states 7 and 8 in the model, which in most cases varied the results less than 2% compared with the base case transition probabilities. Selected scenario analysis are summarised in table 3.

Table 3: Key scenario analysis results

Scenario analysis	ICER
Removing all health state costs	£25,659
Reducing hospitalisation costs to £0	£23,606
Increasing time horizon to 2 years and reducing hospitalisation costs to £0	£20,822
Increasing time horizon to 10 years and reducing hospitalisation costs to £0	£22,070
Discontinuation rate of 30%, increasing time horizon to 2 years and reducing hospitalisation costs to £0	£33,375
Discontinuation rate of 30%, increasing time horizon to 10 years and reducing hospitalisation costs to £0	£35,713

ICER = incremental cost-effectiveness ratio

The main limitations with the analysis were:

- The model considers only one comparator, risperidone, which does not fully reflect the choice of other relevant comparators in clinical practice and the relative efficacy and cost-effectiveness of cariprazine against these is, therefore, unknown.
- The inability to link the primary efficacy outcomes into the Mohr-Lenert health states to determine whether the transition probabilities accurately reflect the RGH-188-005 study results used to inform the clinical effectiveness assessment, and the failure to vary transition probabilities through a wider range in the scenario analysis.
- The resulting impact on the ICER increasing from £3,110 to £23,606 when hospitalisation costs (particularly given the difference in probabilities between the treatments for transitioning out of state 4) are set to zero which may be more appropriate to the clinical study population used in RGH-188-005.
- Although the time horizon of ten years is (for this condition) not unique to this submission, the cumulative effect of zero hospitalisation costs, the longest available time horizon of 10 years and a discontinuation rate of 30% raising the ICER to £35,713 shows the sensitivity of the results to more conservative clinical factors that also limit the relative effectiveness of cariprazine to 1 year. However, this was considered a conservative analysis.
- The failure to consider residential costs and other social care costs that may be relevant to the patient population in Scotland can be considered conservative, and would lower the ICER if included.
- Same weighted average cost of switching was applied in both arms which included risperidone as a switching option; excluding risperidone as a switching option in the comparator arm increases the weighted average cost of switching and reduces the baseline ICER to £981/QALY.

Despite the issues presented above, the economic case has been demonstrated.

Summary of patient and carer involvement

No patient group submissions were received.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published national clinical guideline SIGN 131, *Management of Schizophrenia*, in March 2013.¹⁰ For acute exacerbation or recurrence of schizophrenia, it advises amisulpride, olanzapine or risperidone as the preferred treatment options, with chlorpromazine and other low-potency first-generation antipsychotics providing suitable alternatives. Individuals with schizophrenia which is in remission should be offered maintenance treatment with antipsychotic medication for a minimum of two years. This should usually be with the medication that was used during their last acute episode, assuming efficacy and tolerability. The decision to switch antipsychotic medication should take into account the risk of destabilisation and adverse effects and the dose of medications should be gradually cross tapered. No particular medicine or class is conclusively better in terms of efficacy, overall adverse effect burden, or at reducing relapse rates, than any other. This guideline pre-dates the availability of cariprazine and makes no specific recommendations for antipsychotics in schizophrenia with PNS. However for patients with PNS despite adherence to antipsychotic medicines the guideline advises to consider augmentation with an antidepressant, lamotrigine or sulpride. It is unclear if this recommendation is referring to patients with primary or secondary negative symptoms.¹⁰

The National Institute for Health and Care Excellence (NICE) published *Psychosis and schizophrenia in adults: prevention and management* National Clinical Guideline Number 178 in 2014.⁹ The recommendations for pharmacological therapies were similar to those in SIGN 131.

Additional information: comparators

Risperidone, amisulpride, aripiprazole, haloperidol, olanzapine, quetiapine and sulpiride.

Cost of relevant comparators

Medicine	Dose Regimen	Cost per year (£)
cariprazine	1.5 to 6mg oral daily	1,045
risperidone	4 to 16mg oral daily	193 to 660
quetiapine	300 to 750mg oral daily	847 to 1,618
olanzapine	5 to 20mg oral daily	189 to 650
aripiprazole	10 to 30mg oral daily	157 to 271
sulpiride	400 to 800mg oral daily	44 to 138
amisulpride	50 to 300mg oral daily	31 to 121
haloperidol	2 to 20mg oral daily	16 to 281

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 4 February 2019, cost of cariprazine from MIMS online 4 February 2019. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The number of patients assumed to be eligible to receive cariprazine was 3,224 in year 1, and 3,726 in year 5. Based on a market share of 2% in year 1 increasing to 3% in year 5, this results in an estimated 44 patients being treated in year 1, rising to 85 in year 5. A discontinuation rate of 32.5% per annum is also included. The estimated gross budget impact to Scotland is £46k in year 1 rising to £89k in year 5.

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This assessment is based on data submitted by the applicant company up to and including 15 March 2019.

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.