New Medicine Assessment

Cariprazine (Reagila®▼)

For the treatment of schizophrenia in adults

Recommendation: AMBER1

Cariprazine is recommended as a second-line therapy in patients where predominantly negative symptoms have been identified as an important feature.

- Cariprazine is suitable for prescribing in primary care following recommendation or initiation by a specialist.
- Full prior agreement about patient's on-going care must be reached under a shared care agreement.

Summary of supporting evidence:

- In a trial comparing cariprazine to risperidone over 26 weeks, cariprazine demonstrated greater improvements in negative symptoms scores (PANSS negative subscale score) compared to risperidone.
- The EMEA concluded that the safety profile of cariprazine is comparable to other atypical antipsychotics.
- Cariprazine has been approved for use by the Scottish Medicines Consortium (SMC) as a second-line therapy in patients where predominantly negative symptoms have been identified as an important feature.
- Cariprazine provides an additional treatment option for the management of schizophrenic patients with predominant negative symptoms, an area where there is a lack of evidence to support treatment choices.
- The potential cost for the Lancashire and South Cumbria health economy is estimated to be **£14,672 in year 1, rising to £28,296 in year 5.**

Details of Review

Name of medicine (generic & brand name)**:** Cariprazine (Reagila®▼)

Strength(s) and form(s):

1.5mg, 3mg, 4.5mg and 6mg capsules

Dose and administration:

The recommended starting dose of cariprazine is 1.5 mg once daily. Thereafter the dose can be increased slowly in 1.5 mg increments to a maximum dose of 6 mg/day, if needed. The lowest effective dose should be maintained according to the clinical judgement of the treating physician.

Because of the long half-life of cariprazine and its active metabolites, changes in dose will not be fully reflected in plasma for several weeks. Patients should be monitored for adverse reactions and treatment response for several weeks after starting cariprazine and after each dosage change. [1]

BNF therapeutic class / mode of action:

Antipsychotic / dopamine D3 and D2 receptor partial agonist.

Licensed indication(s):

Treatment of schizophrenia in adult patients.

Proposed use (if different from, or in addition to, licensed indication above):

Non-first line treatment option for adult patients with predominant negative symptoms of schizophrenia.

Course and cost:

28 x Cariprazine capsules (all strengths): £80.36

Dose: 1.5 to 6mg daily [1]

Annual cost: **£1,048**

Current standard of care/comparator therapies:

Annual costs based on the use of immediate release preparations:

- Risperidone 4 to 16mg daily - £151 to £604
- Quetiapine 300 to 750mg daily - £38 to £116
- Olanzapine 5 to 20mg daily - £17 to £36
- Aripiprazole 10 to 30mg daily - £19 to £42
- Sulpiride 400 to 800mg daily - £106 to £213
- Amisulpiride 50 to 300mg daily - £33 to £127
- Haloperidol 2 to 20mg daily - £227 to £550

All prices obtained from the July 2019 electronic Drug Tariff.

Relevant NICE guidance:

NICE Clinical Guideline (CG178): Psychosis and schizophrenia in adults: prevention and management. [2]

1.3.4 Treatment options

1.3.4.1 For people with first episode psychosis offer:

- oral antipsychotic medication in conjunction with
- psychological interventions (family intervention and individual CBT).

1.3.5 Choice of antipsychotic medication

1.3.5.1 The choice of antipsychotic medication should be made by the service user and healthcare professional together, taking into account the views of the carer if the service user agrees. Provide information and discuss the likely benefits and possible side effects of each drug, including:

- metabolic (including weight gain and diabetes)
- extrapyramidal (including akathisia, dyskinesia and dystonia)
- cardiovascular (including prolonging the QT interval)
- hormonal (including increasing plasma prolactin)
- other (including unpleasant subjective experiences).

1.3.6 How to use antipsychotic medication

1.3.6.1 Before starting antipsychotic medication, undertake and record the following baseline investigations:

- weight (plotted on a chart)
- waist circumference
- pulse and blood pressure
- fasting blood glucose, glycosylated haemoglobin (HbA1c), blood lipid profile and
- prolactin levels
- assessment of any movement disorders
- assessment of nutritional status, diet and level of physical activity.

1.3.6.2 Before starting antipsychotic medication, offer the person with psychosis or schizophrenia an electrocardiogram (ECG) if:

- specified in the summary of product characteristics (SPC)
- a physical examination has identified specific cardiovascular risk (such as diagnosis of
- high blood pressure)
- there is a personal history of cardiovascular disease or
- the service user is being admitted as an inpatient.

Background and context

Psychosis and the specific diagnosis of schizophrenia represent a major psychiatric disorder (or cluster of disorders) in which a person's perception, thoughts, mood and behaviour are significantly altered. The symptoms of psychosis and schizophrenia are usually divided into 'positive symptoms', including hallucinations (perception in the absence of any stimulus) and delusions (fixed or falsely held beliefs), and 'negative symptoms' (such as emotional apathy, lack of drive, poverty of speech, social withdrawal and self-neglect). Each person will have a unique combination of symptoms and experiences. [2]

Typically there is a prodromal period, which precedes a first episode of psychosis and can last from a few days to around 18 months. The prodromal period is often characterised by some deterioration in personal functioning. Changes include the emergence of transient (of short duration) and/or attenuated (of lower intensity) psychotic symptoms, memory and concentration problems, unusual behaviour and ideas, disturbed communication and affect, and social

withdrawal, apathy and reduced interest in daily activities. The prodromal period is usually followed by an acute episode marked by hallucinations, delusions and behavioural disturbances, usually accompanied by agitation and distress. Following resolution of the acute episode, usually after pharmacological, psychological and other interventions, symptoms diminish and often disappear for many people, although sometimes a number of negative symptoms remain. This phase, which can last for many years, may be interrupted by recurrent acute episodes that may need additional pharmacological, psychological and other interventions, as in previous episodes. [2]

Although this is a common pattern, the course of schizophrenia varies considerably. Some people may have positive symptoms very briefly; others may experience them for many years. Others have no prodromal period, the disorder beginning suddenly with an acute episode. [2]

Over a lifetime, about 1% of the population will develop psychosis and schizophrenia. The first symptoms tend to start in young adulthood, at a time when a person would usually make the transition to independent living, but can occur at any age. The symptoms and behaviour associated with psychosis and schizophrenia can have a distressing impact on the individual, family and friends. [2]

NICE guidance for the management of schizophrenia and psychosis recommends the use of oral antipsychotic medication in conjunction with psychological therapy taking into consideration the likely benefits and adverse events of the proposed drug treatment. NICE does not make any specific recommendations about the use of antipsychotics to treat predominant negative symptoms (PNS) or the rationale for changing antipsychotic medication. [2]

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. [3]

Summary of evidence

Summary of efficacy data in proposed use:

Nemeth et. al.

The evidence to support the efficacy and safety of cariprazine in the proposed use (patients with schizophrenia with PNS) comes from the RGH-188-005 study. [4] This was a randomised, double-blind, phase IIIb study comparing the efficacy of cariprazine and risperidone in adults (aged 18 to 65 years) with schizophrenia and PNS. 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] as 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 (i.e. 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. [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 1:1 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. [3]

The primary outcome was the change from baseline to week 26 or early termination in the PANSS-FSNS. Use of cariprazine led to a greater least squares mean change from baseline to week 26 in PANSS-FSNS than for risperidone -8.90 points for cariprazine vs -7.44 for risperidone; least squares mean difference (LSMD) -1.46 (CI95% -2.39; -0.53, p=0.022). [4]

The secondary efficacy outcome was the Personal and Social Performance Scale (PSP) total score measured at weeks 6, 10, 14, 18, 22, and 26; higher scores indicating better functioning. For the least squares mean change from baseline to endpoint in PSP total score, use of cariprazine led to a greater change than risperidone (14.30 points for cariprazine vs 9.66 for risperidone; LSMD 4.63 (CI95% 2.71; 6.56; p<0.0001). [4]

Post hoc analyses of the study by Nemeth et al

Additional analyses were performed to assess whether changes were specific to improvements in negative symptoms and not secondary to other improvements (pseudospecificity). [5] These analyses 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. [3]

Other efficacy data:

Three 6-week randomised, double-blind, placebo-controlled studies (RGH-MD-04, RGH-MD-05 and RGH-MD-16) [6] [7] [8] of the short-term efficacy of cariprazine (for both positive and negative symptom subtypes) were submitted to the European Medicines Agency (EMEA). The EMEA concluded that even though robust statistical significance was reached in both primary and secondary endpoints for the short-term studies, the efficacy is illustrated by numerically modest improvement in primary and secondary endpoints, depending on the study and dose. [9]

A 97-week, phase III withdrawal study (RGH- MD-06) [10] 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 (worsening of symptom scores, psychiatric hospitalization, aggressive/violent behaviour, or suicidal risk) 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%CI 0.28; 0.73). [10] A post hoc analysis excluding patients receiving greater than the maximum licensed dose of cariprazine was consistent with the primary analysis. [3] The European Medicines Agency (EMA)

concluded this study did not provide evidence of efficacy on improving negative symptoms, but that it does support a maintenance of efficacy in relapse prevention over a longer term. [9]

Summary of safety data:

The clinical development programme for cariprazine included 9344 healthy subjects or patients with various mental health disorders. A total of 6120 patients received at least 1 dose of cariprazine. The EMEA states that unfavourable effects of cariprazine are comparable to those of other atypical antipsychotics. [9] The most frequent treatment-emergent adverse events included akathisia (14.8%) / extrapyramidal disorder (7.3%), headache (12.5%) and insomnia (13.9%). The most frequent serious adverse events and events leading to premature discontinuation were worsening of schizophrenia / psychotic symptoms followed by akathisia. Several adverse events including akathisia / restlessness, creatine phosphokinase elevation, insomnia, anxiety and blurred vision were dose-dependent. [9]

The SPC for cariprazine contains the following list of adverse events in patients with schizophrenia [1]:

MedDRA System Organ Class	**Very common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Frequency not known**
Blood and lymphatic system disorders			Anaemia Eosinophilia	Neutropenia	
Immune system disorders				Hypersensitivity	
Endocrine disorders			Blood thyroid stimulating hormone decreased	Hypothyroidism	
Metabolism and nutrition disorders		Weight increased Decreased appetite Increased appetite Dyslipidaemia	Blood sodium abnormal Blood glucose increased Diabetes mellitus		
Psychiatric disorders		Sleep disorders Anxiety	Suicidal behaviour Delirium Depression Libido decreased Libido increased Erectile dysfunction		
Nervous system disorders	Akathisia Parkinsonism	Sedation Dizziness Dystonia Other extrapyramidal diseases and abnormal movement disorders	Lethargy Dysaesthesia Dyskinesia Tardive dyskinesia	Seizures/ Convulsion Amnesia Aphasia	Neuroleptic malignant syndrome
Eye disorders		Vision blurred	Eye irritation Intraocular pressure increased Accommodation disorder Visual acuity reduced	Photophobia Cataract	
Ear and labyrinth disorders			Vertigo		
Cardiac disorders		Tachyarrhythmia	Cardiac conduction disorders Bradyarrhythmia Electrocardiogram QT prolonged Electrocardiogram T wave abnormal		
Vascular disorders		Hypertension	Hypotension		

Respiratory, thoracic and mediastinal disorders			Hiccups		
Gastrointestinal disorders		Nausea Constipation Vomiting	Gastrooesophageal reflux disease	Dysphagia	
Hepatobiliary disorders		Hepatic enzymes increased	Blood bilirubin increased		Toxic hepatitis
Skin and subcutaneous tissue disorders			Pruritus Rash		
Musculoskeletal and connective tissue disorders		Blood creatine phosphokinase increased		Rhabdomyolysis	
Renal and urinary disorders			Dysuria Pollakisuria		
Pregnancy, puerperium and perinatal conditions					Drug withdrawal syndrome neonatal
General disorders and administration site conditions		Fatigue	Thirst		

Cariprazine is not recommended in patients with severe renal or hepatic impairment. Concomitant administration with strong or moderate CYP3A5 inhibitors/inducers (e.g. ketoconazole, clarithromycin, diltiazem, erythromycin, fluconazole, verapamil) is contraindicated. Women of childbearing potential must use highly effective contraception while taking cariprazine and at least for 10 weeks after stopping treatment. [1]

Special warnings and precautions for the use of cariprazine are comparable to other atypical antipsychotics e.g. metabolic (including weight gain and diabetes), extrapyramidal (including akathisia, dyskinesia and dystonia), cardiovascular (including prolonging the QT interval) and hormonal (prolactin). In additional to general warnings included for all antipsychotic agents regarding neuroleptic malignant syndrome and suicide risk, the SPC for cariprazine also advises that patients developing symptoms potentially related to cataract should be advised to seek ophthalmologic examination and re-evaluated for treatment continuation.

Strengths and limitations of the evidence:

Strengths

- Cariprazine is administered as a single once-daily capsule which may be titrated up from 1.5mg to 6mg available as (1.5mg, 3mg, 4.5mg and 6mg capsules). [1]
- In a trial comparing cariprazine to risperidone over 26 weeks, cariprazine demonstrated greater improvements in negative symptoms scores (PANSS negative subscale score) compared to risperidone. [4]
- Post-hoc analyses demonstrated that the improvement in the negative symptom score for cariprazine was not driven by improvements in positive symptom measures. [5]
- The clinical development programme for cariprazine has demonstrated short term efficacy in acute schizophrenia.
- The European Medicines Agency (EMA) concluded that a 97-week withdrawal study did not provide evidence of efficacy on improving negative symptoms, but that it does support a maintenance of efficacy in relapse prevention over a longer term. [9]
- The EMEA concluded that the safety profile of cariprazine is comparable to other atypical antipsychotics. [9]
- Cariprazine has been approved for use by the Scottish Medicines Consortium (SMC) as a

second-line therapy in patients where predominantly negative symptoms have been identified as an important feature.
- Cariprazine provides an additional treatment option for the management of schizophrenic patients with PNS, an area where there is a lack of evidence to support treatment choices. [3]

Limitations

- Improvements for negative symptoms and personal and social performance were numerically and statistically better for cariprazine treated patients compared to the risperidone group. This includes responder analyses based on 20% and 30% decreases in negative symptom scores. [4] However, the EMEA concluded that the clinical relevance of the difference in results between cariprazine over risperidone is difficult to interpret. [9]
- There is a lack of clinical trials data comparing cariprazine to comparator antipsychotic agents and data from the available trials is mostly short-term data in non-European patients.
- Patients with current psychiatric hospital admissions, acute exacerbations or imprisonments were excluded from the trial comparing cariprazine and risperidone. [4] This may limit the generalisability of the study data to this group of patients.
- The risperidone dose used in the trial does not reflect the upper end of the licensed dosing range. [3]
- Cariprazine has a higher acquisition cost that standard release generic antipsychotics.

Summary of evidence on cost effectiveness:

The following cost utility analysis was submitted by the manufacturer to the SMC: [3]

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. 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.

Utility data for the 8 health states were taken from a standard gamble exercise conducted in the USA. 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*
Discontinuaton rate of 30%, increasing time horizon to 10 years and reducing hospitalisation costs to £0	*£35,713*

ICER = incremental cost-effectiveness ratio

Prescribing and risk management issues:

The NICE guideline for the management of schizophrenia and psychosis recommends that the secondary care team should maintain responsibility for monitoring service users' physical health and the effects of antipsychotic medication for at least the first 12 months or until the person's

condition has stabilised, whichever is longer. Thereafter, the responsibility for this monitoring may be transferred to primary care under shared care arrangements. [2]

Due to 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 therefore be monitored for adverse reactions and treatment response for several weeks after starting cariprazine and after each dosage change.

When switching from another antipsychotic to cariprazine gradual cross-titration should be considered, with gradual discontinuation of the previous treatment while cariprazine treatment is initiated.

When switching to another antipsychotic from cariprazine, no gradual cross-titration is needed, the new antipsychotic should be initiated in its lowest dose while cariprazine is discontinued. It should be considered that plasma concentration of cariprazine and its active metabolites will decline by 50% in around 1 week. [1]

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Cariprazine capsules	**1.5mg-6mg daily**	**£80.36**	**£1,048**
Risperidone tablets	4-16mg daily	£24.83 for 60 X 4mg tablets	£151 to £604
Quetiapine tablets	300mg-750mg	£6.52 for 60 X 150mg tablets £7.58 for 60 X 200mg tablets	£38 to £116
Olanzapine tablets	5mg-20mg	£1.30 for 28 X 5mg tablets £2.21 for 28 X 20mg tablets	£17 to £36
Aripiprazole tablets	10mg-30mg	£1.46 for 28 X 10mg tablets £1.60 for 28 X 15mg tablets	£19 to £42
Sulpiride tablets	400mg-800mg	£4.37 for 30 X 200mg tablets	£106 to £213
Amisulpiride tablets	50mg-300mg	£5.41 for 60 X 50mg tablets £8.16 for 60 X 100mg tablets £12.67 for 60 X 200mg	£33 to £127
Haloperidol tablets	2mg-20mg	£1.18 for 30 X 0.5mg capsules £16.39 for 28 X 1.5mg tablets £21.08 for 28 X 10mg tablets	£227 to £550

Costs based on electronic Drug tariff list prices July 2019.
This table does not imply therapeutic equivalence of drugs or doses.

Innovation, need and equity implications of the intervention:

Despite the available treatments, there is a substantial unmet medical need especially for treatment of negative symptoms which affect up to two thirds of the patients with schizophrenia. To date, no standard treatment has been established for negative symptoms. Of the available treatments for schizophrenia, clozapine, amisulpride, olanzapine, and risperidone have shown modest efficacy on negative symptoms. The hypothetical expectation of cariprazine's benefits in treatment of schizophrenia including the predominant negative symptoms has been based on its receptor profile with partial agonism and preferential binding to dopamine D3 receptors in addition to D2 and serotonin 5-HT1A receptors. [9]

Financial implications of the intervention:

If the assumptions from the SMC budget impact analysis for Scotland's population of 5.44 million were applied to the Lancashire and South Cumbria population of approximately 1.7 million, 1,008 patients would be eligible for cariprazine in year 1 and 1,164 patients in year 5.

Based on a market share of 2% in year 1 increasing to 3% in year 5, and a discontinuation rate of 32.5% per annum, this results in an estimated **14** patients being treated in year 1, rising to **27** patients in year 5.

The annual acquisition cost of treating one patient with cariprazine for 1 year is **£1,048**

The estimated gross budget impact for Lancashire and South Cumbria is:

- 14 X £1,048 = **£14,672 in year 1**
- 27 X £1,048 = **£28,296 in year 5**

Service Impact Issues Identified:

The service impact of supplying cariprazine is aligned to that of supplying other atypical antipsychotic agents.

The secondary care team should recommend or initiate cariprazine and should maintain responsibility for monitoring service users' physical health and the effects of antipsychotic medication for at least the first 12 months or until the person's condition has stabilised, whichever is longer. Thereafter, the responsibility for this monitoring may be transferred to primary care under shared care arrangements. Cariprazine would therefore need to be added to the existing shared care arrangements for atypical antipsychotics if approved.

Equality and Inclusion Issues Identified:

Cariprazine provides an additional treatment option for patients with schizophrenia and PNS. Approving the use of cariprazine is unlikely to create any significant equality and inclusion issues.

Cross Border Issues Identified:

Greater Manchester Medicines Management Group do not recommend the prescribing of cariprazine across the Greater Manchester health economy.

Pan Mersey are currently consulting on a draft recommendation for cariprazine as a non-first line treatment option for adult patients with predominant negative symptoms of schizophrenia.

Legal Issues Identified:

N/A

Media/ Public Interest:

N/A

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[11] M Debelle et al, “Cariprazine in negative symptoms of schizophrenia: post hoc analyses of a fixed-dose, placebo- and active-controlled trial,” *European neuropsychopharmacology,* vol. 24, no. Suppl534, 2014.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality