This policy statement is approved by Halton, Knowsley, Liverpool, South Sefton, Southport and Formby, St Helens, Warrington, and Wirral CCGs

Ha Kn Li SS SF SH Wa Wi

NHS
Pan Mersey
Area Prescribing Committee

CARIPRAZINE hard capsules (Reagila® ▼)
for the treatment of schizophrenia in adult patients

The Pan Mersey Area Prescribing Committee recommends the prescribing of CARIPRAZINE hard capsules (Reagila® ▼), following specialist initiation, as a non-first line treatment option for adult patients with predominant negative symptoms of schizophrenia.

AMBER patient retained by specialist

Cariprazine is licensed for the treatment of schizophrenia in adult patients [1].

Cariprazine is specifically recommended for specialist-initiation as a non-first-line treatment option for patients with predominant negative symptoms of schizophrenia when existing antipsychotic treatments are ineffective or unsuitable. Typically, patients would have tried amisulpride first.

Negative symptoms of schizophrenia are difficult to treat and are associated with significant long-term morbidity, poor functional outcomes and high rates of disability in patients with schizophrenia [2]. Ultimately, negative symptoms place a substantial burden on people with schizophrenia, their families, and health-care systems.

Current recommendations for the treatment of schizophrenia are covered by NICE clinical guideline 178: Psychosis and Schizophrenia in Adults [2]. Although a variety of first and second generation antipsychotics are available for the treatment of schizophrenia, there is limited evidence to support their efficacy in treating the negative symptoms of schizophrenia. Despite limited evidence, amisulpride remains the most commonly used.

Based on its pharmacology [3] and supportive results from a prospective, randomised, double-blind study [4], cariprazine may prove beneficial in addressing an unmet clinical need for effective treatments for negative symptoms of schizophrenia.

Note: Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.

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or earlier if there is significant new evidence relating to this recommendation
APC administration provided by Midlands and Lancashire Commissioning Support Unit

Prescribing policy statement
Version: 3.0

CARIPRAZINE hard capsules (Reagila® ▼) for schizophrenia in adult patients

Effectiveness

Cariprazine (Reagila® ▼) is a second generation antipsychotic drug licenced for the treatment of schizophrenia in adults [1]. Its therapeutic effects are thought to be mediated via partial agonist activity at dopamine D3, D2 and serotonin 5-HT1A receptors, and antagonist activity at serotonin 5-HT2B, 5-HT2A and histamine H1 receptors [1]. Cariprazine is distinct from other antipsychotics in having a high preferential affinity for the D3 receptor, which is thought to be important in modulating mood and cognition [3].

The short-term efficacy of cariprazine 1.5mg-9mg for the treatment of acute schizophrenia was demonstrated in three multi-centre, multinational, randomised, double-blind, placebo-controlled 6-week trials including 1,754 patients with the age of 18 to 60 years [1]. In all 3 short-term studies, all doses of cariprazine showed statistically significant improvement in primary and secondary efficacy parameters versus placebo [1, 5].

The long-term efficacy of cariprazine for maintaining antipsychotic effect was confirmed in a double-blind, placebo-controlled, randomised-withdrawal study to assess prevention of relapse [1, 5]. 200 stabilised patients were randomised to receive fixed doses of 3 to 9 mg cariprazine (n=101) or placebo (n=99) in a double-blind manner for at least 26 weeks, up to 72 weeks. Time to relapse was significantly longer in the cariprazine group compared to placebo at 224 days vs. 92 respectively, based on the 25th percentile (p=0.001).

The efficacy of cariprazine 3-6 mg (target dose 4.5mg) and risperidone 3-6 mg (target dose 4mg/day) for the treatment of persistent predominant negative symptoms of schizophrenia was evaluated in a randomised, 26-week, multi-centre, double-blind, and active-controlled clinical trial [1, 4, 5]. Significant improvement in negative symptoms was shown for both cariprazine and risperidone ($p < 0.001$), supported by an improvement in personal and social performance. The effects on negative symptoms were numerically and statistically better for the cariprazine group compared to the risperidone group from Week 14 onwards, mean difference -1.5 (95% CI: -2.4, -0.5; p= 0.002) [1, 4, 5]. In addition, a statistically significant difference ($p< 0.001$) in personal and social performance in favour of cariprazine over risperidone was observed from Week 10 onwards.

Safety

The most frequently reported adverse effects with cariprazine in the dose range (1.5-6 mg) were akathisia (19%) and parkinsonism (17.5%). Most events were mild to moderate in severity [1].

Standard antipsychotic class warnings and precautions apply to cariprazine.

Cariprazine is extensively metabolised to its active metabolites desmethyl-cariprazine (DCAR), which in turn is metabolised to didesmethylcariprazine (DDCAR) by CYP3A4 and, to a lesser extent, by CYP2D6. Therefore, inhibitors and inducers of CYP3A4 might influence the formation or elimination of the active metabolites. Co-administration of cariprazine with strong or moderate inhibitors or inducers of hepatic cytochrome CYP3A4 is contraindicated [1].

Cariprazine is a P-gp inhibitor and therefore use of P-gp substrates with narrow therapeutic index such as dabigatran and digoxin may require extra monitoring and dose adjustment.[1]

Cariprazine is not recommended during pregnancy or in women of childbearing potential not using highly effective contraception. Women of childbearing potential must be advised to avoid pregnancy whilst on cariprazine and must be on highly effective contraception prior to initiation, throughout treatment and for at least for 10 weeks after discontinuation. Women using systemically acting hormonal contraceptives should add a second barrier method.[1] Women who become pregnant while taking cariprazine, or who are planning pregnancy, should consult a specialist.

See also Implementation Notes.

Lenticular changes, lens opacity and cataracts were observed during cariprazine non-clinical studies. Patients who develop symptoms potentially related to cataract should be referred for ophthalmologic examination and re-evaluated for treatment continuation.[1]

For further information on the precautions, side effects and interactions of cariprazine, refer to the SPC.

Cost

Cariprazine costs £80.36 for 28 tablets, across all strengths (flat-pricing). Annual acquisition cost is approximately £1047.55 per patient per year.

The number of eligible patients is expected to be low.

The cost of alternative second-generation antipsychotics will vary depending on the drug, dose and formulation.

e.g. Amisulpride for predominant negative symptoms: recommended dose range is 50mg-300mg once daily

Annual acquisition costs range from £27.40 to £107.10.

Costs from online Drug Tariff list price December 2020.

Patient factors

Use of cariprazine is not recommended in patients with severe hepatic or severe renal impairment.[1]

There is limited data for use in elderly patients above 65 years of age; cautious dosing and monitoring is required.[1]

There is limited or no data regarding the use of cariprazine in pregnant women or in breastfeeding.[1]

Supporting information

Prescribing information

Dose regimen and monitoring advice

- The recommended starting dose of cariprazine is 1.5 mg orally once daily. Thereafter the dose can be increased slowly in 1.5 mg increments to a maximum dose of 6 mg/day, if needed.
- To optimise value, the capsule strength appropriate for the required daily dose should be prescribed and dispensed. Using multiple capsules of the same strength to deliver the prescribed dose is not cost-effective.
- Cariprazine and its active metabolites have long half-lives. The effective half-life of total cariprazine is about 1 week. Therefore, drug levels accumulate slowly and changes in dose will not be fully reflected in plasma for several weeks. Clinical efficacy as well as side effects may take a long time to develop. Patients should be monitored for treatment response and adverse reactions for several weeks after starting cariprazine and after each dosage change.
- For full prescribing information, refer to the SPC.

Implementation notes

- Cariprazine is recommended for specialist initiation as a non-first line treatment option for schizophrenia in a subset of patients with persistent predominant negative symptoms of schizophrenia. Cross-titration and dose stabilisation should be done by the specialist prior to transferring prescribing to the GP. The patient must be retained under the care of the specialist mental health service and not discharged to primary care.
- The number of patients eligible for cariprazine is expected to be low. However, there may be an associated increase in costs arising from the use of branded cariprazine versus cheaper antipsychotic treatment options.
- When switching from another antipsychotic to cariprazine, a gradual cross-titration should be considered. When switching to another antipsychotic from cariprazine, the new antipsychotic should be initiated at its lowest dose and cariprazine discontinued [1].
- Cariprazine is not recommended during pregnancy and in women of childbearing potential not using highly effective contraception*. Women of childbearing potential must be advised to avoid pregnancy whilst on cariprazine and must be on highly effective contraception prior to initiation, throughout treatment and for at least for 10 weeks after discontinuation. [1]

*Highly effective contraceptive methods include long-acting reversible contraceptives such as a coil (copper intrauterine device [IUD] or levonorgestrel intrauterine system), contraceptive implant (progestogen-only implant) and sterilisation [6]. It is currently not known whether cariprazine may reduce the effectiveness of hormonal contraceptives, and therefore women using systemically-acting hormonal contraceptives should add a second barrier method [1].

References

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4. Németh 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; 389:1103-13.
5. European Medicines Agency. European Public Assessment Report; Reagila, 18 May 2017. Accessed 29 December 2020.
6. Faculty of Sexual & Reproductive Healthcare of the Royal College of Obstetricians & Gynaecologists. Clinical Effectiveness Unit. FSRH CEU Statement; Contraception for women using known teratogenic drugs or drugs with potential teratogenic effects, 14 February 2018. Accessed 29 December 2020.