Medicines Information Bulletin

Oxford Health NHS
NHS Foundation Trust

Vol. 17 No. 1 **Cariprazine (Reagila) for Schizophrenia** **July 2019**

DTG decision: Formulary Restricted

The Drugs and Therapeutics Group has included cariprazine on the formulary as a restricted medicine. The decision was based on the limited efficacy and safety data, limited comparative data, and cost.

Its use is restricted as a second line therapy in acute or maintenance management of those patients who have schizophrenia where predominant negative symptoms (PNS) have been identified as an important feature.

Cariprazine appears to have a low propensity to cause metabolic adverse effects, weight gain (>/=7%) and hyperprolactinaemia. It may offer an advantage over other antipsychotics where this has caused a problem, however the suitability of more cost-effective alternatives should be considered first.

Amisulpride is the only antipsychotic specifically licensed for use in schizophrenia with PNS. However, it has a high propensity to hyperprolactinaemia. Cariprazine may offer an advantage over amisulpride where symptomatic hyperprolactinaemia has occurred.

It is expensive in comparison with other generically available antipsychotics. Primary care has traffic lighted cariprazine red, so any prescribing will remain in secondary care.

Clinicians wishing to prescribe cariprazine must make an entry in the patient's notes which explains how the decision to use a restricted medicine meets the Trust's restriction criteria.

What is it?

Cariprazine is a second-generation antipsychotic. Therapeutic effects may be mediated through a combination of partial agonist activity at dopamine D_3, D_2 and serotonin 5-HT_{1A} receptors and antagonist activity at serotonin 5-HT_{2B}, 5-HT_{2A} and histamine H_1 receptors. It is licensed for the treatment of schizophrenia in adults aged 18 years or older. It has been on the UK market since September 2018 and has been available in the US since 2015.

How much does it cost?

Cariprazine has a flat based pricing structure – all strengths are £80.36 for a 28-day supply. It is more expensive than most available antipsychotics. Quetiapine XL is more expensive than cariprazine.

Drug	Cost per year (£)
Quetiapine XL all doses up to 800mg daily	1,020 to 2,712
Cariprazine all doses up to 6mg daily	964
Amisulpride all doses up to 300mg daily	65 to 603
Risperidone all doses up to 6mg daily	148 to 580
Haloperidol all doses up to 20mg daily	506 to 554
Lurasidone all doses up to 148mg daily	90 to 181
Aripiprazole all doses up to 30mg daily	19 to 153
Quetiapine all doses up to 750mg daily	37 to 114
Olanzapine all doses up to 20mg daily	15 to 26

**All prices are based on Drug Tariff July 2019*

What is the dose?

The recommended starting dose of cariprazine (Reagila) in adults is 1.5mg once daily, with or without food. The dose can then be increased slowly in 1.5 mg increments at approximately fortnightly intervals to a maximum dose of 6 mg/day. Dose increases should be based on physician judgment and observed clinical response, whilst keeping in mind that the effective half-life for total cariprazine is long (about one week). 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 be monitored for adverse reactions and treatment response for several weeks after starting cariprazine and after each dosage change.

Special patient populations (e.g. renally or hepatically impaired) – refer to SPC on eMC (www.medicines.org.uk/emc)

What size tablets are available?

Film coated tablets are available in four strengths: 1.5mg, 3mg, 4.5mg and 6mg

What adverse effects does it cause?

As with all new drugs, cariprazine is a black triangle drug and all suspected adverse reactions should be reported to the MHRA via the yellow card scheme (www.mhra.gov.uk/yellowcard). Refer to SPC on eMC (www.medicines.org.uk/emc) for full list of adverse effects.

Very common (=/>10%)	Akathisia*, parkinsonism^
Common (>/=1/100 to <1/10)	Weight gain$, decreased/increased appetite, dyslipidaemia, sleep disorders, anxiety, sedation, dizziness, dystonia^, extrapyramidal diseases and abnormal movement disorders^, blurred vision, tachyarrhythmia, hypertension, nausea, constipation, vomiting, raised hepatic enzymes, raised creatine phosphokinase, and fatigue
Less common side effects (>/=1/1000 to <1/100)	Abnormal sodium levels, increased blood glucose, diabetes mellitus, suicidal behaviour, delirium, depression, decreased/increased libido, erectile dysfunction, dysaesthesia, dyskinesia, tardive dyskinesia, cardiac conduction disorders, bradyarrhythmia, prolonged QT, abnormal T wave and hypotension
Rare (>/=1/10000 to <1/1000)	Neutropenia, hypothyroidism, seizures/ convulsion, amnesia, aphasia, photophobia, cataract, dysphagia, and rhabdomyolysis (Other rare and very rare side effects may not yet have been determined.)

** In studies, cariprazine appears to have a higher propensity to akathisia compared with risperidone and aripiprazole.*
^ In studies, cariprazine appears to a higher propensity to extrapyramidal side effects, parkinsonism and dystonia compared to aripiprazole, but a lower propensity compared to risperidone.
$ In short-term studies, there were slightly greater mean increases in body weight in the cariprazine group compared to the placebo group; 1 kg and 0.3 kg, respectively. In long-term maintenance study, there was no clinically relevant difference in change of body weight from baseline to end of treatment (1.1 kg for cariprazine and 0.9 kg for placebo). In an open label, 20-week study, 9% of patients developed potentially clinically significant (PCS) weight gain (defined as increase ≥ 7%) while treated with cariprazine over 20 weeks.

Are there any drug interactions?
Cariprazine is primarily metabolised by the CYP3A4 isoenzyme with a minor contribution of CYP2D6 isoenzyme, and is therefore liable to several interactions:

Drug	**Effect**
Smoking	No effect.
Centrally acting medication and alcohol	**Caution** as potential for additive CNS effects.
QT prolonging drugs	**Caution** advised. A dedicated QT study (n=129) indicated that no QT interval prolongation was detected following supratherapeutic doses (9 mg/day or 18 mg/day). No patients experienced QTc increases ≥ 60ms from baseline, or a QTc of > 500ms.
Grapefruit juice	**Avoid** due to potential rise in cariprazine concentration. (This has not been studied but there is a theoretical risk due to CYP3A4 inhibition)
Strong or moderate CYP3A4 inhibitors *(e.g. boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, diltiazem, erythromycin, fluconazole, verapamil)*	**Contraindicated**
Strong or moderate CYP3A4 inducers *(e.g. carbamazepine, phenobarbital, phenytoin, rifampicin, St John's Wort, bosentan, efavirenz, etravirine, modafinil, nafcillin).*	**Contraindicated**
Digoxin, oral contraceptives	**Unknown effect** Digoxin: additional monitoring with concomitant use Contraceptives: add barrier method

How should patients be switched from their current antipsychotic to cariprazine?
Switch strategies should be tailored to each individual and depend on several factors which include the reason for the switch (i.e. poor response or adverse effects), relapse risk, risks when unwell, physical status of the patient and risks relating to additive antipsychotic side effects. A cross taper is often appropriate but other strategies such as taper-in/taper-out or stop-start may be more appropriate depending on the individual circumstances following a risk-benefit assessment.

Medicines Information Bulletin

Oxford Health NHS
NHS Foundation Trust

The manufacturer of cariprazine provides the following very general recommendations, but each case should be considered separately, and the precise switch regimen tailored accordingly:

Other antipsychotics → cariprazine

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.

Cariprazine → another antipsychotic

When switching from cariprazine to another antipsychotic, no gradual cross-titration is needed. The new antipsychotic should be initiated in its lowest dose while cariprazine is discontinued without the need for gradual dose reduction, irrespective of dose, due to its long half-life. The plasma concentration of cariprazine and its active metabolites will decline by 50% in approximately 1 week.

If further advice about switching is required for individual cases, please contact the Medicines Advice Service on 01865 904365 or email: medicines.advice@oxfordhealth.nhs.uk.

What is the evidence base?

The Scottish Medicines Compendium (SMC) have placed cariprazine as a second-line therapy in patients where predominantly negative symptoms have been identified as an important feature. The SMC reviewed the evidence from four RCTs, one of which compared cariprazine with risperidone as a maintenance treatment over 26 weeks (n=460). The primary outcome was change from baseline to week 26 in the Positive and Negative Syndrome Scale- factor score for negative symptoms (PANSS-FSNS). Cariprazine showed a greater improvement in PANSS-FSNS than risperidone after 26 weeks. Responder analysis based on 20% decreases in PANSS-FSNS both favoured cariprazine over risperidone [69% vs 58%; OR 2.08; p=0.002, NNT=9]. The key secondary outcome on Personal and Social Performance (PSP) was statistically significant in favour of cariprazine [mean difference 4.6 (95% CI, 2.7 to 6.6)] and provides important evidence of improved patient functioning and recovery. The overall rate and profile of adverse effects was similar between cariprazine and risperidone.

Longer term data

Published long term data is currently limited to a 72-week relapse prevention study by Durgam et. al. that compared cariprazine to placebo in participants who had already demonstrated response to cariprazine during an open label phase. There was a significantly longer time to relapse in cariprazine-treated vs placebo-treated participants (p=0.001). Relapse occurred in 25% cariprazine group vs 47% of placebo group (hazard ratio [95% CI], 0.45 [0.28 to 0.73]).

Cariprazine has a very long half-life – occasional missed doses are therefore unlikely to be a significant issue. Studies investigating the possibility of less frequent dosing are currently ongoing.

For further information and advice please contact Oxford Health NHS Foundation Trust's Medicines Advice Service on 01865 904365 or email medicines.advice@oxfordhealth.nhs.uk

Printable information leaflets for patients: https://www.choiceandmedication.org/oxfordhealth/printable-leaflets/patient-information-leaflets/25/ALL/

References:

- Cariprazine 1.5mg, 3mg, 4.5mg and 6mg capsules (Reagila®). Summary of product characteristics. Recordati Pharmaceuticals Ltd. 09 August 2018 [cited 17 January 2019]; Available from: www.medicines.org.uk/emc/.
- Scottishmedicines.org.uk. (2019). Cariprazine 1.5mg, 3mg, 4.5mg and 6mg hard capsules (Reagila®).
- Nemeth G, Laszlovszky I, Czobor P, Szalai E, Szatmari B, Harsanyi J, et al. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in Lancet. 2017;389(10074):1103-13.
- Durgam S, Earley W, Li R, Li D, Lu K, Laszlovszky I, 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(2-3):264-71 (https://www.sciencedirect.com/science/article/pii/S0920996416303127).
- Nasrallah HA, Cutler AJ, Wang Y, et al. Safety and tolerability of cariprazine in long-term treatment of schizophrenia: integrated summary of safety data [abstract no. P. P.3.d.025]. Eur Neuropsychopharmacol. 2014;24(Suppl 2):S536.
- Personal communication with Recordati Pharmaceuticals Ltd., 23rd July 2019.
- Choice and Medication cariprazine. Last modified 26/2/19 (https://www.choiceandmedication.org/oxfordhealth/medication/cariprazine/)