Considerations for Commissioners

Cariprazine *(Reagila®▼)*

For the treatment of schizophrenia

Commissioning guidance:

Commissioners may wish to bear the following in mind when considering the commissioning of cariprazine:

- Cariprazine treatment should be initiated and stabilised within secondary care as per the recommendations of the NICE (National Institute for Health and Care Excellence) guidance on the Management of Psychosis and Schizophrenia in adults (CG178; 2015).
- Local specialist opinion was that aripiprazole was a first-line choice for new patients, due to the lower risk of metabolic side effects (e.g. weight gain, changes in blood glucose levels and blood pressure) than other atypical antipsychotics.
- There is a greater drug acquisition cost associated with the choice of cariprazine of £1047.55 per patient per year, compared with generic versions of other available antipsychotic medications.

Strength of the evidence for efficacy

The evidence for the efficacy of cariprazine was based on four randomised controlled trials (RCTs); two trials compared cariprazine with placebo over six weeks as treatment for an acute psychotic episode, one trial compared cariprazine with risperidone as a maintenance treatment over 26 weeks, and the fourth trial evaluated relapse rates after withdrawal of cariprazine over 26 to 72 weeks. Cariprazine was more effective than placebo in improving symptom scores, both as acute treatment and for relapse prevention. It also showed significantly greater improvement in the PANSS negative subscale score than risperidone after 26 weeks, although the clinical relevance of the mean difference in scores of 1.46 points (95% confidence interval 2.39 to 0.53; effect size 0.31) was considered 'difficult to interpret' in the European Medicines Agency (EMA) assessment report for cariprazine.

MTRAC considered cariprazine as a new product with potential for use in primary care.

Description of technology

Cariprazine is a dopamine D3-preferring D_2/D_3 receptor partial agonist, a partial agonist at serotonin 5-HT_{1A} receptors, as well as an antagonist at serotonin 5-HT_{2B}, 5-HT_{2A} and histamine H_1 receptors It is licensed for the treatment of schizophrenia in adult patients.[1]

The recommended starting dose of cariprazine is 1.5 mg once daily. Thereafter, the dose can be increased by 1.5 mg increments to a maximum dose of 6 mg daily. It has a long half-life, and patients should be monitored for adverse reactions and treatment response for several weeks after starting cariprazine, and after each dose change.[1]

Background

Schizophrenia is a severe mental illness, characterised by three broad types of symptoms; positive (loss of contact with reality e.g. hallucinations), negative (diminished emotions and thought processes e.g. social withdrawal, self neglect) and cognitive impairments (e.g. attention and concentration, memory)[2,3]. Affected individuals often present with an acute episode involving positive symptoms, followed by a chronic illness with more negative symptoms *(but the experience of schizophrenia varies widely between individuals)*. The first episode of psychosis can be preceded by a prodromal period from days to around 18 months in duration, with a range of ill-defined, insidious, and non-specific symptoms, resulting in a gradual deterioration in personal functioning.[2,3]

Schizophrenia affects about 7 in 1000 adults, mostly in the 15-35 age group.[4] Compared with the baseline population, the rate of schizophrenia is higher in Black Caribbean and Black African people and their descendants. Men under the age of 45 years have twice the rate of schizophrenia as women.[3] About 220,000 people in the UK currently have a diagnosis of schizophrenia, of whom 14% receive inpatient care.[5,6]

NICE guidance on the management of psychosis and schizophrenia in adults stresses the need for early identification of people with distress, declining social functioning and behaviour suggestive of psychosis, and early access to psychosis services. Antipsychotic medication should be prescribed alongside psychological interventions, especially for subsequent episodes of psychosis. The choice of medication is determined in discussion with the person, taking risks and benefits of individual treatments into account.[3]

Healthy lifestyle measures relating to diet, physical activity and stopping smoking should be encouraged. In addition, the guidance stresses the need to offer early support and education to carers to enable a collaborative approach between patients, their carers and GP or other healthcare practitioner.

Clinical evidence for efficacy and safety

Four phase 3 RCTs evaluated cariprazine for the treatment of people with a diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of mental disorders (DSM IV-TR) of at least one years' duration. Two of the trials evaluated acute treatment of a psychotic episode over 6 weeks with cariprazine *vs*. placebo[7,8], one trial evaluated maintenance treatment *vs*. risperidone[9], and one trial evaluated relapse prevention

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vs, placebo[10]. In one acute trial, aripiprazole was an active control but not directly compared with cariprazine[7]. The main outcome measures were changes in the Positive and Negative Symptoms Scale (PANSS) scores from baseline to the end of treatment and subscales of those scores. Other outcome measures were the Clinician's Global Impression of disease severity and Improvement (CGI-S and CGI-I).

Results

Trials of acute treatment over 6 weeks titrated cariprazine doses up from an initial dose of 1.5 mg daily over two weeks, but one of the trials evaluated fixed doses of 3 mg and 6 mg daily[7], and the other allowed flexible daily dosing within the range 3 to 6 mg or 6 to 9 mg[8].

Both trials showed significantly greater improvement in PANSS total scores with cariprazine at doses of 3 mg to 9 mg daily than with placebo. In the flexible-dosing[8] trial, improvements in the positive symptoms subscale were significantly greater than placebo for all cariprazine groups, but negative symptom subscale scores were only greater in the higher cariprazine dose range (6 to 9 mg). The trial also reported significantly greater improvement for cariprazine *vs*. placebo using the CGI-S scale[8].

Longer-term treatment (26 to 72 weeks) involved either relapse prevention following treatment of an acute episode (1 trial[10]), or preventative treatment in people whose schizophrenia was stable (one trial[9]).

In the open-label dose titration and stabilisation phases of the ***relapse prevention trial***, all participants received cariprazine and those that showed continued or maintained improvement in their condition as measured using PANSS scores were then randomised to continued treatment with cariprazine or placebo. Participants were followed for 26 to 72 weeks for signs of relapse including significantly increased PANSS score, hospitalisation, and other signs of distress/worsening condition.

The time to relapse was significantly longer with cariprazine than placebo. Relapse occurred in 47.5% of placebo-treated and 24.8% of cariprazine-treated participants. The hazard of relapse was estimated to be half that of placebo-treated participants (Hazard Ratio [95% Confidence interval] = 0.45 [0.28, 0.73]). The most commonly met relapse criteria in the placebo- and cariprazine-treatment groups, respectively, were increase in PANSS score (43.4% and 20.8%), increase in CGI-S (28.3% and 4.0%), and score ≥ 4 on any of the assessed PANSS items (25.3% and 10.9%). The psychiatric hospitalisation criterion was met by 9.1% and 8.9% of placebo- and cariprazine-treated patients, respectively; the statistical significance of the comparison was not reported.

In the ***maintenance treatment trial***[9], participants whose schizophrenia had been stable for at least six months were randomised to treatment with cariprazine 4.5 mg daily or risperidone 4 mg daily for 26 weeks. At trial entry, the 460 participants had predominantly negative symptoms and low levels of positive symptoms. During the lead-in period, the participants' current antipsychotic medication dose was tapered down, and doses of cariprazine or risperidone slowly titrated up to target doses over 13 days. Participants received double-blind treatment for a further 26 weeks, followed by a 2-week safety follow up period.

The main outcome measure was the change in PANSS negative subscale scores after 26 weeks' treatment. Participants receiving cariprazine treatment showed significantly greater improvements in negative subscale scores than risperidone-treated participants, and more cariprazine-treated participants showed a response to treatment of at least a 20% decrease in PANSS negative subscale score (69% *vs*. 58%; Odds ratio [OR 2.08]; p = 0.002; Number needed to treat [NNT] = 9). Significant improvements for cariprazine *vs*. risperidone were also shown for Personal and Social Performance scale (PSP) total score and subscales (self-care, social relationships and activities) and the CGI-I.

Adverse events

The most frequent treatment-emergent adverse events (TEAEs) with cariprazine included akathisia (14.8%) / extrapyramidal disorder (7.3%), headache (12.5%) and insomnia (13.9%)[11]. Serious adverse events (SAEs) and adverse events (AEs) leading to premature discontinuation were worsening of schizophrenia, psychotic symptoms, and akathisia[11]. Several AEs including akathisia / restlessness, CPK (creatinine phosphokinase) elevation, insomnia, anxiety and blurred vision were dose-dependent[11].

Considerations for cost impact

In 2014, there were an estimated 365,394 people taking antipsychotic drugs in England and Wales, 39% of whom (142,504) were taking drugs for schizophrenia[12]. At current prices, the yearly costs of selected antipsychotics are (prices rounded to nearest pound):

- Risperidone (Generic) 4 to 6 mg daily £ 84 to £533
- Aripiprazole (Generic) 15 to 30 mg daily £ 38 to £157
- Cariprazine 1.5 to 6mg daily £1,048

Source: MIMs January 2019; Drug Tariff January 2019

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Keele University Centre for Medicines Optimisation
School of Pharmacy, Keele University, Keele, Staffordshire ST5 5BG Tel: 01782 733831 Email: mtrac@keele.ac.uk Web: www.mtrac.co.uk