Investigational Medication: Cariprazine

**Background:** Cariprazine (RGH-188) is an antipsychotic drug discovered by pharmaceutical company Gedeon Richter and is licensed by Actavis (formally Forest pharmaceutical). Cariprazine was resubmitted for a New Drug Application for schizophrenia and bipolar mania with the FDA in January 2015 with a pending decision in the second quarter of 2015. In November 2013, the FDA rejected approval of the drug indicating that more trial data was needed, though the effectiveness of the medication was clearly established. Action on the dopaminergic systems makes it also potentially useful as an add-on therapy in major depressive disorder.

**Mechanism of Action:** Cariprazine appears to be effective against the positive and negative symptoms of schizophrenia through its activity as a partial agonist on D₂ and D₃ receptor. It has a higher affinity for D₃ receptors than currently available antipsychotics. The partial agonist effects may block overactive dopamine receptors and stimulate dopamine in areas of the brain where dopamine levels are low.

**What makes Cariprazine Unique?** Most of the newer atypical antipsychotics are D₂ and 5-HT₂A receptor antagonists. Cariprazine is a partial agonist on D₂ and D₃ receptor with higher affinity for D₃. There could be less motor side effects since D₃ receptors are not located in areas such as the dorsal striatum where extrapyramidal side effects from this class of medications are seen. There may be some pro-cognitive benefits as demonstrated in rat studies which showed improved performance in a scopolamine-induced learning impairment paradigm in a water labyrinth test. It was been hypothesized that this could be from the selective antagonist nature of D₃ receptors. In schizophrenia and bipolar disorder, cognitive deficits often account for some of the functional impairment associated with these diseases.

**Previous Clinical Studies:**

Schizophrenia- Three positive trials in over 1700 patients, two fixed dose studies with active controls and one fixed-flexible placebo-controlled dose study using the change from baseline in Positive and Negative Syndrome Scale (PANSS) total score as primary efficacy endpoint.
Relapse Prevention of Schizophrenia-A 97 week randomized, double-blind, placebo-controlled clinical trial in adult patients with schizophrenia. The study included a 20-week open-label phase where patients with schizophrenia were treated with cariprazine 3, 6 or 9 mg per day. Patients who responded and met the stabilization criteria during the open-label period were then randomized to continue their cariprazine dose (3, 6 or 9 mg per day) or switched to placebo for up to 72 weeks or until a relapse occurred. The primary endpoint was time to first symptom relapse during the double blind phase.

There were 101 patients randomized to cariprazine 3 to 9 mg per day and 99 randomized to placebo. The primary efficacy measure was time to first relapse during the double-blind period. There were 25 relapses (24.8%) in the cariprazine group versus 47 relapses (47.5%) in the placebo group. Treatment with cariprazine was associated with a 55% reduction in risk of relapse versus placebo (hazard ratio 0.45, 95% CI [0.28, 0.73] p=0.0010).

Bipolar Mania- Three studies with over 1000 patients have been conducted that included a washout period of up to one week, three weeks of double-blind treatment, and two weeks of safety follow-up. Two of the studies administered cariprazine in flexible doses of 3 to 12 mg per day and one study used a fixed/flexible-dose design with two cariprazine treatment arms of 3 to 6 mg per day and 6 to 12 mg per day.

Investigators measured the effects of cariprazine using total score change on the Young Mania Rating Scale (YMRS), as well as change from baseline to Week 3 on single items of the YMRS. There was also more improvement than placebo in all three studies on the Positive and Negative Syndrome Scale (PANSS) total score as primary efficacy endpoint. Cariprazine was generally well tolerated.

The most commonly reported adverse reactions (≥5% and twice placebo), which were predominantly mild to moderate in severity, were akathisia, extrapyramidal disorder, dyspepsia, restlessness, tremor, fatigue and vomiting.

**Current Studies**

[Completed-Safety, Tolerability, and Efficacy of Cariprazine in Patients With Bipolar Depression]
Actively recruiting-An Efficacy, Safety and Tolerability of Cariprazine as an Adjunctive Treatment to Antidepressant Therapy (ADT) in Patients With Major Depressive Disorder (MDD)

References:


http://www.psychcongress.com/article/cariprazine-may-be-effective-manic-symptoms-bipolar-disorder-13677