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ADISINSIGHT REPORT

Cariprazine: First Global Approval

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Abstract Cariprazine (Vraylar™) is an oral atypical antipsychotic originated by Gedeon Richter. It is a potent dopamine D_3 and D_2 receptor partial agonist, which preferentially binds to the D_3 receptor. Cariprazine also has partial agonist activity at serotonin 5-HT_{1A} receptors. In September 2015, cariprazine received its first global approval in the USA for the treatment of schizophrenia and for the acute treatment of manic or mixed episodes associated with bipolar I disorder. It is also in development in a variety of countries for the treatment of schizophrenia with predominant negative symptoms (phase III), as adjunctive therapy for major depressive disorder (phase II/III) and for the treatment of bipolar depression (phase II). This article summarizes the milestones in the development of cariprazine leading to this first approval for schizophrenia and manic or mixed episodes associated with bipolar I disorder.

1 Introduction

The efficacy of antipsychotic drugs has long been considered to be mediated by antagonism at dopamine D_2 receptors, a mechanism common to all currently approved antipsychotics [1]. Treatment with D_2 receptor antagonists, particularly first generation antipsychotics, mainly alleviates positive symptoms of psychosis and is frequently associated with adverse extrapyramidal symptoms. Atypical (second generation) antipsychotics with partial agonist activity at D_2 receptors are less likely to produce extrapyramidal symptoms and their activity at other receptors provides additional benefits on mood, negative symptoms and cognitive function [2]. In particular, antagonism at D_3 receptors, which are primarily located in the limbic system, in addition to D_2 receptors is considered to provide additional therapeutic benefits in the treatment of schizophrenia and related disorders [3–5].

Cariprazine (Vraylar™) is a new orally administered dopamine D_3 and D_2 partial agonist with preferential binding to D_3 receptors that was approved by the US FDA in September 2015 for the treatment of schizophrenia and the acute treatment of manic or mixed episodes associated with bipolar I disorder [6].

The recommended dosage in the treatment of schizophrenia is 1.5–6 mg orally once daily with or without food. The starting dose is 1.5 mg, which can be increased to 3 mg on day 2, with further increments in 1.5 or 3 mg steps depending upon response and tolerability [7]. The recommended dosage in the treatment of manic or mixed episodes associated with bipolar I disorder is 3–6 mg orally once daily without regard to food. As with schizophrenia, the starting dose is 1.5 mg, increased to 3 mg on day 2 and then further increments of 1.5 or 3 mg as necessary according to response and tolerability up to the maximum dosage of 6 mg once daily [7].

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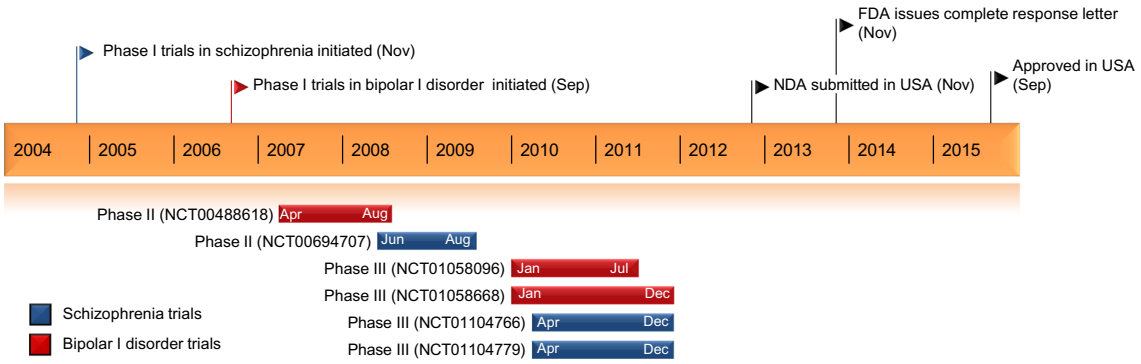


Key development milestones for cariprazine, focussing on pivotal US registration trials

The dosage of cariprazine should be reduced by half if a strong cytochrome P450 (CYP) 3A4 inhibitor is initiated concurrently; if patients are taking 4.5 mg once daily, the dosage should be reduced to 1.5 or 3 mg once daily; and if taking 1.5 mg once daily, the dosage should be reduced to 1.5 mg every second day [7]. In patients already taking a strong CYP3A4 inhibitor, the recommended starting dose of cariprazine is a 1.5 mg single dose on days 1 and 3, then 1.5 mg once daily from day 4 onwards, with an increase to a maximum dosage of 3 mg once daily. Concomitant use of cariprazine and a CYP3A4 inducer is not recommended [7].

The prescribing information carries a boxed warning that cariprazine is not approved for the treatment of patients with dementia-related psychosis, since elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death [7].

Cariprazine is at phase III development for the treatment of patients with schizophrenia and bipolar disorders in some countries of the EU, India, Russia, South Africa, Serbia, Colombia and Ukraine. Phase III development of the product for schizophrenia with predominant negative symptoms is underway in the Czech Republic, Hungary, Spain, Poland, Croatia, France, Serbia, Romania, Russia, Ukraine and Bulgaria, while phase III development as adjunctive therapy for major depressive disorder (MDD) is underway in Puerto Rico and the US. Phase III development is also underway in India, Romania, Slovakia, the US and Ukraine for the prevention of relapse of schizophrenia. The product is at phase II/III development for the treatment of schizophrenia in Japan, South Korea and Taiwan, and is in phase II development as adjunctive therapy for MDD in Estonia, Finland, Slovakia, Sweden, Ukraine and the UK. Cariprazine is also being investigated for the treatment of patients with bipolar depression and is at phase II development in Bulgaria, Canada, Colombia, Russia, Ukraine and the US.

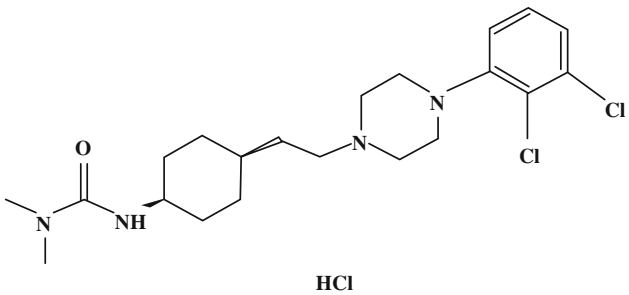
1.1 Company Agreements

In November 2004, Gedeon Richter and Forest Laboratories entered into a collaboration to develop cariprazine and related compounds. In exchange for exclusive rights to the product in Canada and the US, Forest paid Richter an upfront payment and Richter will be eligible for milestone payments, as well as royalties on sales. Richter will have rights in the rest of the world, and both companies will collaborate and jointly fund the development of cariprazine and related compounds [8].

Gedeon Richter and Mitsubishi Pharma Corporation entered into a licensing and co-operation agreement in 2004. Under the terms of the agreement, Mitsubishi Pharma gained exclusive rights to develop, manufacture, and commercialize cariprazine, and related compounds, in Japan and Asia [9].

1.2 Patent Information

Cariprazine is protected by a US composition-of-matter patent that expires in 2027, without patent term extension, and a US patent covering polymorphic forms that expires in 2028.



Chemical structure of cariprazine hydrochloride

2 Scientific Summary

2.1 Pharmacodynamics

High occupancy antagonism at D_2 receptors has been shown to be related to clinical antipsychotic efficacy, particularly for positive symptoms of schizophrenia, but it has been hypothesized that sub-nanomolar D_3 receptor antagonism combined with nanomolar D_2 receptor antagonism would provide greater benefits in improving cognition and reducing adverse events such as catalepsy [10]. Cariprazine is an orally active, potent D_3 and D_2 receptor partial agonist, although the exact mechanism of action of cariprazine is not known [7, 10]. It displays ≈six- to eightfold higher affinity for D_3 receptors [inhibition constant (Ki) = 0.085 nmol/L] than for D_2 receptors (D_{2L} Ki = 0.49 nmol/L; D_{2S} Ki = 0.69 nmol/L) in vitro [7, 10]. It is also a partial agonist at 5-HT_{1A} receptors (Ki = 2.6 nmol/L), a high-affinity antagonist at 5-HT_{2B} receptors (Ki = 0.58 nmol/L), and a moderate-affinity antagonist at 5-HT_{2A} (Ki = 18.8 mmol/L) and histamine H_1 receptors (Ki = 23 nmol/L) [7, 10, 11]. It shows low affinity for 5-HT_{2C} (Ki = 134 nmol/L) and α_{1A}-adrenergic receptors (Ki = 155 nmol/L), and no appreciable affinity for muscarinic receptors [7, 10].

The beneficial effects of cariprazine on cognitive deficits [12] and mania [13], as well as its lack of cataleptogenicity [14] have been demonstrated in animal models.

In patients with schizophrenia, dose-dependent, high occupancy of brain D_3 and D_2 receptors was demonstrated following treatment with cariprazine 0.5–12 mg/day for up to 15 days [15]. After treatment with cariprazine for 15 days, the mean D_3 and D_2 receptor occupancy rates were 99 and 95 %, respectively, for the 12 mg/day dosage, and 76 and 45 % for the 1 mg/day dosage. The D_3/D_2 selectivity ratio after cariprazine administration for 15 days was 3.43 [15].

Cariprazine at three times the maximum recommended dose did not prolong the corrected QT interval, indicating a low arrhythmogenic potential [7].

2.2 Pharmacokinetics

Cariprazine is extensively metabolized by hydroxylation and demethylation. The two main active metabolites desmethyl cariprazine and didesmethyl cariprazine display similar functional profiles (partial agonism) and are pharmacologically equipotent to the parent drug [7]. Therefore, the combined concentration of cariprazine plus the two main metabolites is considered to be the most clinically relevant drug concentration.

In healthy volunteers, the times (t_{max}) to reach maximum plasma concentration (C_{max}) following oral administration were 3.6 h for cariprazine, 6.5 h for desmethyl cariprazine and 18.1 h for didesmethyl cariprazine [16, 17]. In Japanese patients with schizophrenia receiving cariprazine 3, 6 or 9 mg/day, steady state was reached within 1–2 weeks for cariprazine and desmethyl cariprazine, within 4 weeks for didesmethyl cariprazine and within 3 weeks for the three moieties combined [18]. The absorption of cariprazine was not affected by food [7]. The plasma concentrations at steady state were approximately dose-proportional for cariprazine and the two main metabolites [18]. At steady state, didesmethyl cariprazine was the main drug entity in plasma, with values for the area under the plasma concentration-time curve from time zero to 24 h (AUC_{24}) that were two- to threefold higher than those of cariprazine [18]. The AUC_{24} values for desmethyl cariprazine were 20–40 % of those for cariprazine [17, 18]. Cariprazine and its major metabolites are highly bound (91–97 %) to plasma proteins [7].

Cariprazine is extensively metabolized by CYP3A4, and to a smaller extent by CYP2D6, to desmethyl and didesmethyl cariprazine [7]. Desmethyl cariprazine is further metabolized to didesmethyl cariprazine by these same isoenzymes. The didesmethyl metabolite is metabolized by CYP3A4 to a hydroxylated metabolite [7]. The functional half-life of the combined drug activity was estimated at ≈1 week [18]. After the last dose, plasma concentrations decreased ≥90 % within 1 week for cariprazine and desmethyl cariprazine, and by ≈50 % within 1 week for didesmethyl cariprazine [18]. In patients with schizophrenia, 21 % of the daily dose was excreted in urine; 1.2 % of the daily dose was present in urine as unchanged drug [7].

The pharmacokinetics of cariprazine and its major metabolites are not altered to a clinically significant extent in patients with hepatic or renal impairment [7, 16]. Similarly, the pharmacokinetics were not clinically significantly affected by age, sex, race or CYP2D6 poor metabolizer status [7].

Features and properties of cariprazine

Alternative names	Vraylar™; MP-214; RGH-188
Class	Antidepressants, antipsychotics, chlorobenzenes, cyclohexanes, piperazines, small molecules, urea compounds
Mechanism of action	Dopamine D_2 receptor partial agonists, dopamine D_3 receptor partial agonists
Route of administration	PO
Pharmacodynamics	Sub-nanomolar binding affinity for D_3 receptors, with ≈six- to eightfold lower affinity binding to D_2 receptors
	Partial agonist at 5-HT_{1A} receptors, and antagonist at 5-HT_{2B} and 5-HT_{2A} receptors
	High D_3 and D_2 receptor occupancy rates in treated patients' brains; D_3/D_2 selectivity ratio of 3.43
Pharmacokinetics	Two major active metabolites; steady state achieved in 3 weeks for combined parent + metabolites; functional half-life of ≈1 week for combined drug; metabolized mostly by CYP3A4 (partially by CYP2D6); 21 % of dose excreted in urine
	Exposure not affected by food, renal or hepatic impairment or CYP2D6 poor metabolizer status
	Potential drug interactions with strong inhibitors of CYP3A4
Most frequent adverse events	Akathisia, extrapyramidal symptoms
ATC codes	
WHO ATC code	N05A-X15 (cariprazine), N06A-X (other antidepressants)
EphMRA ATC code	N5A (antipsychotics), N6A9 (antidepressants, all others)
Chemical name	7-[4-[4-(1-Benzothiophen-4-yl)piperazin-1-yl]butoxy]quinolin-2(1H)-one

Cariprazine and its major metabolites do not induce CYP isoenzymes and are poor inhibitors of CYP isoenzymes [7]. They are also not substrates for or strong inhibitors of transporter proteins. Ketoconazole, a strong inhibitor of CYP3A4, increased the C_{max} and AUC_{24} of cariprazine (by ≈3.5 to 4-fold) and didesmethyl cariprazine (by ≈1.5-fold), and decreased the C_{max} and AUC_{24} of desmethyl cariprazine (by approximately one-third). The impact of moderate CYP3A4 inhibitors or CYP3A4 inducers is not known [7].

2.3 Therapeutic Trials

The approval of cariprazine in the US was based on three fully published 6-week clinical trials in patients with schizophrenia (NCT00694707, NCT01104766 and NCT01104779) and three 3-week trials treating mania associated with bipolar I disorder (NCT00488618, NCT01058096 and NCT01058668) [6]. Cariprazine has also been assessed for the treatment of schizophrenia with predominant negative symptoms, as adjunctive treatment of major depressive disorder and for the treatment of bipolar depression.

2.3.1 Schizophrenia

Oral cariprazine 1.5–9 mg/day was superior ($p < 0.01$–0.0001) to placebo in reducing the Positive and Negative Syndrome Scale (PANSS) total score at 6 weeks (primary endpoint) in patients with schizophrenia in each of the three randomized, double-blind, placebo-controlled, US registration trials [2, 19, 20].

In a phase II, dose-ranging trial (NCT00694707) in 711 patients [intent-to-treat (ITT) population] with acute exacerbation of schizophrenia, PANSS total score at 6 weeks (primary endpoint; 96.7–97.3 per group at baseline) was reduced significantly more than placebo by cariprazine 1.5, 3.0 and 4.5 mg/day (−19.4, −20.7 and −22.3 vs. −11.8 for placebo; each $p \leq 0.001$) beginning from week 1 (3.0 and 4.5 mg/day) or week 2 (1.5 mg/day) [19]. Significant reductions were seen for both the PANSS positive and negative subscales. Risperidone 40 mg/day, which was included as an internal control for assay sensitivity, also reduced PANSS total score significantly more than placebo (−26.9 vs. −11.8; $p \leq 0.001$). Superiority of cariprazine 1.5, 3 and 4.5 mg/day over placebo was also apparent for improvements in Clinical Global Impressions-Severity (CGI-S) ($p \leq 0.01$–0.001), CGI-Improvement (CGI-I) ($p \leq 0.01$–0.001) and the 16-item Negative Symptom Assessment (NSA-16) total score (all $p \leq 0.001$). The proportions of PANSS responders (≥30 % improvement from baseline) were significantly higher with cariprazine 1.5 (31.4 %; $p < 0.05$), 3.0 (35.7 %; $p \leq 0.01$) and 4.5 mg/day (35.9 %; $p \leq 0.001$) than with placebo (18.9 %) at 6 weeks [19].

The PANSS total score at 6 weeks (primary endpoint; 95.7–96.5 per group at baseline) was reduced significantly more with cariprazine 3 (−6.0 difference; $p < 0.01$) and 6 mg/day (−8.8 difference; $p < 0.0001$) than with placebo in a phase III, fixed-dose trial (NCT01104766) in 617

patients with acute exacerbation of schizophrenia (published as an abstract) [20]. Cariprazine was also superior to placebo for reductions in CGI-S (secondary endpoint) at both 3 (−0.4; $p < 0.01$) and 6 mg/day (−0.5; $p < 0.0001$). Aripiprazole was included as an internal control and was likewise superior to placebo for reductions in PANSS total score (−7.0; $p < 0.001$) and CGI-S score (−0.4; $p = 0.0001$) [20]. A post hoc analysis indicated that cariprazine showed superiority to placebo over all of the PANSS subdomains assessed within 2 weeks for the 6 mg/day dosage and within 3 weeks for the 3 mg/day dosage (published as an abstract) [21].

In a phase III trial (NCT01104779) in 439 patients (ITT population) with acute exacerbation of schizophrenia, the PANSS total score (baseline 96.3–96.6) at 6 weeks (primary endpoint) was reduced significantly more than with placebo in the cariprazine 3–6 mg/day group (−22.8 vs. −16.0; $p = 0.003$) beginning at week 2 and in the cariprazine 6–9 mg/day group (−25.9 vs. −16.0; $p < 0.001$) beginning at week 1 [2]. The PANSS response rates for cariprazine 3–6 (28.6 %) and 6–9 (34.7 %) mg/day did not differ significantly from that with placebo (24.8 %). Significant improvements at 6 weeks for both dose ranges of cariprazine compared with placebo were observed for CGI-S score (−1.4 and −1.6 vs. −1.0; $p < 0.05$ and $p < 0.001$) and CGI-I score (2.6 and 2.4 vs. 3.2; both $p < 0.001$). Cariprazine was superior to placebo for NSA-16 total score at the 6–9 mg/day dosage (−9.1 vs. −5.6; $p < 0.01$), but not at the 3–6 mg/day dosage (−8.0 vs. −5.6). Improvements in the Schizophrenia Quality of Life Scale Revision 4 total score were significantly greater than with placebo for cariprazine 3–6 mg/day (−9.5 vs. −4.5; $p = 0.044$), but not with cariprazine 6–9 mg/day (−8.0 vs. −4.5) [2].

In a phase III trial (NCT01412060), long-term treatment with cariprazine in stabilized patients with schizophrenia was shown to almost halve the rate of relapse compared with placebo over 72 weeks of treatment [22]. Patients with an acute episode of schizophrenia who were stabilized with open-label cariprazine 3–9 mg/day treatment over 20 weeks were randomized ($n = 200$) to double-blind treatment with cariprazine 3–9 mg/day or placebo for up to 72 weeks. Relapse occurred in 24.8 % of cariprazine recipients compared with 47.5 % of placebo recipients (hazard ratio 0.45; 95 % CI 0.28–0.73). The time to relapse was significantly ($p = 0.001$) longer in cariprazine recipients than in placebo recipients [22].

2.3.2 Manic or Mixed Episodes in Bipolar I Disorder

In all three randomized, double-blind, placebo-controlled, US registration trials, cariprazine 3–12 mg/day reduced the Young Mania Rating Scale (YMRS) total score (primary endpoint) and the CGI-I score (secondary endpoint) at 3 weeks significantly ($p < 0.01$–0.0001) more than placebo in patients with acute mania or mixed episodes associated with bipolar I disorder [23–25]. Superiority over placebo was noted within the first 2–7 days in the trials [23–25].

In a phase II, multinational trial (NCT00488618) in 235 patients (ITT population) with acute mania associated with bipolar I disorder, flexible-dose cariprazine (3–12 mg/day; mean 8.8 mg/day) significantly reduced compared with placebo the least squares mean (LSM) YMRS total score [−15.0 vs. −8.9 (baseline score 30.2–30.6 per group); $p < 0.0001$] and the CGI-S score [−1.6 vs. −0.9 (baseline score 4.6–4.7); $p = 0.0001$] at 3 weeks [23]. Significantly more cariprazine than placebo recipients met the criteria for YMRS response (≥50 % reduction from baseline) [48 vs. 25 %; $p < 0.001$] and YMRS remission (YMRS total score ≤12) [42 vs. 23 %; $p < 0.01$] at 3 weeks [23]. Cariprazine also significantly improved the CGI-I score (2.4 vs. 3.2; $p < 0.0001$) and the PANSS total score (−9.9 vs. −6.3; $p < 0.05$), but not the Montgomery–Åsberg Depression Rating Scale (MADRS) total score (−2.6 vs. −2.0), compared with placebo at 3 weeks [23].

In a similar phase III, flexible-dose (cariprazine 3–12 mg/day) trial (NCT01058096) in 310 patients (ITT population) with acute mania associated with bipolar I disorder, cariprazine significantly reduced the YMRS total score (primary endpoint; baseline value 32.1–32.3) significantly more than placebo at 3 weeks (−19.6 vs. −15.3; $p = 0.0004$) [25]. The proportions of cariprazine recipients receiving a final dosage of 3, 6, 9 or 12 mg/day were 9, 22, 30 and 39 %, respectively. Cariprazine was also superior to placebo with respect to improvements in the secondary endpoint of CGI-S score (−1.9 vs. −1.5; $p < 0.01$), as well as the additional endpoints of CGI-I score (2.0 vs. 2.5; $p < 0.001$), PANSS total score (−16.5 vs. −13.2; $p < 0.01$), YMRS response (58.9 vs. 44.1 %; $p < 0.01$) and YMRS remission (51.9 vs. 34.9 %; $p < 0.01$). Cariprazine was not superior to placebo with regard to reductions in MADRS total score (−3.7 vs. −3.3) [25].

A phase III trial (NCT01058668) assessed the efficacy of low- (3–6 mg/day) and high-dose (9–12 mg/day) cariprazine in 492 patients (ITT population) with acute manic or mixed episodes associated with bipolar I disorder [24]. Reductions in the YMRS total score (primary endpoint; baseline score of 32.6–33.2) at 3 weeks with both low- and high-dose cariprazine were significantly greater than with placebo (−18.6 and −18.5 vs. −12.5; both $p < 0.001$). Both the low- and high-dose ranges of cariprazine were superior to placebo for the secondary endpoint of CGI-S (both −1.9 vs. −1.3; $p < 0.001$) and the additional endpoints of CGI-I (both 2.2 vs. 2.9; $p < 0.001$), PANSS total score (−14.3 and −13.6 vs. −6.9; both $p < 0.001$), MADRS total score (−4.0 and −3.6 vs. −2.4; $p <$0.01 and

Key clinical trials of cariprazine

Drugs(s)	Indication	Phase	Status	Location(s)	Sponsor	Identifier
Cariprazine, placebo	Bipolar I disorder	II	Completed	Multinational	Forest	NCT00488618
Cariprazine, placebo	Bipolar I disorder	III	Completed	US, India	Forest	NCT01058096
Cariprazine, placebo	Bipolar I disorder	III	Completed	Multinational	Forest	NCT01058668
Cariprazine	Bipolar I disorder	III	Completed	Multinational	Forest	NCT01059539
Cariprazine, placebo	Bipolar depression	II	Completed	US	Forest	NCT00852202
Cariprazine, placebo	Bipolar depression	II	Completed	Multinational	Forest	NCT01396447
Cariprazine, placebo, +ADT	MDD	II	Completed	US	Forest	NCT00854100
Cariprazine, placebo, +ADT	MDD	II	Completed	Multinational	Forest	NCT01469377
Cariprazine, placebo, +ADT	MDD	III	Recruiting	US, Puerto Rico	Forest	NCT01715805
Cariprazine, +ADT	MDD	III	Active	US, Puerto Rico	Forest	NCT01838876
Cariprazine, placebo	Schizophrenia	II	Completed	US	Forest	NCT00404573
Cariprazine, risperidone, placebo	Schizophrenia	II	Completed	Multinational	Forest	NCT00694707
Cariprazine	Schizophrenia	II	Completed	Multinational	Forest	NCT00839852
Cariprazine	Schizophrenia	II	Completed	Japan	Mitsubishi Tanabe	NCT00862992
Cariprazine, risperidone, placebo	Schizophrenia	II/III	Recruiting	Japan, Korea, Taiwan	Mitsubishi Tanabe	NCT01625000
Cariprazine, risperidone	Schizophrenia	II/III	Completed	Japan	Mitsubishi Tanabe	NCT01625897
Cariprazine, risperidone	Schizophrenia	II/III	Recruiting	Japan, Korea, Taiwan	Mitsubishi Tanabe	NCT01626872
Cariprazine	Schizophrenia	II/III	Completed	Japan	Mitsubishi Tanabe	NCT01626885
Cariprazine, aripiprazole, placebo	Schizophrenia	III	Completed	Multinational	Forest	NCT01104766
Cariprazine, placebo	Schizophrenia	III	Completed	Multinational	Forest	NCT01104779
Cariprazine	Schizophrenia	III	Completed	Multinational	Forest	NCT01104792
Cariprazine, placebo	Schizophrenia-relapse prevention	III	Completed	Multinational	Forest	NCT01412060
Cariprazine, risperidone	Schizophrenia-PNS	III	Completed	Multinational	Gedeon Richter	EudraCT2012-005485-36

+ADT adjunctive to antidepressant therapy, *MDD* major depressive disorder, *PNS* predominant negative symptoms

$p < 0.05$), YMRS responders (60.6 and 59.3 vs. 37.5 %; both $p < 0.001$) and YMRS remitters (44.8 and 44.3 vs. 29.4 %; both $p < 0.01$) [24].

2.3.3 Schizophrenia with Predominant Negative Symptoms

Cariprazine was significantly more effective than risperidone at improving the negative symptoms of schizophrenia in a phase III trial (EudraCT2012-005485-36) in patients with predominant negative symptoms of schizophrenia [26]. Patients enrolled in the study had to have a PANSS factor score for negative symptoms (PANSS-FSNS) ≥24 and scores ≥4 for at least two of the three core negative symptoms. In addition, patients had to have a PANSS score for positive symptoms ≤19 and no clinically relevant depression or extrapyramidal symptoms. A total of 461 patients were randomized to double-blind treatment with cariprazine 4.5 mg/day or risperidone 4 mg/day for 24 weeks. The improvement (reduction) from baseline in PANSS-FSNS at 24 weeks (primary endpoint) was significantly greater with cariprazine than with risperidone (mean difference −1.47; 95 % CI −2.39 to −0.53; $p = 0.002$) [26]. In addition, functional improvement from baseline as assessed with the Personal and Social Performance Scale total score was significantly greater with cariprazine than with risperidone (mean difference 4.63; 95 % CI 2.71–6.56; $p < 0.001$) [26].

2.3.4 Major Depressive Disorder

A phase II, randomized, double-blind, placebo-controlled, dose-ranging trial (NCT01469377) assessed the efficacy of cariprazine 1–2 or 2–4.5 mg/day for 8 weeks as adjunctive treatment to standard antidepressant therapy in 819 patients with major depressive disorder (published as an abstract) [27]. The LSM change from baseline in MADRS total score at 8 weeks (primary endpoint), using a mixed-effects model for repeated measures, was significantly greater than with placebo for cariprazine 2–4.5 mg/day (difference −2.2; $p = 0.0114$), but not for cariprazine 1–2 mg/day (difference −0.9). Neither cariprazine dosage was superior to placebo with respect to change from baseline in the Sheehan Disability Scale score [27].

2.3.5 Bipolar Depression

The reduction from baseline in MADRS total score at week 6 (primary endpoint) was significantly greater than with placebo for cariprazine 1.5 mg/day than with placebo (LSM difference −4.0; $p = 0.0030$), but not for cariprazine 0.75 mg/day (LSM difference −1.9) or cariprazine 3.0 mg/day (LSM difference −2.5) in a phase II, randomized, double-blind, placebo-controlled trial (NCT01396447) involving 571 patients (ITT population) with bipolar I disorder and current depression (baseline MADRS score >20) (published as abstracts) [28, 29]. Similarly, for CGI-S score, cariprazine 1.5 mg/day was superior to placebo (LSM difference −0.4; $p = 0.01$), but the CGI-S changes with cariprazine 0.75 (LSM difference +0.1) and 3.0 (LSM difference −0.3) mg/day did not differ significantly from those with placebo [28, 29]. Both cariprazine 1.5 and 3.0 mg/day, but not cariprazine 0.75 mg/day, were superior to placebo for change in the 17-item Hamilton Depression Rating Scale (HAMD-17) score ($p \leq 0.01$) and the MADRS response ($p < 0.05$–0.01). The cariprazine 1.5 mg/day group, but not either of the other two dosage groups, was superior ($p < 0.01$) to placebo with respect to rates of MADRS remission and HAMD-17 remission [28].

2.4 Adverse Events

Cariprazine was generally well tolerated in published short-term (3–8 weeks) clinical trials, with most treatment-emergent adverse events (TEAEs) being of mild or moderate severity [2, 19, 20, 23–25]. The most frequent TEAEs with an incidence at least twice that of placebo recipients in one or more trials were akathisia, extrapyramidal disorder, tremor, dyspepsia, nausea, vomiting, dizziness, diarrhoea, constipation, insomnia and sedation [2, 19, 20, 23–25]. Akathisia was the most common extrapyramidal symptom, followed by parkinsonism and restlessness; dystonia was less common [7]. The most common TEAEs leading to discontinuation of treatment with cariprazine were worsening of disease (psychosis or mania) and akathisia [2, 19, 20, 23–25].

Cariprazine was not associated with clinically significant changes in clinical laboratory parameters, vital signs, bodyweight or cardiac parameters compared with placebo, except for a higher increase in fasting glucose level in two trials [23, 25]. Some studies noted a higher incidence of elevated liver enzymes with cariprazine compared with placebo, but none met Hy's law criteria [ALT or AST ≥3× the upper limit of normal (ULN), plus total bilirubin ≥2× ULN, plus alkaline phosphatase <2× ULN] [2, 19, 23].

Similar tolerability for cariprazine was observed in an open-label, 53-week trial (48 weeks of cariprazine treatment) in 586 patients with schizophrenia (NCT01104792) (published as an abstract) [30]. The most common TEAEs were akathisia, headache, insomnia and increase in bodyweight. Worsening disease state was the most common serious adverse event and the most common reason for discontinuation of treatment. The incidence of parkinsonism (Simpson–Angus Scale >3) was 11 % and that for akathisia (Barnes Akathisia Rating Scale >2) was 18 %. Suicidal ideation was recorded in 2.8 % of patients, but no suicidal behaviour was recorded. There were no clinically meaningful changes in laboratory parameters or vital signs [30].

In an open-label, 20-week study (16 weeks of treatment with cariprazine 3–12 mg/day) in 402 patients with bipolar I disorder (NCT01059539) (published as an abstract), the most common TEAEs were akathisia (33 % of patients), headache (17 %), constipation (11 %) and nausea (10 %) [31]. Serious adverse events occurred in 8 % of patients; mostly worsening disease or akathisia. Extrapyramidal symptom-related TEAEs occurred in 46 % of patients, although only 6 % of patients discontinued therapy as a result of TEAEs related to extrapyramidal symptoms [31]. Suicidal ideation assessed on the Columbia-Suicide Severity Rating Scale occurred in 9 % of patients and suicidal behaviour in 1 %. There were no meaningful changes in laboratory parameters, ECG, vital signs or ophthalmology parameters [31].

The US prescribing information for cariprazine carries a boxed warning of increased mortality (mostly related to cardiovascular or infectious causes) in elderly patients with dementia-related psychosis who are treated with antipsychotic drugs and cautions that cariprazine is not approved for the treatment of patients with dementia-related psychosis [7].

2.5 Ongoing Clinical Trials

2.5.1 Schizophrenia

Mitsubishi Tanabe Pharma initiated a phase II/III trial of cariprazine in adult patients with acute exacerbation of schizophrenia (NCT01625000) in 2012. The randomized, double-blind, placebo-controlled study will enroll approximately 480 patients in Japan, South Korea and Taiwan. It will assess low, middle and high once-daily doses of cariprazine, and will include a risperidone active comparator arm. The primary endpoint is defined as a change in the PANSS total score at week 6. A double-blind, 60-week extension to this study is planned (NCT01626872) and is expected to include half of the patients from the 6-week trial. The primary goal of the extension study is to evaluate the long-term safety and tolerability of orally administered cariprazine.

2.5.2 Major Depressive Disorder

Forest Laboratories and Gedeon Richter are conducting a phase III trial of cariprazine as an adjunctive therapy to antidepressants in adult patients with major depressive disorder (NCT01715805). In this randomized, double-blind trial, patients will receive oral cariprazine 1.5 to 4.5 mg/day or placebo, for 8 weeks, in addition to background antidepressant therapy. The primary endpoint is the change in MADRS score at 8 weeks, while the secondary endpoint is change in Sheehan Disability Scale score at 8 weeks. The trial is recruiting approximately 1100 patients in the US and Puerto Rico.

Allergan and Gedeon are also conducting a phase III, 26-week, open-label, flexible-dose (1.5 to 4.5 mg/day) extension trial (NCT01838876) to assess the long-term safety and tolerability of cariprazine as an adjunct to antidepressant therapy in adult patients with major depressive disorder. The study has enrolled 347 patients and the final data collection date was projected to be July 2015.

3 Current Status

Cariprazine received its first global approval on 17 September 2015 for the treatment of schizophrenia and the acute treatment of manic or mixed episodes associated with bipolar I disorder in the USA [6].

Compliance with Ethical Standards

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