For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

CARIQUEL

1. Generic Name

Cariprazine Capsules 1.5mg, 3mg, 4.5mg & 6mg

2. Qualitative and quantitative composition

Each hard gelatin capsule contains

Cariprazine hydrochloride equivalent to

Cariprazine……. 1.5mg/ 3mg/ 4.5mg/ 6mg

Excipients…… q.s.

Approved colors used in capsule shell.

The excipients used are Mannitol, Talc, Magnesium Stearate.

3. Dosage form and strength

Dosage form: Capsules

Strength: 1.5 mg, 3 mg, 4.5 mg & 6 mg

4. Clinical particulars

4.1 Therapeutic indication

Cariprazine Capsules are indicated for the treatment of Schizophrenia in adults. Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.

4.2 Posology and method of administration

Posology

CARIQUEL is given orally once daily. Because of the long half-life of cariprazine and its active metabolites, changes in dose will not be fully reflected in plasma for several weeks. Prescribers should monitor patients for adverse reactions and treatment response for several weeks after starting CARIQUEL and after each dosage change.

Schizophrenia

The recommended dosage range is 1.5 mg to 6 mg once daily. The starting dosage of cariprazine is 1.5 mg daily. The dosage can be increased to 3 mg on Day 2. Depending upon clinical response and tolerability, further dose adjustments can be made in 1.5 mg or 3 mg increments. The maximum recommended dosage is 6 mg daily. In short-term controlled trials, dosages above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

Manic or Mixed Episodes Associated with Bipolar I Disorder

The recommended dosage range is 3 mg to 6 mg once daily. The starting dose of cariprazine is 1.5 mg and should be increased to 3 mg on Day 2. Depending upon clinical response and tolerability, further dose adjustments can be made in 1.5 mg or 3 mg increments. The maximum recommended dosage is 6 mg daily. In short-term controlled trials, dosages above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

Depressive Episodes Associated with Bipolar I Disorder (Bipolar Depression)

The starting dose of cariprazine is 1.5 mg once daily. Depending upon clinical response and tolerability, the dosage can be increased to 3 mg once daily on Day 15. Maximum recommended dosage is 3 mg once daily.

Dosage Adjustments for CYP3A4 Inhibitors and Inducers

CYP3A4 is responsible for the formation and elimination of the major active metabolites of cariprazine.

Dosage recommendation for patients initiating a strong CYP3A4 inhibitor while on a stable dose of cariprazine: If a strong CYP3A4 inhibitor is initiated, reduce the current dosage of cariprazine by half. For patients taking 4.5 mg daily, the dosage should be reduced to 1.5 mg or 3 mg daily. For patients taking 1.5 mg daily, the dosing regimen should be adjusted to every other day. When the CYP3A4 inhibitor is withdrawn, cariprazine dosage may need to be increased.

Dosage recommendation for patients initiating cariprazine therapy while already on a strong CYP3A4 inhibitor: Patients should be administered 1.5 mg of cariprazine on Day 1 and on Day 3 with no dose administered on Day 2. From Day 4 onward, the dose should be administered at 1.5 mg daily, then increased to a maximum dose of 3 mg daily. When the CYP3A4 inhibitor is withdrawn, cariprazine dosage may need to be increased.

Dosage recommendation for patients concomitantly taking cariprazine with CYP3A4 inducers: Concomitant use of cariprazine and a CYP3A4 inducer has not been evaluated and is not recommended because the net effect on active drug and metabolites is unclear.

Method of administration

Oral use, it can be taken with or without food

4.3 Contraindications

Cariprazine is contraindicated in patients with history of a hypersensitivity reaction to cariprazine. Reactions have ranged from rash, pruritus, urticaria, and events suggestive of angioedema (e.g., swollen tongue, lip swelling, face edema, pharyngeal edema, and swelling face).

4.4 Special warnings and precautions for use

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Antipsychotic drugs increase the all-cause risk of death in elderly patients with dementia-related psychosis. Analyses of 17 dementia-related psychosis placebo-controlled studies (modal duration of 10 weeks and largely in patients taking atypical antipsychotic drugs)

revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that in placebo-treated patients. Over the course of a typical 10-week controlled study, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in placebo-treated patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. CARIQUEL is not approved for the treatment of patients with dementia-related psychosis

Suicidal Thoughts and Behaviors in Children, Adolescents and Young Adults

In pooled analyses of placebo-controlled studies of antidepressant drugs (SSRIs and other antidepressant classes) that included approximately 77,000 adult patients and 4,500 pediatric patients, the incidence of suicidal thoughts and behaviors in antidepressant-treated patients age 24 years and younger was greater than in placebo-treated patients. There was considerable variation in risk of suicidal thoughts and behaviors among drugs, but there was an increased risk identified in young patients for most drugs studied. There were differences in absolute risk of suicidal thoughts and behaviors across the different indications, with the highest incidence in patients with MDD. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1.

Table 1: Risk Differences of the Number of Patients of Suicidal Thoughts and Behaviour in the Pooled Placebo-Controlled Studies of Antidepressants in Paediatric* and Adult Patients

Age Range	Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviours per 1000 Patients Treated
	Increases Compared to Placebo
<18 years old	14 additional patients
18-24 years old	5 additional patients
	Decreases Compared to Placebo
25-64 years old	1 fewer patient
≥65 years old	6 fewer patients

* Cariprazine is not approved for use in pediatric patients.

It is unknown whether the risk of suicidal thoughts and behaviors in children, adolescents, and young adults extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with MDD that antidepressants delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

Monitor all antidepressant-treated patients for any indication for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing CARIQUEL, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis

In reported placebo-controlled studies in elderly subjects with dementia, patients randomized to risperidone, aripiprazole, and olanzapine had a higher incidence of stroke and transient ischemic attack, including fatal stroke. CARIQUEL is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS)

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported in association with administration of antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, delirium, and autonomic instability. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

If NMS is suspected, immediately discontinue CARIQUEL and provide intensive symptomatic treatment and monitoring.

Tardive Dyskinesia

Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with antipsychotic drugs, including CARIQUEL. The risk appears to be highest among the elderly, especially elderly women, but it is not possible to predict which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of tardive dyskinesia and the likelihood that it will become irreversible increase with the duration of treatment and the cumulative dose. The syndrome can develop after a relatively brief treatment period, even at low doses. It may also occur after discontinuation of treatment.

Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is discontinued. Antipsychotic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, possibly masking the underlying process. The effect that symptomatic suppression has upon the long-term course of tardive dyskinesia is unknown.

Given these considerations, CARIQUEL should be prescribed in a manner most likely to reduce the risk of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients: 1) who suffer from a chronic illness that is known to respond to antipsychotic drugs; and 2) for whom alternative, effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, use the lowest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. Periodically reassess the need for continued treatment.

If signs and symptoms of tardive dyskinesia appear in a patient on CARIQUEL, drug discontinuation should be considered. However, some patients may require treatment with CARIQUEL despite the presence of the syndrome.

Late-Occurring Adverse Reactions

Adverse events may first appear several weeks after the initiation of CARIQUEL treatment, probably because plasma levels of cariprazine and its major metabolites accumulate over time.

As a result, the incidence of adverse reactions in short-term studies may not reflect the rates after longer term exposures Monitor for adverse reactions, including extrapyramidal symptoms (EPS) or akathisia, and patient response for several weeks after a patient has begun CARIQUEL and after each dosage increase. Consider reducing the dose or discontinuing the drug.

Metabolic Changes

Atypical antipsychotic drugs, including CARIQUEL, have caused metabolic changes, including hyperglycemia, diabetes mellitus, dyslipidemia, and weight gain. Although all of the drugs in the class to date have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assess fasting plasma glucose before or soon after initiation of antipsychotic medication, and monitor periodically during long-term treatment.

Schizophrenia

In the 6-week, placebo-controlled studies of adult patients with schizophrenia, the proportion of patients with shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) and borderline (≥100 and <126 mg/dL) to high were similar in patients treated with CARIQUEL and placebo. In the long-term, open-label schizophrenia studies, 4% patients with normal hemoglobin A1c baseline values developed elevated levels (≥6.5%).

Bipolar Disorder

In six placebo-controlled studies up to 8-weeks of adult patients with bipolar disorder (mania or depression), the proportion of patients with shifts in fasting glucose from normal (<100 mg/dL) to high (≥126 mg/dL) and borderline (≥100 and <126 mg/dL) to high were similar in patients treated with CARIQUEL and placebo. In the long-term, open-label bipolar disorder studies, 4% patients with normal hemoglobin A1c baseline values developed elevated levels (≥6.5%).

Dyslipidemia

Atypical antipsychotics cause adverse alterations in lipids. Before or soon after initiation of antipsychotic medication, obtain a fasting lipid profile at baseline and monitor periodically during treatment.

Schizophrenia

In the 6-week, placebo-controlled studies of adult patients with schizophrenia, the proportion of patients with shifts in fasting total cholesterol, LDL, HDL and triglycerides were similar in patients treated with CARIQUEL and placebo.

Bipolar Disorder

In six placebo-controlled studies up to 8-weeks of adult patients with bipolar disorder (mania or depression), the proportion of patients with shifts in fasting total cholesterol, LDL, HDL and triglycerides were similar in patients treated with CARIQUEL and placebo.

Weight Gain

Weight gain has been observed with use of atypical antipsychotics, including CARIQUEL. Monitor weight at baseline and frequently thereafter. Tables 2, 3, and 4 show the change in body weight occurring from baseline to endpoint in 6-week schizophrenia, 3-week bipolar mania, and 6-week and 8-week bipolar depression studies, respectively.

Table 2. Change in Body Weight (kg) in 6-Week Schizophrenia Studies CARIQUEL*

	CARIQUEL			
	Placebo (N=573)	1.5 - 3 mg/day (N=512)	4.5 - 6 mg/day (N=570)	9 - 12◦ mg/day (N=203)
Mean Change at Endpoint	+0.3	+0.8	+1	+1
Proportion of Patients with Weight Increase (≥7%)	5%	8%	8%	17%

*Data shown by modal daily dose, defined as most frequently administered dose per patient

◦The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

In long-term, uncontrolled trials with VRAYLAR in schizophrenia, the mean changes from baseline in weight at 12, 24, and 48 weeks were 1.2 kg, 1.7 kg, and 2.5 kg, respectively.

Table 3. Change in Body Weight (kg) in 3-Week Bipolar Mania Trials

		CARIQUEL	
	Placebo (N=439)	3 - 6 mg/day (N=259)	9 - 12◦ mg/day (N=360)
Mean Change at Endpoint	+0.2	+0.5	+0.6
Proportion of Patients with	2%	1%	3%

*Data shown by modal daily dose, defined as most frequently administered dose per patient

◦The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

Table 4. Change in Body Weight (kg) in two 6-Week and one 8-Week Bipolar Depression Trails

		CARIQUEL	
	Placebo (N=463)	1.5 mg/day	3 mg/day
Mean Change at Endpoint	-0.1	+0.7	+0.4

Proportion of Patients with Weight Increase (≥7%)	1%	3%	3%

Leukopenia, Neutropenia, and Agranulocytosis

Leukopenia and neutropenia have been reported during treatment with antipsychotic agents, including CARIQUEL. Agranulocytosis (including fatal cases) has been reported with other agents in the class.

Possible risk factors for leukopenia and neutropenia include pre-existing low white blood cell count (WBC) or absolute neutrophil count (ANC) and history of drug-induced leukopenia or neutropenia. In patients with a pre-existing low WBC or ANC or a history of drug-induced leukopenia or neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of CARIQUEL at the first sign of a clinically significant decline in WBC in the absence of other causative factors. Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue CARIQUEL in patients with absolute neutrophil count < 1000/mm3 and follow their WBC until recovery.

Orthostatic Hypotension and Syncope

Atypical antipsychotics cause orthostatic hypotension and syncope. Generally, the risk is greatest during initial dose titration and when increasing the dose. Symptomatic orthostatic hypotension was infrequent in studies of CARIQUEL and was not more frequent on CARIQUEL than placebo. Syncope was not observed.

Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension (e.g., elderly patients, patients with dehydration, hypovolemia, and concomitant treatment with antihypertensive medications), patients with known cardiovascular disease (history of myocardial infarction, ischemic heart disease, heart failure, or conduction abnormalities), and patients with cerebrovascular disease. CARIQUEL has not been evaluated in patients with a recent history of myocardial infarction or unstable cardiovascular disease. Such patients were excluded from pre-marketing clinical studies.

Falls

Antipsychotics, including CARIQUEL, may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

Seizures

Like other antipsychotic drugs, CARIQUEL may cause seizures. This risk is greatest in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in older patients.

Potential for Cognitive and Motor Impairment

CARIQUEL, like other antipsychotics, has the potential to impair judgment, thinking, or motor skills.

In 6-week schizophrenia studies, somnolence (hypersomnia, sedation, and somnolence) was reported in 7% of CARIQUEL-treated patients compared to 6% of placebo-treated patients. In 3-week bipolar mania studies, somnolence was reported in 8% of CARIQUEL-treated patients compared to 4% of placebo-treated patients.

Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with CARIQUEL does not affect them adversely.

Body Temperature Dysregulation

Atypical antipsychotics may disrupt the body's ability to reduce core body temperature. Strenuous exercise, exposure to extreme heat, dehydration, and anticholinergic medications may contribute to an elevation in core body temperature; use CARIQUEL with caution in patient who may experience these conditions.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Dysphagia has been reported with CARIQUEL. CARIQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration.

4.5 Drugs interactions

Drugs Having Clinically Important Interactions with CARIQUEL

Clinically Important Drug Interactions with CARIQUEL Strong CYP3A4 Inhibitors

Strong CYP3A4 Inhibitors	
Clinical Impact:	Concomitant use of CARIQUEL with a strong CYP3A4 inhibitor increases the exposures of cariprazine and its major active metabolite, didesmethylcariprazine (DDCAR), compared to use of CARIQUEL alone
Intervention:	If CARIQUEL is used with a strong CYP3A4 inhibitor, reduce CARIQUEL dosage
Examples:	Itraconazole, ketoconazole
CYP3A4 Inducers	
Clinical Impact:	CYP3A4 is responsible for the formation and elimination of the active metabolites of cariprazine. The effect of CYP3A4 inducers on the exposure of CARIQUEL has not been evaluated, and the net effect is unclear
Intervention:	Concomitant use of CARIQUEL with a CYP3A4 inducer is not recommended
Examples:	Rifampin, Carbamazepine

4.6 Use in special populations

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to CARIQUEL during pregnancy.

Risk Summary

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There are no available data on CARIQUEL use in pregnant women to inform any drug-associated risks for birth defects or miscarriage. The major active metabolite of cariprazine, DDCAR, has been detected in adult patients up to 12 weeks after discontinuation of CARIQUEL. Based on animal data, CARIQUEL may cause fetal harm.

Administration of cariprazine to rats during the period of organogenesis caused malformations, lower pup survival, and developmental delays at drug exposures less than the human exposure at the maximum recommended human dose (MRHD) of 6 mg/day. However, cariprazine was not teratogenic in rabbits at doses up to 4.6 times the MRHD of 6 mg/day The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. Advise pregnant women of the potential risk to a fetus.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates whose mothers were exposed to antipsychotic drugs during the third trimester of pregnancy. These symptoms have varied in severity. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately.

Animal Data

Administration of cariprazine to pregnant rats during the period of organogenesis at oral doses of 0.5, 2.5, and 7.5 mg/kg/day which are 0.2 to 3.5 times the maximum recommended human dose (MRHD) of 6 mg/day based on AUC of total cariprazine (i.e. sum of cariprazine, DCAR, and DDCAR) caused fetal developmental toxicity at all doses which included reduced body weight, decreased male anogenital distance and skeletal malformations of bent limb bones, scapula and humerus. These effects occurred in the absence or presence of maternal toxicity. Maternal toxicity, observed as a reduction in body weight and food consumption, occurred at doses 1.2 and 3.5-times the MRHD of 6 mg/day based on AUC of total cariprazine. At these doses, cariprazine caused fetal external malformations (localized fetal thoracic edema), visceral variations (undeveloped/underdeveloped renal papillae and/or distended urethrae), and skeletal developmental variations (bent ribs, unossified sternebrae). Cariprazine had no effect on fetal survival.

Administration of cariprazine to pregnant rats during pregnancy and lactation at oral doses of 0.1, 0.3, and 1 mg/kg/day which are 0.03 to 0.4 times the MRHD of 6 mg/day based on AUC of total cariprazine caused a decrease in postnatal survival, birth weight, and post-weaning

body weight of first generation pups at the dose that is 0.4 times the MRHD of 6 mg/day based on AUC of total cariprazine in absence of maternal toxicity. First generation pups also had pale, cold bodies and developmental delays (renal papillae not developed or underdeveloped and decreased auditory startle response in males). Reproductive performance of the first generation pups was unaffected; however, the second generation pups had clinical signs and lower body weight similar to those of the first generation pups.

Administration of cariprazine to pregnant rabbits during the period of organogenesis at oral doses of 0.1, 1, and 5 mg/kg/day, which are 0.02 to 4.6 times the MRHD of 6 mg/day based on AUC of total cariprazine was not teratogenic. Maternal body weight and food consumption were decreased at 4.6 times the MRHD of 6 mg/day based on AUC of total cariprazine; however, no adverse effects were observed on pregnancy parameters or reproductive organs.

Lactation

Risk Summary

In reported lactation studies have not been conducted to assess the presence of cariprazine in human milk, the effects on the breastfed infant, or the effects on milk production. Cariprazine is present in rat milk. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for CARIQUEL and any potential adverse effects on the breastfed infant from CARIQUEL or from the underlying maternal condition.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established. Pediatric studies of CARIQUEL have not been conducted. Antidepressants increased the risk of suicidal thoughts and behaviors in pediatric patients

Geriatric Use

In reported clinical studies of CARIQUEL in the treatment of schizophrenia and bipolar mania did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal,or cardiac function, and of concomitant disease or other drug therapy.

Elderly patients with dementia-related psychosis treated with CARIQUEL are at an increased risk of death compared to placebo. CARIQUEL is not approved for the treatment of patients with dementia-related psychosis

Hepatic Impairment

No dosage adjustment for CARIQUEL is required in patients with mild to moderate hepatic impairment (Child-Pugh score between 5 and 9). Usage of CARIQUEL is not recommended in patients with severe hepatic impairment (Child-Pugh score between 10 and 15). CARIQUEL has not been evaluated in this patient population.

Renal Impairment

No dosage adjustment for CARIQUEL is required in patients with mild to moderate (CrCL ≥ 30 mL/minute) renal impairment.

Usage of CARIQUEL is not recommended in patients with severe renal impairment (CrCL < 30 mL/minute). CARIQUEL has not been evaluated in this patient population.

Smoking

No dosage adjustment for CARIQUEL is needed for patients who smoke. CARIQUEL is not a substrate for CYP1A2, smoking is not expected to have an effect on the pharmacokinetics of CARIQUEL.

Other Specific Populations

No dosage adjustment is required based on patient's age, sex, or race. These factors do not affect the pharmacokinetics of CARIQUEL

4.7 Effects on ability to drive and use machines

Caution patients about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that CARIQUEL therapy does not affect them adversely.

4.8 Undesirable effects

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis
- Suicidal Thoughts and Behaviors
- Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-Related Psychosis
- Neuroleptic Malignant Syndrome
- Tardive Dyskinesia
- Late Occurring Adverse Reactions
- Metabolic Changes
- Leukopenia, Neutropenia, and Agranulocytosis
- Orthostatic Hypotension and Syncope
- Falls
- Seizures
- Potential for Cognitive and Motor Impairment
- Body Temperature Dysregulation
- Dysphagia

Clinical Trials Experience:

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The information below is derived from an integrated in reported clinical study database for CARIQUEL consisting of 4753 adult patients exposed to one or more doses of CARIQUEL for the treatment of schizophrenia, manic or mixed episodes associated with bipolar I disorder, and bipolar depression in placebo-controlled studies. This experience corresponds with a total experience of 940.3 patient-years. A total of 2568 CARIQUEL-treated patients had at least 6 weeks and 296 CARIQUEL-treated patients had at least 48 weeks of exposure.

Patients with Schizophrenia

The following findings are based on four placebo-controlled, 6-week schizophrenia trials with CARIQUEL doses ranging from 1.5 to 12 mg once daily. The maximum recommended dosage is 6 mg daily.

Adverse Reactions Associated with Discontinuation of Treatment: There was no single adverse reaction leading to discontinuation that occurred at a rate of ≥ 2% in CARIQUEL-treated patients and at least twice the rate of placebo.

Common Adverse Reactions (≥ 5% and at least twice the rate of placebo): extrapyramidal symptoms and akathisia.

Adverse Reactions with an incidence of ≥ 2% and greater than placebo, at any dose are shown in Table 5.

Table 5. Adverse Reactions Occurring in ≥ 2% of CARIQUEL-treated Patients and > Placebo-treated Adult Patients in 6-Week Schizophrenia Trials

System Organ Class / Preferred Term	Placebo (N= 584) (%)	**CARIQUEL***		
		1.5 - 3 mg/day (N=539) **(%)**	4.5 - 6 mg/day (N=575) **(%)**	9 - 12 mg/day (N=203) **(%)**
Cardiac Disorders				
Tachycardia[a]	**1**	**2**	**2**	**3**
Gastrointestinal Disorders				
Abdominal pain[b]	**5**	**3**	**4**	**7**
Constipation	**5**	**6**	**7**	**10**
Diarrhea[c]	**3**	**1**	**4**	**5**

Dry Mouth	**2**	**1**	**2**	**3**
Dyspepsia	**4**	**4**	**5**	**5**
Nausea	**5**	**5**	**7**	**8**
Toothache	**4**	**3**	**3**	**6**
Vomiting	**3**	**4**	**5**	**5**
General Disorders/Administration Site Conditions				
Fatigue[d]	**1**	**1**	**3**	**2**
Infections and Infestations				
Nasopharyngitis	**1**	**1**	**1**	**2**
Urinary tract infection	**1**	**1**	**<1**	**2**
Investigations				
Blood creatine phosphokinase increased	**1**	**1**	**2**	**3**
Hepatic enzyme increased[e]	**<1**	**1**	**1**	**2**
Weight increased	**1**	**3**	**2**	**3**
Metabolism and Nutrition Disorders				
Decreased appetite	**2**	**1**	**3**	**2**
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	**1**	**2**	**1**	**2**
Back pain	**2**	**3**	**3**	**1**
Pain in extremity	**3**	**2**	**2**	**4**
Nervous System Disorders				
Akathisia	**4**	**9**	**13**	**14**
Extrapyramidal symptoms[f]	**8**	**15**	**19**	**20**
Headache[g]	**13**	**9**	**11**	**18**

Somnolence[h]	**5**	**5**	**8**	**10**
Dizziness	**2**	**3**	**5**	**5**
Psychiatric Disorders				
Agitation	**4**	**3**	**5**	**3**
Insomnia[i]	**11**	**12**	**13**	**11**
Restlessnes[s]	**3**	**4**	**6**	**5**
Anxiety	**4**	**6**	**5**	**3**
Respiratory, Thoracic and Mediastinal disorders				
Cough	**2**	**1**	**2**	**4**
Skin and Subcutaneous Disorders				
Rash	**1**	**<1**	**1**	**2**
Vascular Disorders				
Hypertension[j]	**1**	**2**	**3**	**6**

Note: Figures rounded to the nearest integer

* Data shown by modal daily dose, defined as most frequently administered dose per patient

[a]**Tachycardia terms:** heart rate increased, sinus tachycardia, tachycardia

[b]**Abdominal pain terms:** abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain

[c]**Diarrhea terms**: diarrhea, frequent bowel movements

[d]**Fatigue terms:** asthenia, fatigue

[e]**Hepatic enzyme increase terms:** alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased

[f]**Extrapyramidal Symptoms terms:** bradykinesia, cogwheel rigidity, drooling, dyskinesia, dystonia, extrapyramidal disorder, hypokinesia, masked facies, muscle rigidity, muscle tightness, Musculoskeletal stiffness, oculogyric crisis, oromandibular dystonia, parkinsonism, salivary hypersecretion, tardive dyskinesia, torticollis, tremor, trismus

[g]**Headache terms:** headache, tension headache

[h]**Somnolence terms:** hypersomnia, sedation, somnolence

[i]**Insomnia terms:** initial insomnia, insomnia, middle insomnia, terminal insomnia

[j]**Hypertension terms:** blood pressure diastolic increased, blood pressure increased, blood pressure systolic increased, hypertension

◦ The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer

increased effectiveness sufficient to outweigh dose-related adverse reactions.

Patients with Bipolar Mania

The following findings are based on three placebo-controlled, 3-week bipolar mania trials with CARIQUEL doses ranging from 3 to 12 mg once daily. The maximum recommended dosage is 6 mg daily.

Adverse Reactions Associated with Discontinuation of Treatment: The adverse reaction leading to discontinuation that occurred at a rate of ≥ 2% in CARIQUEL-treated patients and at least twice the rate of placebo was akathisia (2%). Overall, 12% of the patients who received CARIQUEL discontinued treatment due to an adverse reaction, compared with 7% of placebo-treated patients in these trials.

Common Adverse Reactions (≥ 5% and at least twice the rate of placebo): extrapyramidal symptoms, akathisia, dyspepsia, vomiting, somnolence, and restlessness.

Adverse Reactions with an incidence of ≥ 2% and greater than placebo at any dose are shown in Table 6.

Table 6. Adverse Reactions Occurring in ≥ 2% of CARIQUEL-treated Patients and > Placebo-treated Adult Patients in 3-Week Bipolar Mania Trials

System Organ Class / Preferred Term	Placebo (N= 442) (%)	CARIQUEL*	
		3 - 6 mg/day (N=263) (%)	9 - 12 mg/day° (N=360) (%)
Cardiac Disorders			
Tachycardia[a]	1	2	1
Eye Disorders			
Vision blurred	1	4	4
Gastrointestinal Disorders			
Nausea	7	13	11
Constipation	5	6	11
Vomiting	4	10	8
Dry mouth	2	3	2
Dyspepsia	4	7	9
Abdominal pain[b]	5	6	8
Diarrhea[c]	5	5	6
Toothache	2	4	3
General Disorders/Administration Site Conditions			
Fatigue[d]	2	4	5
Pyrexia[e]	2	1	4
Investigations			
Blood creatine phosphokinase increased	2	2	3
Hepatic enzymes increased[f]	<1	1	3
Weight increased	2	2	3
Metabolism and Nutrition Disorders			

Decreased appetite	3	3	4
Musculoskeletal and Connective Tissue Disorders			
Pain in extremity	2	4	2
Back pain	1	1	3
Nervous System Disorders			
Akathisia	5	20	21
Extrapyramidal Symptoms[g]	12	26	29
Headache[h]	13	14	13
Dizziness	4	7	6
Somnolence[i]	4	7	8
Psychiatric Disorders			
Insomnia[j]	7	9	8
Restlessness	2	7	7
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	2	1	3
Vascular Disorders			
Hypertensionk	1	5	4

Note: Figures rounded to the nearest integer

*Data shown by modal daily dose, defined as most frequently administered dose per patient

[a]**Tachycardia terms:** heart rate increased, sinus tachycardia, tachycardia

[b]**Abdominal pain terms:** abdominal discomfort, abdominal pain, abdominal pain upper, abdominal tenderness,

[c]**Diarrhea:** diarrhea, frequent bowel movements

[d]**Fatigue terms:** asthenia, fatigue

[e]**Pyrexia terms:** body temperature increased, pyrexia

[f]**Hepatic enzymes increased terms:** alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, transaminases increased

[g]**Extrapyramidal Symptoms terms:** bradykinesia, drooling, dyskinesia, dystonia, extrapyramidal disorder, hypokinesia, muscle rigidity, muscle tightness, musculoskeletal stiffness, oromandibular dystonia, parkinsonism, salivary hypersecretion, tremor

[h]**Headache terms:** headache, tension headache

[i]**Somnolence terms:** hypersomnia, sedation, somnolence

[j]**Insomnia terms:** initial insomnia, insomnia, middle insomnia

[k]**Hypertension terms:** blood pressure diastolic increased, blood pressure increased, hypertension

The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

Patients with Bipolar Depression

The following findings are based on three placebo-controlled, two 6-week and one 8-week bipolar depression trials with CARIQUEL doses of 1.5 mg, and 3 mg once daily.

Adverse Reactions Associated with Discontinuation of Treatment: There were no adverse reaction leading to discontinuation that occurred at a rate of ≥ 2% in CARIQUEL-treated patients and at least twice the rate of placebo. Overall, 6% of the patients who received

CARIQUEL discontinued treatment due to an adverse reaction, compared with 5% of placebo-treated patients in these trials.

Common Adverse Reactions (≥ 5% and at least twice the rate of placebo): nausea, akathisia, restlessness, and extrapyramidal symptoms.

Adverse Reactions with an incidence of ≥ 2% and greater than placebo at 1.5 mg or 3 mg doses are shown in Table 7.

Table 7. Adverse Reactions Occurring in ≥ 2% of CARIQUEL-treated Patients and > Placebo-treated Adult Patients in two 6-week trials and one 8-week trial

	Placebo (N=468) (%)	CARIQUEL	
		1.5 mg/day (N=470) (%)	3 mg/day (N=469) (%)
Restlessness	3	2	7
Akathisia	2	6	10
Extrapyramidal symptoms[a]	2	4	6
Dizziness	2	4	3
Somnolence[b]	4	7	6
Nausea	3	7	7
Increased appetite	1	3	3
Weight increase	<1	2	2
Fatigue[c]	2	4	3
Insomnia[d]	7	7	10

[a]**Extrapyramidal symptoms terms**: akinesia, drooling, dyskinesia, dystonia, extrapyramidal disorder, hypokinesia, muscle tightness, musculoskeletal stiffness, myoclonus, oculogyric crisis, salivary hypersecretion, tardive dyskinesia, tremor

[b]**Somnolence terms**: hypersomnia, sedation, somnolence

[c]**Fatigue terms**: asthenia, fatigue, malaise

[d]**Insomnia terms**: initial insomnia, insomnia, insomnia related to another mental condition, middle insomnia, sleep disorder terminal insomnia

Dystonia

Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. Although these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Extrapyramidal Symptoms (EPS) and Akathisia

In schizophrenia, bipolar mania, and bipolar depression trials, data were objectively collected using the Simpson Angus Scale (SAS) for treatment-emergent EPS (Parkinsonism) (SAS total score ≤ 3 at baseline and > 3 post-baseline) and the Barnes Akathisia Rating Scale (BARS) for treatment-emergent akathisia (BARS total score ≤ 2 at baseline and > 2 post-

baseline).

In 6-week schizophrenia trials, the incidence of reported events related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness was 17% for CARIQUEL-treated patients versus 8% for placebo- treated patients. These events led to discontinuation in 0.3% of CARIQUEL-treated patients versus 0.2% of placebo-treated patients. The incidence of akathisia was 11% for CARIQUEL-treated patients versus 4% for placebo-treated patients. These events led to discontinuation in 0.5% of CARIQUEL-treated patients versus 0.2% of placebo-treated patients. The incidence of EPS is shown in Table 8.

Table 8. Incidence of EPS Compared to Placebo in 6-Week Schizophrenia Studies

Adverse Event Term	Placebo	**CARIQUEL***		
	(N= 584) (%)	1.5 - 3 mg/day (N=539) (%)	4.5 - 6 mg/day (N=575) (%)	9-12 mg/day° (N=203) (%)
All EPS Events	14	24	32	33
All EPS Events, excluding Akathisia/Restlessness	8	15	19	20
Akathisia	4	9	13	14
Dystonia**	<1	2	2	2
Parkinsonism§	7	13	16	18
Restlessness	3	4	6	5
Musculoskeletal stiffness	1	1	3	1

Note: Figures rounded to the nearest integer

*Data shown by modal daily dose, defined as most frequently administered dose per patient

**** Dystonia includes adverse event terms:** dystonia, oculogyric crisis, oromandibular dystonia, trismus, and torticollis

§ **Parkinsonism includes adverse event terms:** bradykinesia, cogwheel rigidity, drooling, dyskinesia, extrapyramidal disorder, hypokinesia, masked facies, muscle rigidity, muscle tightness, parkinsonism, tremor, salivary hypersecretion

The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

In 3-week bipolar mania trials, the incidence of reported events related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness, was 28% for CARIQUEL-treated patients versus 12% for placebo- treated patients. These events led to a discontinuation in 1% of CARIQUEL-treated patients versus 0.2% of placebo-treated patients. The incidence of akathisia was 20% for CARIQUEL-treated patients versus 5% for placebo-treated patients. These events led to discontinuation in 2% of CARIQUEL-treated patients versus 0% of placebo-treated patients. The incidence of EPS is provided in Table 9.

Table 9. Incidence of EPS Compared to Placebo in 3-Week Bipolar Mania Trials

Adverse Event Term	Placebo (N= 442) (%)	**CARIQUEL***	
		3 - 6 mg/day (N=263) (%)	9 - 12 mg/day° (N=360) (%)
All EPS Events	18	41	45

All EPS Events, excluding Akathisia/Restlessness	12	26	29
Akathisia	5	20	21
Dystonia**	1	5	3
Parkinsonism§	10	21	26
Restlessness	2	7	7
Musculoskeletal stiffness	1	2	2

Note: Figures rounded to the nearest integer

*Data shown by modal daily dose, defined as most frequently administered dose per patient

** **Dystonia includes adverse event terms:** dystonia, oromandibular dystonia

§ **Parkinsonism includes adverse event terms:** bradykinesia, drooling, dyskinesia, extrapyramidal disorder, hypokinesia, muscle rigidity, muscle tightness, parkinsonism, salivary hypersecretion, tremor

The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

In the two 6-week and one 8-week bipolar depression trials, the incidence of reported events related to EPS, excluding akathisia and restlessness was 4% for CARIQUEL-treated patients versus 2% for placebo-treated patients. These events led to discontinuation in 0.4% of CARIQUEL-treated patients versus 0% of placebo-treated patients. The incidence of akathisia was 8% for CARIQUEL-treated patients versus 2% for placebo-treated patients. These events led to discontinuation in 1.5% of CARIQUEL-treated patients versus 0% of placebo-treated patients. The incidence of EPS is shown in Table 10.

Table 10. Incidence of EPS Compared to Placebo in two 6-Week and one 8-Week Bipolar Depression Trials

Adverse Event Term	Placebo (N=468) (%)	**CARIQUEL** 1.5 mg/day (N=470) (%)	**CARIQUEL** 3 mg/day (N=469) (%)
All EPS Events	7	10	19
All EPS Events, excluding Akathisia/Restlessness	2	4	6
Akathisia	2	6	10
Dystonia*	<1	<1	<1
Parkinsonism§	2	3	4
Restlessness	3	2	7
Musculoskeletal stiffness	<1	<1	1
Tardive Dyskinesia	0	0	<1

Note: Figures rounded to the nearest integer

* **Dystonia includes adverse event terms:** dystonia, myoclonus, oculogyric crisis

§ **Parkinsonism includes adverse event terms:** akinesia, drooling, dyskinesia, extrapyramidal disorder, hypokinesia, muscle tightness, salivary hypersecretion, and tremor.

Cataracts

In the reported long-term uncontrolled schizophrenia (48-week) and bipolar mania (16-week)

trials, the incidence of cataracts was 0.1% and 0.2%, respectively. The development of cataracts was observed in reported non clinical studies. The possibility of lenticular changes or cataracts cannot be excluded at this time.

Vital Signs Changes

There were no clinically meaningful differences between CARIQUEL-treated patients and placebo-treated patients in mean change from baseline to endpoint in supine blood pressure parameters except for an increase in supine diastolic blood pressure in the 9 - 12 mg/day CARIQUEL-treated patients with schizophrenia.

Pooled data from 6-week schizophrenia trials are shown in Table 11 and from 3-week bipolar mania trials are shown in Table 12.

Table 11. Mean Change in Blood Pressure at Endpoint in 6-Week Schizophrenia Trials

		CARIQUEL*		
	Placebo (N=574)	1.5 - 3 mg/day (N=512)	4.5 - 6 mg/day (N=570)	9- 12 mg/day◦ (N=203)
Supine Systolic Blood Pressure	+0.9	+0.6	+1.3	+2.1
Supine Diastolic Blood Pressure	+0.4	+0.2	+1.6	+3.4

* Data shown by modal daily dose, defined as most frequently administered dose per patient

◦ The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

Table 12. Mean Change in Blood Pressure at Endpoint in 3-Week Bipolar Mania Trials

		CARIQUEL*	
	Placebo (N=439)	3 - 6 mg/day (N=259)	9 – 12 mg/day◦ (N=360)
Supine Systolic Blood Pressure (mmHg)	-0.5	+0.8	+1.8
Supine Diastolic Blood Pressure (mmHg)	+0.9	+1.5	+1.9

* Data shown by modal daily dose, defined as most frequently administered dose per patient

◦ The maximum recommended daily dose is 6 mg. Doses above 6 mg daily do not confer increased effectiveness sufficient to outweigh dose-related adverse reactions.

In the two 6-week and one 8-week bipolar depression trials, there were no clinically meaningful differences between CARIQUEL-treated patients and placebo-treated patients in mean change from baseline to endpoint in supine systolic and diastolic blood pressure.

Pooled data from two 6-week and one 8-week bipolar depression trials are shown in Table 13**.**

Table 13. Mean Change in Blood Pressure at Endpoint in two 6-Week and one 8-Week Bipolar Depression Trials

	Placebo (N=468)	CARIQUEL	
		1.5 mg/day (N=572)	3 mg/day (N=426)
Supine Systolic Blood Pressure (mmHg)	-0.2	0.2	-0.1
Supine Diastolic Blood Pressure (mmHg)	0.2	0.1	-0.3

Changes in Laboratory Tests

The proportions of patients with transaminase elevations of ≥3 times the upper limits of the normal reference range in 6-week schizophrenia trials ranged between 1% and 2% for CARIQUEL-treated patients, increasing with dose, and was 1% for placebo-treated patients. The proportions of patients with transaminase elevations of ≥3 times the upper limits of the normal reference range in 3-week bipolar mania trials ranged between 2% and 4% for CARIQUEL-treated patients depending on dose group administered and 2% for placebo-treated patients. The proportions of patients with transaminase elevations of ≥3 times the upper limits of the normal reference range in 6-week and 8-week bipolar depression trials ranged between 0% and 0.5% for CARIQUEL-treated patients depending on dose group administered and 0.4% for placebo-treated patients.

The proportions of patients with elevations of creatine phosphokinase (CPK) greater than 1000 U/L in 6-week schizophrenia trials ranged between 4% and 6% for CARIQUEL-treated patients, increasing with dose, and was 4% for placebo-treated patients. The proportions of patients with elevations of CPK greater than 1000 U/L in 3-week bipolar mania trials was about 4% in CARIQUEL and placebo-treated patients. The proportions of patients with elevations of CPK greater than 1000 U/L in 6-week and 8-week bipolar depression trials ranged between 0.2% and 1% for CARIQUEL-treated patients versus 0.2% for placebo-treated patients.

Other Adverse Reactions Observed During the Pre-marketing Evaluation of CARIQUEL

Adverse reactions listed below were reported by patients treated with CARIQUEL at doses of ≥ 1.5 mg once daily within the premarketing database of 3988 CARIQUEL-treated patients. The reactions listed are those that could be of clinical importance, as well as reactions that are plausibly drug-related on pharmacologic or other grounds. Reactions that appear elsewhere in the CARIQUEL label are not included.

Reactions are further categorized by organ class and listed in order of decreasing frequency, according to the following definition: those occurring in at least 1/100 patients (frequent) [only those not already listed in the tabulated results from placebo-controlled studies appear in this listing]; those occurring in 1/100 to 1/1000 patients (infrequent); and those occurring in fewer than 1/1000 patients (rare).

Gastrointestinal Disorders: Infrequent: gastroesophageal reflux disease, gastritis Hepatobiliary Disorders: Rare: hepatitis

Metabolism and Nutrition Disorders: Frequent: decreased appetite; Infrequent: hyponatremia Musculoskeletal and Connective Tissue Disorders: Rare: rhabdomyolysis

Nervous System Disorders: Rare: ischemic stroke

Psychiatric Disorders: Infrequent: suicide attempts, suicide ideation; Rare: completed suicide
Renal and Urinary Disorders: Infrequent: pollakiuria

Skin and Subcutaneous Tissue Disorders: Infrequent: hyperhidrosis

Postmarketing Experience

The following adverse reaction has been identified during post approval use of CARIQUEL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship to drug exposure.

Skin and Subcutaneous Tissue Disorders – Stevens-Johnson syndrome

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

4.9 Overdose

In reported pre-marketing clinical studies involving CARIQUEL in approximately 5000 patients or healthy subjects, accidental acute overdosage (48 mg/day) was reported in one patient. This patient experienced orthostasis and sedation. The patient fully recovered the same day.

Management of Overdosage: No specific antidotes for CARIQUEL are known. In managing overdose, provide supportive care, including close medical supervision and monitoring, and consider the possibility of multiple drug involvement.

5. Pharmacological properties

5.1 Mechanism of action

The mechanism of action of cariprazine in schizophrenia and bipolar I disorder is unknown. However, the efficacy of cariprazine could be mediated through a combination of partial agonist activity at central dopamine D2 and serotonin 5-HT1A receptors and antagonist activity at serotonin 5-HT2A receptors. Cariprazine forms two major metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR) that have *in vitro* receptor binding profiles similar to the parent drug.

5.2 Pharmacodynamics properties

Cariprazine acts as a partial agonist at the dopamine D3 and D2 receptors with high binding affinity (Ki values 0.085 nM, and 0.49 nM (D2L) and 0.69 nM (D2S), respectively) and at the serotonin 5-HT1A receptors (Ki value 2.6 nM). Cariprazine acts as an antagonist at 5-HT2B and 5-HT2A receptors with high and moderate binding affinity (Ki values 0.58 nM and 18.8 nM respectively) as well as it binds to the histamine H1 receptors (Ki value 23.2 nM). Cariprazine shows lower binding affinity to the serotonin 5-HT2C and α1A- adrenergic receptors (Ki values 134 nM and 155 nM, respectively) and has no appreciable affinity for

cholinergic muscarinic receptors (IC50>1000 nM).

Effect on QTc Interval

At a dose three-times the maximum recommended dose, cariprazine does not prolong the QTc interval to clinically relevant extent.

5.3 Pharmacokinetic properties

CARIQUEL activity is thought to be mediated by cariprazine and its two major active metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), which are pharmacologically equipotent to cariprazine.

In reported study after multiple dose administration of CARIQUEL, mean cariprazine and DCAR concentrations reached steady state at around Week 1 to Week 2 and mean DDCAR concentrations appeared to be approaching steady state at around Week 4 to Week 8 in a 12-week study. The half-lives based on time to reach steady state, estimated from the mean concentration-time curves, are 2 to 4 days for cariprazine, about 1 to 2 days for DCAR, and approximately 1 to 3 weeks for DDCAR. The time to reach steady state for the major active metabolite DDCAR was variable across patients, with some patients not achieving steady state at the end of the 12 week treatment. Mean concentrations of DCAR and DDCAR are approximately 30% and 400%, respectively, of cariprazine concentrations by the end of 12-week treatment.

After discontinuation of CARIQUEL, cariprazine, DCAR, and DDCAR plasma concentrations declined in a multi-exponential manner. Mean plasma concentrations of DDCAR decreased by about 50%, 1 week after the last dose and mean cariprazine and DCAR concentration dropped by about 50% in about 1 day. There was an approximately 90% decline in plasma exposure within 1 week for cariprazine and DCAR, and at about 4 weeks for DDCAR. Following a single dose of 1 mg of cariprazine administration, DDCAR remained detectable 8 weeks post-dose.

After multiple dosing of CARIQUEL, plasma exposure of cariprazine, DCAR, and DDCAR, increases approximately proportionally over the therapeutic dose range.

Absorption

After single dose administration of CARIQUEL, the peak plasma cariprazine concentration occurred in approximately 3-6 hours.

Administration of a single dose of 1.5 mg CARIQUEL capsule with a high-fat meal did not significantly affect the C_{max} and AUC of cariprazine or DCAR.

Distribution

Cariprazine and its major active metabolites are highly bound (91 to 97%) to plasma proteins.

Elimination

Metabolism

Cariprazine is extensively metabolized by CYP3A4 and, to a lesser extent, by CYP2D6 to DCAR and DDCAR. DCAR is further metabolized into DDCAR by CYP3A4 and CYP2D6. DDCAR is then metabolized by CYP3A4 to a hydroxylated metabolite.

Excretion

Following administration of 12.5 mg/day cariprazine to patients with schizophrenia for 27 days, about 21% of the daily dose was found in urine, with approximately 1.2% of the daily dose was excreted in urine as unchanged cariprazine.

Studies in Specific Populations

Hepatic Impairment

In reported study compared to healthy subjects, exposure (Cmax and AUC) in patients with either mild or moderate hepatic impairment (Child-Pugh score between 5 and 9) was approximately 25% higher for cariprazine and 20% to 30% lower for the major metabolites (DCAR and DDCAR) following daily doses of 0.5 mg cariprazine for 14 days.

Renal Impairment

Cariprazine and its major active metabolites are minimally excreted in urine. Pharmacokinetic analyses indicated no significant relationship between plasma clearance and creatinine clearance.

CYP2D6 Poor Metabolizers

CYP2D6 poor metabolizer status does not have clinically relevant effect on pharmacokinetics of cariprazine, DCAR, or DDCAR.

Age, Sex, Race

Age, sex, or race does not have clinically relevant effect on pharmacokinetics of cariprazine, DCAR, or DDCAR.

Drug Interaction Studies

In vitro studies

Cariprazine and its major active metabolites did not induce CYP1A2 and CYP3A4 enzymes and were weak inhibitors of CYP1A2, CYP2C9, CYP2D6, and CYP3A4 *in vitro*. Cariprazine was also a weak inhibitor of CYP2C19, CYP2A6, and CYP2E1 *in vitro.*

Cariprazine and its major active metabolites are not substrates of P-glycoprotein (P-gp), the organic anion transporting polypeptides 1B1 and 1B3 (OATP1B1 and OATP1B3), or the breast cancer resistance protein (BCRP).

Cariprazine and its major active metabolites were poor or non-inhibitors of transporters OATP1B1, OATP1B3, BCRP, organic cation transporter 2 (OCT2), and organic anion transporters 1 and 3 (OAT1 and OAT3) *in vitro*. The major active metabolites were also poor or non-inhibitors of transporter P-gp although cariprazine was probably a P-gp inhibitor based on the theoretical GI concentrations at high doses *in vitro*.

Based on reported in vitro studies, CARIQUEL is unlikely to cause clinically significant pharmacokinetic drug interactions with substrates of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E, and CYP3A4, or OATP1B1, OATP1B3, BCRP, OCT2, OAT1 and OAT3

In vivo studies

CYP 3A4 inhibitors

Co-administration of ketoconazole (400 mg/day), a strong CYP3A4 inhibitor, with CARIQUEL (0.5 mg/day) increased cariprazine Cmax and AUC0-24h by about 3.5-fold and 4-fold, respectively; increased DDCAR Cmax and AUC0-24h by about 1.5-fold; and decreased DCAR Cmax and AUC0-24h by about one-third. The impact of moderate CYP3A4 inhibitors has not been studied.

CYP3A4 inducers

CYP3A4 is responsible for the formation and elimination of the active metabolites of cariprazine. The effect of CYP3A4 inducers on the plasma exposure of cariprazine and its major active metabolites has not been evaluated, and the net effect is unclear.

CYP2D6 inhibitors

CYP2D6 inhibitors are not expected to influence pharmacokinetics of cariprazine, DCAR or DDCAR based on the observations in CYP2D6 poor metabolizers.

Proton pump inhibitors

In reported study co-administration of pantoprazole (40 mg/day), a proton pump inhibitor, with CARIQUEL (6 mg/day) in patients with schizophrenia for 15 days did not affect cariprazine exposure at steady-state, based on Cmax and AUC0-24. Similarly, no significant change in exposure to DCAR and DDCAR was observed.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

Carcinogenesis

There was no increase in the incidence of tumors following daily oral administration of cariprazine to rats for 2 years and to Tg.rasH2 mice for 6 months at doses which are up to 4 and 19 times respectively, the MRHD of 6 mg/day based on AUC of total cariprazine, (i.e. sum of AUC values of cariprazine, DCAR and DDCAR).

Rats were administered cariprazine at oral doses of 0.25, 0.75, and 2.5 (males)/1, 2.5, and 7.5 mg/kg/day (females) which are 0.2 to 1.8 (males)/ 0.8 to 4.1 (females) times the MRHD of 6 mg/day based on AUC of total cariprazine.

Tg.rasH2 mice were administered cariprazine at oral doses of 1, 5, and 15 (males)/5, 15, and 50 mg/kg/day (females) which are 0.2 to 7.9 (males)/2.6 to 19 (females) times the MRHD of 6 mg/day based on AUC of total cariprazine.

Mutagenesis

Cariprazine was not mutagenic in the reported *in vitro* bacterial reverse mutation assay, nor clastogenic in the in vitro human lymphocyte chromosomal aberration assay or in the *in vivo* mouse bone marrow micronucleus assay. However, cariprazine increased the mutation frequency in the in vitro mouse lymphoma assay under conditions of metabolic activation. The major human metabolite DDCAR was not mutagenic in the *in vitro* bacterial reverse mutation assay, however, it was clastogenic and induced structural chromosomal aberration in the *in vitro* human lymphocyte chromosomal aberration assay.

Impairment of Fertility

In reported study cariprazine was administered orally to male and female rats before mating, through mating and up to day 7 of gestation at doses of 1, 3, and 10 mg/kg/day which are 1.6 to 16 times the MRHD of 6 mg/day based on mg/m2. In female rats, lower fertility and conception indices were observed at all dose levels which are equal to or higher than 1.6 times the MRHD of 6 mg/day based on mg/m2. No effects on male fertility were noted at any dose up to 4.3 times the MRHD of 6 mg/day based on AUC of total cariprazine.

Animal Toxicology and/or Pharmacology

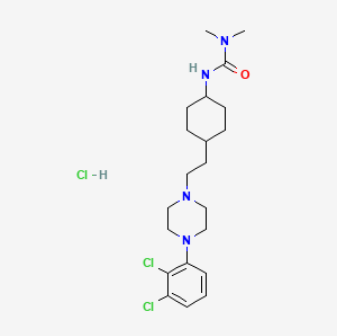
In reported study cariprazine caused bilateral cataract and cystic degeneration of the retina in the dog following oral daily administration for 13 weeks and/or 1 year and retinal degeneration/atrophy in the rat following oral daily administration for 2 years. Cataract in the dog was observed at 4 mg/kg/day which is 7.1 (male) and 7.7 (female) times the MRHD of 6 mg/day based on AUC of total cariprazine. The NOEL for cataract and retinal toxicity in the dog is 2 mg/kg/day which is 5 (males) to 3.6 (females) times the MRHD of 6 mg/day based on AUC of total cariprazine. Increased incidence and severity of retinal degeneration/atrophy in the rat occurred at all doses tested, including the low dose of 0.75 mg/kg/day, at total cariprazine plasma levels less than clinical exposure (AUC) at the MRHD of 6 mg/day. Cataract was not observed in other repeat dose studies in pigmented mice or albino rats. Phospholipidosis was observed in the lungs of rats, dogs, and mice (with or without inflammation) and in the adrenal gland cortex of dogs at clinically relevant exposures (AUC) of total cariprazine. Phospholipidosis was not reversible at the end of the 1-2 month drug-free periods. Inflammation was observed in the lungs of dogs dosed daily for 1 year with a NOEL of 1 mg/kg/day which is 2.7 (males) and 1.7 (females) times the MRHD of 6 mg/day based on AUC of total cariprazine. No inflammation was observed at the end of 2-month drug free period following administration of 2 mg/kg/day which is 5 (males) and 3.6 (females) times the MRHD of 6 mg/day based on AUC of total cariprazine; however, inflammation was still present at higher doses.

Hypertrophy of the adrenal gland cortex was observed at clinically relevant total cariprazine plasma concentrations in rats (females only) and mice following daily oral administration of cariprazine for 2 years and 6 months, respectively. Reversible hypertrophy/hyperplasia and vacuolation/vesiculation of the adrenal gland cortex were observed following daily oral administration of cariprazine to dogs for 1 year. The NOEL was 2 mg/kg/day which is 5 (males) and 3.6 (females) times the MRHD of 6 mg/day based on AUC of total cariprazine. The relevance of these findings to human risk is unknown.

7. Description

Cariprazine

Cariprazine hydrochloride is 3-[4-[2-[4-(2,3-dichlorophenyl)piperazin-1-yl]ethyl]cyclohexyl]-1,1-dimethylurea;hydrochloride. The molecular formula is $C_{21}H_{33}Cl_3N_4O$ and the molecular weight is 463.9. The chemical structure of Cariprazine hydrochloride is:



Cariprazine Capsules are size ‘4’ hard gelatin capsules with white opaque cap and white opaque body, filled with white powder. The excipients used are Mannitol, Talc, Magnesium Stearate.

8. Pharmaceutical particulars

8.1 Incompatibilities

None stated

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packaging information

CARIQUEL is available in pack of 10 Capsules

8.4 Storage and handing instructions

Store at a temperature not exceeding 30°C. Protect from moisture.

9. Patient Counselling Information

Package leaflet: Information for the user

Package leaflet: Information for the user

CARIQUEL

Cariprazine Capsules 1.5 mg, 3 mg, 4.5 mg & 6 mg

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

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9.1 What CARIQUEL is and what it is used for

CARIQUEL contain active substance CARIPRAZINE.

CARIQUEL is use for the treatment of Schizophrenia in adults. Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults.

9.2 What you need to know before you use CARIQUEL

Before taking CARIQUEL, tell your healthcare provider about all of your medical conditions, including if you:

• have or have had heart problems or a stroke

• have or have had low or high blood pressure

• have or have had diabetes or high blood sugar, or a family history of diabetes or high blood sugar. Your healthcare provider should check your blood sugar before you start and during treatment with CARIQUEL.

• have or have had high levels of total cholesterol, LDL cholesterol, or triglycerides or low levels of HDL cholesterol.

• have or had seizures (convulsions)

• have or have had kidney or liver problems

• have or had a low white blood cell count

• are pregnant or plan to become pregnant. CARIQUEL may harm your unborn baby. Talk to your healthcare provider about the risk to your unborn baby if you take CARIQUEL during pregnancy.

• Tell your healthcare provider if you become pregnant or think you are pregnant during treatment with CARIQUEL.

• If you become pregnant during treatment with CARIQUEL, talk to your healthcare provider.

• are breastfeeding or plan to breastfeed. It is not known if CARIQUEL passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with CARIQUEL.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

CARIQUEL and other medicines may affect each other causing possible serious side effects. CARIQUEL may affect the way other medicines work, and other medicines may affect how CARIQUEL works.

Know the medicines you take. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine.

Warnings and precautions

If you are allergic to cariprazine. See the end of this Medication Guide for a complete list of ingredients in CARIQUEL.

Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis: Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack).

Neuroleptic Malignant Syndrome: Manage with immediate discontinuation and close monitoring.

• *Tardive Dyskinesia*: Discontinue if appropriate.

• *Late-Occurring Adverse Reactions:* Because of CARIQUEL's long half-life, monitor for adverse reactions and patient response for several weeks after starting CARIQUEL and with each dosage change.

• *Metabolic Changes*: Monitor for hyperglycemia/diabetes mellitus, dyslipidemia and weight gain.

• *Leukopenia, Neutropenia, and Agranulocytosis*: Perform complete blood counts (CBC) in patients with pre-existing low white blood cell counts (WBC) or history of leukopenia or neutropenia. Consider discontinuing CARIQUEL if a clinically significant decline in WBC occurs in absence of other causative factors.

• *Orthostatic Hypotension*: Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope.

• *Seizures:* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold.

• *Potential for Cognitive and Motor Impairment:* Use caution when operating machinery

9.3 How to take CARIQUEL

• Take CARIQUEL exactly as your healthcare provider tells you to take it. Do not change the dose or stop taking CARIQUEL without first talking to your healthcare provider.

• CARIQUEL can be taken with or without food.

If you take more CARIQUEL than you should

If you take too much CARIQUEL, call your healthcare provider or Poison Control Center or go to the nearest hospital emergency room, right away.

If you stop taking CARIQUEL

If you stop taking this medicine you will lose the effects of the medicine. You should not stop this medicine unless told to do so by your doctor as your symptoms may return.

How long to take CARIQUEL

Take CARIPRAZINE every day for as long as your doctor tells you.

Your doctor will regularly monitor your condition to check that the treatment is having the desired effect.

9.4 Possible Side Effects

Neuroleptic malignant syndrome (NMS) is a serious condition that can lead to death. Call your healthcare provider or go to the nearest hospital emergency room right away if you have some or all of the following signs and symptoms of NMS:

- high fever
- confusion
- changes in your breathing, heart rate, and blood pressure
- stiff muscles
- increased sweating

Uncontrolled body movements (tardive dyskinesia). CARIQUEL may cause movements that you cannot control in your face, tongue, or other body parts. Tardive dyskinesia may not go away, even if you stop taking CARIQUEL. Tardive dyskinesia may also start after you stop taking CARIQUEL.

Late occurring side effects. CARIQUEL stays in your body for a long time. Some side effects may not happen right away and can start a few weeks after you start taking CARIQUEL, or if your dose of CARIQUEL increases. Your healthcare provider should monitor you for side effects for several weeks after you start and after any increase in your dose of CARIQUEL.

• Problems with your metabolism such as:

high blood sugar (hyperglycemia) and diabetes. Increases in blood sugar can happen in some people who take CARIQUEL. Extremely high blood sugar can lead to coma or death. Your healthcare provider should check your blood sugar before you start, or soon after you start CARIQUEL, and then regularly during long-term treatment with CARIQUEL.

Call your healthcare provider if you have any of these symptoms of high blood sugar during treatment with CARIQUEL:

▪ feel very thirsty

▪ feel very hungry

▪ feel sick to your stomach

▪ need to urinate more than usual

▪ feel weak or tired

▪ feel confused, or your breath smells fruity

increased fat levels (cholesterol and triglycerides) in your blood. Your healthcare provider should check the fat levels in your blood before you start, or soon after you start CARIQUEL, and then periodically during treatment with CARIQUEL.

weight gain. You and your healthcare provider should check your weight before you start and often during treatment with CARIQUEL.

Low white blood cell count. Your healthcare provider may do blood tests during the first few

months of treatment with CARIQUEL.

Decreased blood pressure (orthostatic hypotension). You may feel lightheaded or faint when you rise too quickly from a sitting or lying position.

Falls. CARIQUEL may make you sleepy or dizzy, may cause a decrease in your blood pressure when changing position (orthostatic hypotension), and can slow your thinking and motor skills which may lead to falls that can cause fractures or other injuries.

Seizures (convulsions).

Problems controlling your body temperature so that you feel too warm. See "What should I avoid while taking CARIQUEL?"

Difficulty swallowing that can cause food or liquid to get into your lungs.

The most common side effects of CARIQUEL include: difficulty moving or slow movements, tremors, uncontrolled body movements, restlessness and feeling like you need to move around, sleepiness, nausea, vomiting, and indigestion.

These are not all the possible side effects of CARIQUEL.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: http://www.torrentpharma.com/index.php/site/info/adverse_event_reporting.

9.5 How to store CARIQUEL

Store at a temperature not exceeding 30°C. Protect from moisture.

9.6 Contents of the pack and other information

The active substance in CARIQUEL is cariprazine.

Cariprazine Capsules are size '4' hard gelatin capsules with white opaque cap and white opaque body, filled with white powder. The excipients used are Mannitol, Talc, Magnesium Stearate.

CARIQUEL is available in pack of 10 Capsules

10 Details of manufacturer

Optimus Pharma Private Limited

Plot No.73/B,73/B/2, EPIP, Pashamylaram (V),

Patancheru (M), Sangareddy (Dist.) – 502307,

Telangana State, India**.**

11 Details of permission or license number with date

22/SRD/TS/2017/F/G

12 Date of revision

NA

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TORRENT PHARMACEUTICALS LTD.

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