SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

KAPRAZDI 3 mg hard capsule

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

Cariprazine ……3 mg

Excipients:

Sodium starch glycolate……121.375 mg
FD&C Red 40 (E129)……0.0021 mg
See section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Hard capsule
Green-white hard capsules filled with white or off-white granular powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

KAPRAZDI is indicated for the following conditions:

- Treatment of schizophrenia in adult patients
- For the treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults

4.2. Posology and method of administration

Posology/frequency and duration of administration:

In the treatment of schizophrenia:
The recommended starting dose of KAPRAZDI is 1.5 mg once daily. The dose may be increased in increments of 1.5 mg as needed, up to a maximum of 6 mg/day. The lowest effective dose should be maintained based on the treating physician's clinical assessment. Due to the long half-life of cariprazine and its active metabolites, any change in dosage may not be fully reflected in plasma levels for several weeks. Patients should be monitored for adverse reactions and treatment response for several weeks after starting cariprazine and after each dose change (see Section 5.2).

For the treatment of depressive episodes associated with bipolar I disorder (bipolar depression):
The recommended starting dose of KAPRAZDI is 1.5 mg once daily. Depending on clinical response and tolerability, the dose may be increased to 3 mg once daily on day 15. The recommended maximum dose is 3 mg once daily.

Switching from other antipsychotics to cariprazine
When switching from another antipsychotic to cariprazine, gradual cross-titration should be considered, with cariprazine treatment initiated while gradually discontinuing the previous treatment.

Switching from cariprazine to another antipsychotic
When switching from cariprazine to another antipsychotic, gradual cross-titration is not necessary; the new antipsychotic should be started at the lowest dose while cariprazine is being discontinued. It should be noted that plasma concentrations of cariprazine and its active metabolites decrease by approximately 50% within 1 week (see Section 5.2).

Missed dose:
If the patient misses a dose, they should take the missed dose as soon as possible. However, if it is close to the time for the next dose, the missed dose should be skipped and the next dose should be taken according to the normal dosing schedule. A double dose should not be taken to make up for a missed dose.

Method of administration:
KAPRAZDI is for oral use and is administered once daily at the same time each day, either with food or on an empty stomach.
Alcohol should be avoided while taking cariprazine (see Section 4.5).

Additional information on specific populations:
Renal impairment
No dose adjustment is necessary in patients with mild to moderate renal impairment (Creatinine Clearance (CrCl) ≥30 mL/min and <89 mL/min). The safety and efficacy of cariprazine in patients with severe renal impairment (CrCl <30 mL/min) have not been evaluated. The use of cariprazine is not recommended in patients with severe renal impairment (see Section 5.2).

Hepatic impairment
No dose adjustment is required in patients with mild to moderate hepatic impairment (Child-Pugh score 5-9). The safety and efficacy of cariprazine in patients with severe hepatic impairment (Child-Pugh score 10 to 15) have not been evaluated. The use of cariprazine is not recommended in patients with severe hepatic impairment (see Section 5.2).

Geriatric population:
The available data on elderly patients aged 65 years and older treated with cariprazine are insufficient to determine whether this patient group responds differently than younger patients (see Section 5.2). Dosage selection for elderly patients should be done with greater caution.

Pediatric population
The safety and efficacy of cariprazine in children and adolescents under 18 years of age have not been established. No data are available.

4.3. Contraindications
Hypersensitivity to the active substance or any of the excipients listed in Section 6.1.
Concomitant use with strong or moderate CYP3A4 inhibitors (see Section 4.5).
Concomitant use with strong or moderate CYP3A4 inducers (see Section 4.5) is contraindicated.

4.4. Special warnings and precautions for use
Suicidal thoughts and behavior
The possibility of suicidal tendencies (suicidal thoughts, suicide attempts, and completed suicide) is inherent in psychotic disorders and is often reported shortly after starting or changing antipsychotic treatment. Close monitoring of patients at high risk of suicide should accompany antipsychotic treatment.

Akathisia, restlessness
Akathisia and restlessness are common adverse reactions to antipsychotics. Akathisia is characterized by a feeling of inner restlessness and a compelling need to be in constant motion; it is also a movement disorder characterized by rocking while standing or sitting, pacing as if walking in place, and crossing or uncrossing the legs while sitting. Since cariprazine may cause akathisia and restlessness, it should be used with caution in patients who are prone to akathisia or already show signs of akathisia. Akathisia develops early in treatment. Therefore, close monitoring is important during the initial phase of treatment. Prevention of this condition involves slow dose titration; treatment involves mild dose reduction titration of cariprazine or administration of anti-extrapyramidal symptoms (EPS) medicinal products. The dose may be adjusted according to individual response and tolerability (see Section 4.8).

Tardive dyskinesia
Tardive dyskinesia is a potentially irreversible syndrome that may occur in patients treated with antipsychotics, characterized by rhythmic, involuntary movements, particularly of the tongue and/or face. If signs and symptoms of tardive dyskinesia appear in a patient treated with cariprazine, discontinuation of the drug should be considered.

Parkinson's disease
When prescribed to patients with Parkinson's disease, antipsychotic medicinal products may exacerbate the underlying disease and worsen Parkinson's disease symptoms. Therefore, physicians should carefully weigh the risks against the potential benefits when prescribing cariprazine to patients with Parkinson's disease.

Ocular symptoms/cataracts
In preclinical studies of cariprazine, lens opacities/cataracts were observed in dogs (see sections 4.8 and 5.3). However, no causal relationship has been established between the lens changes/cataracts observed in human studies and the use of cariprazine. Nevertheless, patients who may develop potential symptoms associated with cataracts should be advised to undergo an ophthalmological examination and should be re-evaluated for continued treatment.

Neuroleptic malignant syndrome (NMS)
A potentially fatal symptom complex known as NMS has been reported in association with antipsychotic treatment. The clinical manifestations of NMS include hyperpyrexia, muscle rigidity, increased serum creatine phosphokinase levels, altered mental status, and signs of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac arrhythmia). Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. If a patient develops signs and symptoms indicative of NMS or presents with unexplained high fever without additional clinical signs of NMS, cariprazine should be discontinued immediately.

Seizures and convulsions
Cariprazine should be used with caution in patients with a history of seizures or in conditions that may potentially lower the seizure threshold.

Elderly patients with dementia

Conventional and atypical antipsychotic drugs increase the risk of death when used to treat elderly patients with dementia-related psychosis.

Cariprazine has not been studied in elderly patients with dementia and is not recommended for the treatment of elderly patients with dementia due to an increased risk of overall mortality.

Risk of cerebrovascular events (CVE)
In randomized placebo-controlled clinical trials in the dementia population, an approximately 3-fold increase in the risk of CVE has been observed with some atypical antipsychotics. The mechanism of this increased risk is unknown. The increased risk for other antipsychotics or

other patient populations cannot be ruled out. Cariprazine should be used with caution in patients with risk factors for stroke.

Cardiovascular disorders

Blood pressure changes

Cariprazine may cause orthostatic hypotension as well as hypertension (see Section 4.8). Cariprazine should be used with caution in patients with cardiovascular disease known to be prone to blood pressure changes. Blood pressure should be monitored.

Electrocardiogram (ECG) changes

QT prolongation may occur in patients treated with antipsychotics.

In a clinical study designed to evaluate QT prolongation with cariprazine, no QT interval prolongation was observed with cariprazine compared to placebo (see Section 5.1). In clinical studies, only a few cases of non-serious QT prolongation have been reported with cariprazine (see Section 4.8). Therefore, cariprazine should be used with caution in patients with known cardiovascular disease, in patients with a family history of QT prolongation, and in patients receiving medicinal products that may cause QT prolongation (see Section 5.1).

Venous thromboembolism (VTE)

Cases of VTE have been reported with antipsychotic drugs. Since patients treated with antipsychotics often also have acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during cariprazine treatment, and all preventive measures should be taken.

Hyperglycemia and diabetes mellitus

Patients diagnosed with diabetes mellitus or patients at risk for diabetes mellitus who are starting treatment with atypical antipsychotics (e.g., obesity, family history of diabetes) should be monitored for serum glucose levels. In clinical studies, glucose-related adverse reactions have been reported with cariprazine (see Section 5.1).

Changes in body weight

Significant weight gain has been observed with the use of cariprazine. Patients' weight should be monitored regularly (see Section 4.8).

Sleep apnea syndrome:

Sleep apnea syndrome has been reported in patients using atypical antipsychotics such as KAPRAZDI. Caution should be exercised when using KAPRAZDI in patients who are concurrently using central nervous system depressants, have a history of sleep apnea, or are at risk for sleep apnea (e.g., overweight/obese individuals or males).

Concomitant treatment with moderate CYP3A4 inhibitors
Concomitant administration of cariprazine with moderate CYP3A4 inhibitors may lead to an increase in total cariprazine exposure. Monitoring of individual response and tolerability is recommended, and if necessary, the cariprazine dose should be (temporarily) reduced to account for the potential increase in exposure (see Section 4.5).

Excipients:
KAPRAZDI contains FD&C Red 40, which may cause allergic reactions.

This medication contains less than 1 mmol of sodium (23 mg) per hard capsule, i.e. it is essentially 'sodium-free.'

4.5. Interaction with other medicinal products and other forms of interaction

Potential for other medicinal products to affect cariprazine
The metabolism of cariprazine and its main active metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), is primarily mediated by CYP3A4, with a minor contribution from CYP2D6.

CYP3A4 inhibitors
Ketoconazole, a potent CYP3A4 inhibitor, caused a twofold increase in total cariprazine (total of cariprazine and active metabolites) plasma exposure during short-term (4 days) co-administration, considering both unbound and bound fractions. Due to the long half-life of cariprazine's active components, a greater increase in total cariprazine plasma exposure is expected during long-term co-administration. Therefore, concomitant use of cariprazine with strong CYP3A4 inhibitors (e.g., boseprevir, clarithromycin, cobicistat, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) is contraindicated (see Section 4.3).

Erythromycin (500 mg twice daily) is a moderate CYP3A4 inhibitor and resulted in an average 1.4-fold (range 1.03-2.32-fold) increase in total plasma exposure to cariprazine after 3 weeks of concomitant administration. Therefore, when cariprazine is administered concomitantly with a moderate CYP3A4 inhibitor (e.g., erythromycin, fluconazole, diltiazem, verapamil), monitoring of individual response and tolerability is recommended, and if necessary, the cariprazine dose should be (temporarily) reduced to account for the potential increase in exposure. Due to the long half-life of cariprazine and its active metabolites, initiation of treatment with a moderate CYP3A4 inhibitor, discontinuation of treatment, or dose modification will not be fully reflected in plasma drug levels for several weeks. Patients should be monitored for adverse reactions and treatment response for several weeks after starting or stopping an interacting drug or after any change in the dose of cariprazine.

Grapefruit juice consumption should be avoided.

CYP3A4 Inducers
Concomitant administration of cariprazine with strong and moderate CYP3A4 inducers results in a significant decrease in total cariprazine exposure, and therefore concomitant administration of cariprazine with strong or moderate CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampicin, St. John's wort (Hypericum perforatum), bosentan, efavirenz, etravirin, modafinil, nafcillin) is contraindicated (see Section 4.3).

CYP2D6 inhibitors
The CYP2D6 pathway plays a minor role in the metabolism of cariprazine; the main pathway is CYP3A4-mediated (see Section 5.2). Therefore, the effects of CYP2D6 inhibitors on the metabolism of cariprazine are unlikely to be clinically significant.

Potential of cariprazine to affect other medicinal products
P-glycoprotein (P-gp) substrates
Cariprazine is an *in vitro* P-gp inhibitor at the maximum concentration it would theoretically reach in the intestine. The clinical implications of this effect are not fully understood, but the use of P-gp substrates with a narrow therapeutic index, such as dabigatran and digoxin, may require additional monitoring and dose adjustment.

Hormonal contraceptives
In a drug interaction study, 28 days of treatment with 6 mg of cariprazine daily had no clinically significant effect on the pharmacokinetics of oral contraceptives (ethinyl estradiol and levonorgestrel).

Pharmacodynamic interactions
Given the primary central nervous system effects of cariprazine, KAPRAZDI should be used with caution in combination with other centrally acting medicinal products and alcohol.

Additional information for specific populations:
Pediatric population
Interaction studies have only been conducted in adults.

4.6. Pregnancy and lactation

General recommendation
Pregnancy category: C

Women of childbearing potential/Birth control (Contraception):

Women of childbearing potential should be advised to avoid pregnancy while using KAPRAZDI. Women of childbearing potential should use highly effective contraceptive methods during treatment and for at least 10 weeks after the last dose of KAPRAZDI.

Pregnancy
There are no or limited data on the use of cariprazine in pregnant women. Animal studies have shown reproductive toxicity, including developmental malformations in rats (see Section 5.3).

KAPRAZDI is not recommended during pregnancy and in women of childbearing potential who are not using effective contraception. Contraception should be continued for at least 10 weeks after discontinuation of cariprazine treatment due to the slow elimination of the active ingredients.

Newborns exposed to antipsychotics (including cariprazine) during the third trimester of pregnancy are at risk of adverse reactions, including extrapyramidal symptoms and/or withdrawal symptoms, the severity and duration of which may vary after birth. Agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress or feeding difficulties have been reported. These complications occur with varying severity; in some cases, symptoms are self-limiting, while in others, they have required neonatal intensive care unit support and prolonged hospitalization. Consequently, newborns should be closely monitored.

Lactation
It is unknown whether cariprazine or its primary active metabolites are excreted in human milk. Cariprazine and its metabolites have been excreted in milk in rats during lactation (see Section 5.3). This risk to newborns/infants cannot be disregarded. Breastfeeding should be discontinued during cariprazine treatment.

Reproductive ability/Fertility
The effect of cariprazine on human fertility has not been evaluated. In rat studies, lower female fertility and conception indices were observed (see Section 5.3).

4.7. Effects on the ability to drive and use machines

Cariprazine has little or moderate effect on the ability to drive and use machines. Patients should be warned against using dangerous machinery, including motor vehicles, until they are sure that treatment with KAPRAZDI does not adversely affect them.

4.8. Undesirable effects

Summary of safety profile

The most commonly reported adverse drug reactions (ADRs) with cariprazine within the dose range (1.5-6 mg) were akathisia (19%) and parkinsonism (17.5%). Most events were mild to moderate in severity.

Adverse reaction table

ADRs based on data collected from studies of cariprazine in schizophrenia and depressive episodes associated with bipolar depression are listed in Table 1 and Table 2, respectively, by system organ class and preferred term.

Adverse reactions are listed below according to their frequency, starting with the most common, using the following rule: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Adverse drug reactions observed in patients with schizophrenia

MedDRA System Organ Class	**Very common**	**Common**	**Uncommon**	**Rare**	**Unknown**
Blood and lymphatic system disorders			Anemia Eosinophilia	Neutropenia	
Immune system disorders				Hypersensitivity	
Endocrine disorders			Decreased thyroid-stimulating hormone in the	Hypothyroidism	
Metabolic and nutritional disorders		Dyslipidemia Weight gain Decreased appetite Increased appetite	Abnormal blood sodium level Diabetes mellitus Increased blood glucose level		

Psychiatric disorders		Sleep disorders[1] Anxiety	Suicidal behavior Delirium Depression Decreased libido Increased libido Erectile dysfunction		
Nervous system disorders	Akathisia[2] Parkinsonism[3]	Sedation Dizziness Dystonia[4] Other extrapyramidal disorders and abnormal movement disorders[5]	Tardive dyskinesia Dyskinesia[6] Dysesthesia Lethargy	Seizures/ Convulsions Amnesia Aphasia	Neuroleptic malignant syndrome
Eye disorders		Blurred vision	Increased intraocular pressure Accommodation disorder Decreased visual acuity Eye irritation	Cataract Photophobia	
Ear and inner ear diseases			Vertigo		
Cardiac diseases		Tachyarrhythmia	Cardiac conduction disorders Bradyarrhythmia Electrocardiogram prolonged QT Electrocardiogram abnormal T wave		

Vascular diseases		Hypertension	Hypotension		
Respiratory, chest disorders, and mediastinal diseases			Hiccups		Sleep apnea syndrome[7]
Gastrointestinal disorders		Vomiting Nausea Constipation	Gastro-esophageal reflux disease	Dysphagia	
Hepatobiliary diseases		Elevated liver enzymes	Increased blood bilirubin levels		Toxic hepatitis
Skin and subcutaneous tissue disorders			Itching Rash		
Musculoskeletal disorders, connective tissue and bone diseases		Increased blood creatine phosphokinase levels		Rhabdomyolysis	
Kidney and urinary tract disorders			Dysuria Polyuria		
Pregnancy, puerperium conditions, and perinatal conditions					Neonatal drug withdrawal syndrome (see Section 4.6)

General disorders and conditions related to the administration site		Fatigue	Thirst		

[1]Sleep disorders: Insomnia, abnormal dreams/nightmares, circadian rhythm sleep disorder, dyssomnia, hypersomnia, difficulty falling asleep, waking up in the middle of sleep, nightmares, sleep disorder, somnambulism, terminal insomnia disorder

[2]Akathisia: Akathisia, psychomotor hyperactivity, restlessness

[3] Parkinsonism: Akinesia, bradykinesia, bradyphrenia, muscle rigidity seen in Parkinson's disease, extrapyramidal disorder, gait disorder, hypokinesia, joint stiffness, tremor, mask-like face, muscle rigidity, musculoskeletal rigidity, neck stiffness, parkinsonism

[4] Dystonia: Blepharospasm, dystonia, muscle rigidity, oromandibular dystonia, torticollis, trismus

[5] Other extrapyramidal diseases and abnormal movement disorders: Balance disorder, bruxism, drooling, dysarthria, staggering gait, abnormal glabellar reflex, hyporeflexia, movement disorder, restless legs syndrome, hypersecretion of saliva, tongue movement disorder

[6] Dyskinesia: Choreoathetosis, dyskinesia, facial grimacing, oculogyric crisis, tongue protrusion.

[7]Sleep apnea syndrome: Sleep apnea cases have been reported with other atypical antipsychotics in the rare frequency category.

Table 2 Adverse drug reactions observed in patients with bipolar depression

MedDRA System Organ Class	Very common	Common	Uncommon	Rare	Unknown
Metabolic and nutritional disorders		Increased appetite Weight gain			
Psychiatric disorders	Insomnia[d,] *	Restlessness			
Nervous system disorders	Akathisia*	Extrapyramidal symptoms[a] Dizziness Somnolence[b]			
Gastrointestinal disorders		Nausea			

General disorders and administration site conditions		Fatigue[c]			

[a] Extrapyramidal symptom terms: Akinesia, drooling, dyskinesia, dystonia, extrapyramidal disorder, hypokinesia, muscle rigidity, musculoskeletal stiffness, myoclonus, oculogyric crisis, hypersecretion of saliva, tardive dyskinesia, tremor

[b]Somnolence terms: Hypersomnia, sedation, somnolence

[c]Fatigue terms: Asthenia, fatigue, weakness

[d] Insomnia terms: Initial insomnia, insomnia, insomnia associated with another mental condition, middle insomnia, sleep disorder, terminal insomnia

*In clinical trials with cariprazine, these were common at 1.5 mg/day and very common at 3 mg/day.

Definitions of selected adverse reactions

Lens opacity/Cataract

Cataract development has been observed in non-clinical studies with kariprazine (see Section 5.3). Therefore, in clinical studies, cataract formation was closely monitored using slit (dashed) lamp examinations, and patients with existing cataracts were excluded from the study. During the clinical development program for schizophrenia, several cases of cataracts characterized by small lens opacities without visual impairment have been reported with cariprazine (13/3192; 0.4%). Some of these patients had interacting factors. The most commonly reported ocular adverse event was blurred vision (placebo: 1/683; 0.1%, cariprazine: 22/2048; 1.1%).

Extrapyramidal symptoms (EPS) and akathisia

In short-term schizophrenia studies, the incidence of EPS was found to be 27%, 11.5%, 30.7%, and 15.1% in patients treated with cariprazine, placebo, risperidone, and aripiprazole, respectively. The incidence of akathisia in patients treated with cariprazine, placebo, risperidone, and aripiprazole was 13.6%, 5.1%, 9.3%, and 9.9%, respectively. Parkinsonism was observed in 13.6%, 5.7%, 22.1%, and 5.3% of patients treated with cariprazine, placebo, risperidone, and aripiprazole, respectively. Dystonia was observed in 1.8%, 0.2%, 3.6%, and 0.7% of patients treated with cariprazine, placebo, risperidone, and aripiprazole, respectively.

In the placebo-controlled section of the long-term efficacy study conducted in patients with schizophrenia, EPS was detected in 13.7% of the cariprazine group and 3% of patients treated with placebo. Akathisia was reported in 3.9% of patients treated with cariprazine and 2% in the placebo group. Parkinsonism was observed in 7.8% of the cariprazine group and 1% of the placebo group.

In a clinical study of cariprazine in patients with schizophrenia, EPS was reported in 14.3% of the cariprazine group and 11.7% of patients treated with risperidone. Akathisia was reported in 10% of patients treated with cariprazine and 5.2% in the risperidone group. Parkinsonism was

detected in 5.2% and 7.4% of patients treated with cariprazine and risperidone, respectively. Most EPS cases were mild to moderate and could be treated with known anti-EPS preparations. The discontinuation rate due to EPS-related ADRs was low.

In two 6-week and one 8-week bipolar depression studies, the incidence of reported adverse reactions related to EPS, excluding akathisia and restlessness, was 4% in patients treated with cariprazine and 2% in patients treated with placebo. These reactions led to discontinuation of treatment in 0.4% of patients treated with cariprazine and 0% of patients treated with placebo. The incidence of akathisia was 8% in patients treated with cariprazine and 2% in patients treated with placebo. These reactions led to discontinuation of treatment in 1.5% of patients treated with cariprazine and 0% of patients treated with placebo.

Venous thromboembolism (VTE)
Cases of VTE, including pulmonary embolism and deep vein thrombosis, have been reported with antipsychotics—the frequency is unknown.

Elevated liver transaminases
Elevated liver transaminase levels [Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST)] are frequently observed with antipsychotic treatment. In clinical trials of cariprazine in patients with schizophrenia, the incidence of ADRs related to ALT and AST elevations was 2.2% in patients treated with cariprazine, 1.6% in patients treated with risperidone, and 0.4% in patients treated with placebo. No liver damage was observed in any of the patients treated with cariprazine.

In 6-week and 8-week bipolar depression studies, the proportion of patients with transaminase elevations ≥3 times the upper limit of the normal reference range ranged from 0% to 0.5% in patients treated with cariprazine and 0.4% in patients treated with placebo, depending on the dose group administered.

Changes in body weight
In short-term studies, the mean increase in body weight was slightly greater in the cariprazine group compared to the placebo group; 1 kg and 0.3 kg, respectively. In the long-term efficacy-substitution study, no clinically significant change in body weight was observed from baseline to the end of treatment; cariprazine 1.1 kg and placebo 0.9 kg. In the open-label phase of the study, potentially clinically significant (PCS) weight gain (defined as an increase >7%) was observed in 9% of patients receiving cariprazine treatment for 20 weeks, compared to 9.8% of patients continuing cariprazine during the double-blind phase, and 7.1% of patients randomized to placebo after 20 weeks of open-label cariprazine treatment. In another clinical trial with cariprazine, the mean body weight change was -0.3 kg for cariprazine and +0.6 kg for

risperidone, and PCS weight gains were observed in 6% of the cariprazine group and 7.4% of the risperidone group.

QT prolongation
In a clinical study designed to evaluate QT prolongation with cariprazine, no QT interval prolongation was detected with cariprazine compared to placebo (see Section 5.1). In other clinical studies, only a few non-serious QT prolongations have been reported with cariprazine. During the long-term, open-label treatment period, QTcB > 500 ms occurred in 3 patients (0.4%), and QTcF > 500 ms occurred in one of these patients. An increase of >60 ms from baseline was observed in 7 patients (1%) for QTcB and in 2 patients (0.3%) for QTcF. In the long-term effect-substitution study, during the open-label phase, an increase of >60 ms from baseline was observed in 12 patients (1.6%) for QTcB and in 4 patients (0.5%) for QTcF. During the double-blind treatment period, increases in QTcB of >60 ms from baseline were observed in 3 patients (3.1%) treated with cariprazine and in 2 patients (2%) treated with placebo.

Other adverse reactions observed during the pre-marketing evaluation of cariprazine
The adverse reactions listed below were reported in patients treated with cariprazine at a dose of ≥1.5 mg once daily in a pre-marketing database of 5,763 patients treated with cariprazine. The listed reactions include those that may be clinically significant as well as those reasonably considered to be drug-related for pharmacological or other reasons. Other adverse reactions are not included.

Reactions are also categorized by system organ class and listed in descending order of frequency according to the following definition: those occurring in at least 1/100 patients (common) [this list includes only reactions not yet listed in tabulated results from placebo-controlled studies]; those occurring in 1/100 to 1/1,000 patients (uncommon); and those occurring in fewer than 1/1,000 patients (rare).

Gastrointestinal disorders
Uncommon: Gastroesophageal reflux disease, gastritis

Hepatobiliary disorders
Rare: Hepatitis

Metabolic and nutritional disorders
Common: Decreased appetite
Rare: Hyponatremia

Musculoskeletal disorders, connective tissue and bone diseases

Rare: Rhabdomyolysis

Nervous system disorders
Rare: Ischemic stroke

Psychiatric disorders
Uncommon: Suicidal thoughts
Rare: Completed suicide, suicide attempts

Kidney and urinary tract disorders
Uncommon: Pollakiuria

Skin and subcutaneous tissue disorders
Uncommon: Hyperhidrosis

Post-marketing experience
The following adverse reactions have been identified during the post-approval use of cariprazine. Since these reactions are voluntarily reported from a population of uncertain size, it is not always possible to estimate their frequency or establish a causal relationship with drug exposure.

Skin and subcutaneous tissue disorders
Unknown: Stevens-Johnson syndrome

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9. Overdose and treatment

Symptoms
An accidental acute overdose (48 mg/day) was reported in one patient. This patient developed orthostatic hypotension and sedation. The patient fully recovered on the same day.

Overdose treatment:
Treatment of overdose should focus on supportive care, including maintaining adequate airway patency, oxygenation, and ventilation, and controlling symptoms. Cardiovascular monitoring, including continuous electrocardiographic monitoring for possible arrhythmias, should be initiated immediately. Anticholinergic drugs should be administered if severe extrapyramidal

symptoms occur. Since cariprazine binds to plasma proteins to a high degree, hemodialysis is unlikely to be useful in the treatment of overdose. Close medical supervision and monitoring should continue until the patient recovers. There is no specific antidote for cariprazine.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Psycholeptics, other antipsychotics
ATC code: N05AX15

Mechanism of action:
The mechanism of action of cariprazine is not fully understood. However, the therapeutic effect of cariprazine appears to be related to its antagonism of dopamine D_3 , D_2 (K_i values 0.49-0.71 nM vs. 0.085-0.3 nM, respectively) and partial agonist activity at serotonin 5-HT_{1A} receptors (K_i values 1.4-2.6 nM) with serotonin 5-HT_{2B} , 5-HT_{2A} and histamine H_1 receptors (K_i values of 0.58-1.1 nM, 18.8 nM and 23.3 nM, respectively). Cariprazine has low affinity for serotonin 5-HT_{2C} and adrenergic α-1 receptors (K_i values of 134 nM and 155 nM, respectively). Cariprazine has no significant affinity for cholinergic muscarinic receptors (IC_{50}>1000 nM). The two main active metabolites of cariprazine, desmethyl-cariprazine and didesmethyl-cariprazine, have similar *in vitro* receptor binding and functional activity profiles to the parent compound.

Pharmacodynamic effects:
Non-clinical studies conducted *in vivo* have shown that at pharmacologically effective doses, cariprazine has a D_3 receptor occupancy rate similar to that of D_2 receptors. In schizophrenic patients, there is a dose-dependent occupancy ratio of brain dopamine D_3 a nd D_2 receptors within the therapeutic dose range over 15 days (preferential occupancy in regions with higher D_3 expression).

The effects of cariprazine on the QT interval were evaluated in patients with schizophrenia or schizoaffective disorder. Electrocardiographic assessments in 129 patients over a 12-hour period at baseline and at steady state were provided by data derived from Holter monitors. No prolongation of the QT interval was detected at supratherapeutic doses (9 mg/day or 18 mg/day). In no patient treated with cariprazine was the QTc interval ≥60 ms from baseline, nor was a QTc interval >500 ms detected in any patient.

Clinical efficacy and safety
Efficacy with long-term use
The efficacy of cariprazine in maintaining antipsychotic effects was investigated in a long-term randomized withdrawal clinical trial. A total of 751 patients with acute schizophrenia symptoms received cariprazine at a dose of 3-9 mg/day for 20 weeks; 337 of these patients received

cariprazine at a dose range of 3 or 6 mg/day. Stabilized patients were then randomized to receive either 3 or 6 mg of cariprazine (n=51) or placebo (n=51) at fixed doses for up to 72 weeks in a double-blind manner. The primary endpoint of the study was time to relapse. At the end of the study, relapse of schizophrenic symptoms was observed in 21.6% of patients treated with cariprazine, compared to 49% of patients treated with placebo. Therefore, the relapse duration in the cariprazine group (326 days vs. 92 days, according to the 25th percentile) was significantly longer than in the placebo group (p = 0.009).

Depressive episodes associated with bipolar I disorder (bipolar depression):
The efficacy of cariprazine in the treatment of depressive episodes associated with bipolar I disorder (bipolar depression) was determined in patients meeting the DSM-IV-TR or DSM-5 criteria for depressive episodes associated with bipolar I disorder (mean age 43 years, age range 18 to 65 years; 61% female; 75% Caucasian) in one 8-week and two 6-week placebo-controlled studies.

The primary endpoint in all studies was defined as the change in the total score on the Montgomery-Asberg Depression Rating Scale (MADRS) at the end of week 6 compared to baseline. The MADRS is a 10-item scale rated by a clinician, with total scores ranging from 0 (no depressive features) to 60 (highest score). The change in MADRS total score achieved with cariprazine compared to placebo relative to baseline is shown in Table 3. The time course of efficacy results for Study 2 is shown in Figure 1. In all studies, the 1.5 mg dose of cariprazine was shown to be statistically significantly superior to placebo. The secondary endpoint is the change in CGI-S score from baseline to week 6. CGI-S is a validated, clinician-rated measure that assesses the patient's current illness and overall clinical condition on a scale of 1 (normal, not ill at all) to 7 (extremely ill).

Study 1: In an 8-week placebo-controlled study (N = 571) using three fixed doses of cariprazine (0.75 mg/day, 1.5 mg/day, and 3 mg/day), cariprazine 1.5 mg was superior to placebo at the end of week 6 in terms of MADRS total score and CGI-S score.

Study 2: In a 6-week placebo-controlled study (N = 474) using two fixed doses of cariprazine (1.5 mg/day and 3 mg/day), cariprazine 1.5 mg and 3 mg were superior to placebo in terms of MADRS total score at the end of week 6.

Study 3: In a 6-week placebo-controlled study (N = 478) using two fixed doses of cariprazine (1.5 mg/day and 3 mg/day), cariprazine 1.5 mg was superior to placebo in terms of MADRS total score and CGI-S score at the end of week 6.

No clear evidence of different responses was found when examining population subgroups by age (few patients over 55 years of age), gender, and race.

Table 3. Primary analysis results of bipolar depression studies

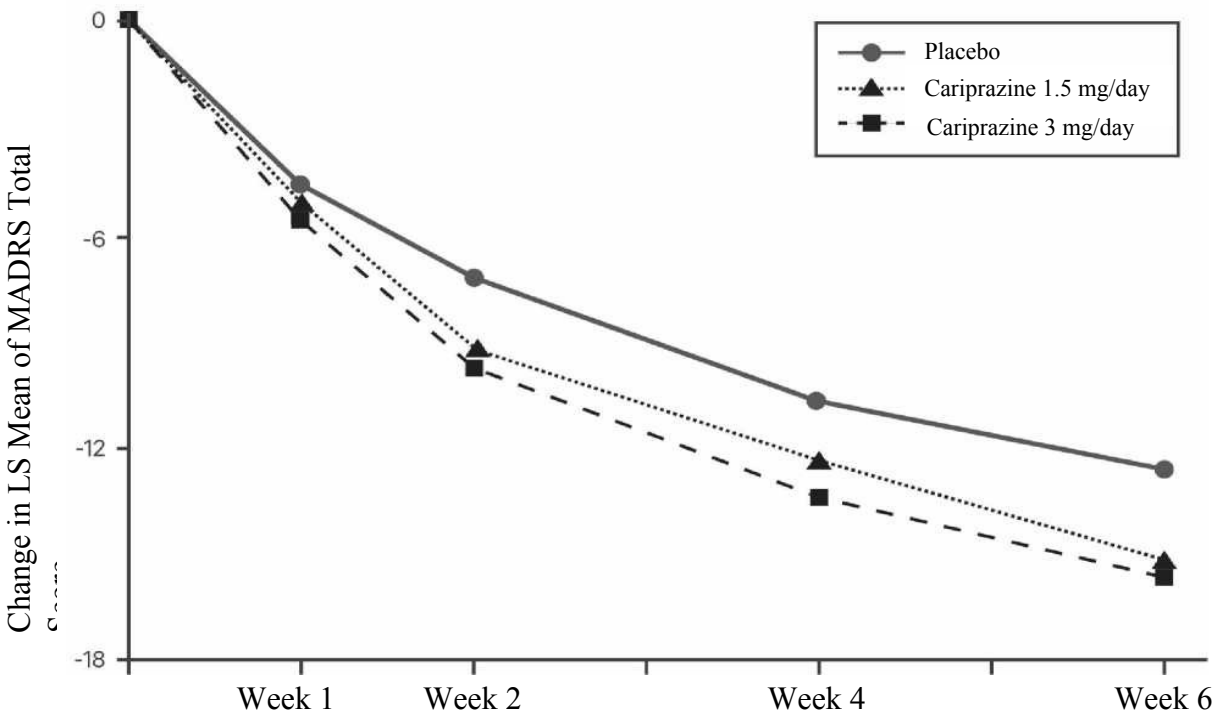
Study number	Treatment group (ITT patient count)	Primary efficacy endpoint: MADRS total		
		Mean baseline score (SD)	Change in LS mean from baseline (SH)	Placebo-adjusted difference[a] (%95 CI)
Study 1	Cariprazine (1.5 mg/day)* (n=145)	30.3 (4.4)	-15.1 (0.8)	-4.0 (-6.3; -1.6)
	Cariprazine (3 mg/day) (n=145)	30.6 (4.7)	-13.7 (0.9)	-2.5 (-4.9; -0.1)
	Placebo (n=141)	30.4 (4.6)	-11.1 (0.9)	
Study 2	Cariprazine (1.5 mg/day)* (n=154)	30.7 (4.3)	-15.1 (0.8)	-2.5 (-4.6; -0.4)
	Cariprazine (3 mg/day)* (n=164)	31 (4.9)	-15.6 (0.8)	-3.0 (-5.1; -0.9)
	Placebo (n=156)	30.2 (4.4)	-12.6 (0.8)	
Study 3	Cariprazine (1.5 mg/day)* (n=162)	31.5 (4.3)	-14.8 (0.8)	-2.5 (-4.6; -0.4)
	Cariprazine (3 mg/day) (n=153)	31.5 (4.8)	-14.1 (0.8)	-1.8 (-3.9; 0.4)
	Placebo (n=163)	31.4 (4.5)	-12.4 (0.8)	

ITT: Intention-to-treat; SD: Standard deviation; SE: Standard error; LS Mean: Least squares mean; CI: Confidence interval

[a] Difference in change from baseline in least squares mean (drug minus placebo)

* Doses that were statistically significantly superior to placebo

Figure 1. Change in LS Mean* of MADRS Total Score at Visits Compared to Baseline (Study 2)



*LS Mean: Least squares mean

5.2. Pharmacokinetic properties

General characteristics

Cariprazine has two pharmacologically active metabolites with similar efficacy to cariprazine: desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR). Total cariprazine (cariprazine + metabolites/DCAR and DDCAR) exposure approaches 50% of steady-state exposure at ~1 week of daily dosing and reaches 90% of steady-state exposure at 3 weeks. Steady-state exposure to DDCAR is approximately two to three times higher than that to cariprazine, while exposure to DCAR is approximately 30% of cariprazine exposure.

Absorption:

The absolute bioavailability of cariprazine is unknown. Cariprazine is well absorbed after oral administration. Following multiple-dose administration, peak plasma concentrations for cariprazine and its major active metabolites generally occur approximately 3-8 hours after dosing.

A single 1.5 mg dose of cariprazine administered with a high-fat meal (900 to 1000 calories) did not significantly affect the C_{max} or AUC of cariprazine or its primary active metabolites.

($AUC_{0-\infty}$ increased by 12%, C_{max} decreased by <5% when administered with food compared to administration on an empty stomach). The effect of food on exposure to the DCAR and DDCAR metabolites is also minimal.

Cariprazine can be administered with or without food.

Distribution:
Based on a population pharmacokinetic analysis, the apparent central distribution volume (V/F) was determined to be 916 L for cariprazine, 475 L for DCAR, and 1568 L for DDCAR, indicating that cariprazine and its primary active metabolites are widely distributed. Cariprazine and its major active metabolites bind to plasma proteins to a high degree (cariprazine 96-97%, DCAR 94-97%, and DDCAR 92-97%).

Biotransformation:
The metabolism of cariprazine involves demethylation (DCAR and DDCAR), hydroxylation (hydroxy cariprazine, HCAR), and a combination of demethylation and hydroxylation (hydroxy desmethyl cariprazine, HDCAR, and hydroxy didesmethyl cariprazine, HDDCAR). The metabolites HCAR, HDCAR, and HDDCAR are subsequently biotransformed to their corresponding sulfate and glucuronide conjugates. An additional metabolite, desdichlorophenyl piperazine cariprazine (DDCPPCAR) acid, is produced by the dealkylation and subsequent oxidation of cariprazine.

Cariprazine is metabolized to DCAR and HCAR by CYP3A4 and, to a lesser extent, CYP2D6. DCAR is metabolized to DDCAR and HDCAR by CYP3A4 and, to a lesser extent, CYP2D6. DDCAR is metabolized to HDDCAR by CYP3A4.

Cariprazine and its main active metabolites are not substrates for P-glycoprotein (P-gp), organic anion transporting polypeptide 1B1 and 1B3 (OATP1B1 and OATP1B3), and breast cancer resistance protein (BCRP). This indicates that cariprazine is unlikely to interact with P-gp, OATP1B1, OATP1B3, and BCRP inhibitors.

Elimination:
The elimination of cariprazine and its main active metabolites occurs primarily through hepatic metabolism. After administering 12.5 mg/day of cariprazine to patients with schizophrenia, 20.8% of the dose was excreted in the urine as cariprazine and its metabolites.

Unchanged cariprazine is excreted in urine as 1.2% of the dose and in feces as 3.7% of the dose.

The mean terminal half-life (1 to 3 days for cariprazine and DCAR and 13 to 19 days for DDCAR) is not a determinant of the time to reach steady-state plasma concentrations or the time to reach decline in plasma following discontinuation of treatment. For the management of patients treated with cariprazine, the functional half-life is more important than the terminal half-life. The functional half-life is ~2 days for cariprazine and DCAR, 8 days for DDCAR, and is considered to be ~1 week for cariprazine overall. The total plasma concentration of cariprazine will gradually decrease after the dose is discontinued or interrupted. The total plasma concentration of cariprazine decreases by 50% within ~1 week, and a decrease of more than 90% in the total cariprazine concentration occurs within ~3 weeks.

Linearity/non-linearity:
Following repeated doses, plasma exposure to cariprazine and its two main active metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), increases in a dose-proportional manner within the 1.5 to 6 mg therapeutic dose range.

Characteristic features in patients
Renal impairment
Population pharmacokinetic modeling was performed using data from patients enrolled in a schizophrenia clinical program treated with cariprazine, with varying levels of renal function, including normal renal function (creatinine clearance, CrCl ≥ 90 mL/min) and mild (CrCl 60 to 89 mL/min) and moderate (CrCl 30 to 59 mL/min) renal impairment. No significant correlation was found between cariprazine plasma clearance and creatinine clearance in these studies.

Cariprazine has not been evaluated in patients with severe renal impairment (CrCl <30 mL/min) (see Section 4.2).

Liver impairment
A two-part study (single dose of 1 mg cariprazine [Part A] and 0.5 mg cariprazine daily for 14 days [Part B]) was conducted in patients with varying degrees of hepatic impairment (Child-Pugh Class A and B). Compared to healthy volunteers, patients with mild or moderate hepatic impairment had up to 25% higher exposure (C_{max} and AUC) to cariprazine following both a single 1 mg dose and 14 days of once-daily 0.5 mg dosing, while exposure data for the major active metabolites desmethyl cariprazine and didesmethyl cariprazine were 45% lower.

Exposure to total active components (CAR+DCAR+DDCAR) (AUC and C_{max}), considering unbound + bound concentrations, was reduced by 21-22% and 13-15% in mild or moderate hepatic impairment, respectively, compared to healthy subjects; For the unbound total component, a 12-13% decrease and a 20-25% increase were calculated in patients with mild and moderate hepatic impairment, respectively, after multiple doses of cariprazine.

Cariprazine has not been evaluated in patients with severe hepatic impairment (Child-Pugh Class C) (see Section 4.2).

Age, gender, and race

In the population pharmacokinetic (PK) analysis, no clinically significant differences in PK parameters (AUC and C_{max} values for cariprazine and its major active metabolites) based on age, gender, or race were detected. This analysis included 2,844 patients of different races, including 536 patients aged 50-65 years. Of these 2,844 patients, 933 were women (see Section 4.2). Data in elderly patients over 65 years of age are limited.

Tobacco use

Since cariprazine is not a CYP1A2 substrate, smoking is not expected to have an effect on the pharmacokinetics of cariprazine.

Potential for cariprazine to affect other medicinal products

Cariprazine and its primary active metabolites did not induce CYP1A2, CYP2B6, and CYP3A4 enzymes and did not act as inhibitors of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP219, CYP2D6, CYP2E1, and CYP3A4 *in vitro*. Cariprazine and its main active metabolites are not inhibitors of OATP1B1, OATP1B3, BCRP, organic cation transporter 2 (OCT2), and organic anion transporters 1 and 3 (OAT1 and OAT3) *in vitro*. While DCAR and DDCAR transporters are not P-gp inhibitors, cariprazine has been identified as a P-gp inhibitor in the intestines (see Section 4.5).

5.3. Preclinical safety data

Cariprazine caused bilateral cataracts and secondary retinal changes (retinal detachment and cystic degeneration) in dogs. The no-observed-adverse-effect level (NOAEL) exposure (total cariprazine AUC) for ocular toxicity is 6 mg/day, which is 4.2 times the clinical AUC exposure at the maximum recommended human dose. In a 2-year study, an increased incidence of retinal degeneration/atrophy was observed in albino rats at clinically relevant exposures.

Phospholipidosis was observed in the lungs (inflammatory or non-inflammatory) of rats, dogs, and mice and in the adrenal cortex of dogs at clinically relevant exposures. Inflammation was observed in the lungs of dogs dosed for 1 year at 2.7 (male) and 1.7 (female) times the NOAEL at the recommended maximum human dose. Inflammation was not observed at the end of a 2-month drug-free period at an exposure 4.2 times the clinical exposure at the maximum recommended human dose; however, inflammation was still detected at high doses.

Adrenal cortex hypertrophy was observed in rats (females only) at 4.1 times the maximum recommended human dose exposure and in mice at clinically meaningful total cariprazine plasma concentrations.

Reversible adrenal cortex hypertrophy/hyperplasia and vacuolization/vesiculation in dogs were observed at a NOAEL 4.2 times higher than the maximum recommended human dose.

In female rats, lower fertility and pregnancy indices were observed at clinically relevant exposures based on mg/m² body surface area. No effects on male fertility were recorded at exposures up to 4.3 times the clinical exposure at the maximum recommended human dose.

Administration of cariprazine to rats at 6 mg/day, the maximum recommended human dose, during organogenesis, at a drug exposure lower than human exposure, resulted in malformations, low survival of offspring, and developmental retardation. In rabbits, cariprazine caused maternal toxicity, but no fetal toxicity was observed at 5.8 times the maximum recommended human dose.

Administration of cariprazine to pregnant rats during organogenesis, throughout pregnancy, and during lactation at clinically relevant exposure levels resulted in decreased postnatal survival, birth weight, and post-weaning body weight in first-generation offspring. In addition, pale, cold bodies and developmental delays (underdeveloped/poorly developed renal papillae and decreased auditory startle response in males) were observed without maternal toxicity. While the reproductive performance of first-generation offspring was unaffected, low body weights with similar clinical symptoms were observed in second-generation offspring.

Cariprazine and its metabolites are excreted into rat milk during lactation.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium starch glycolate
Magnesium stearate
Hard gelatin capsule (No. 4):
- Yellow iron oxide (E172)
- Titanium dioxide (E171)
- FD&C Blue 1 (E133)
- FD&C Red 40 (E129)
- Purified water
- Gelatin (beef gelatin)

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store at room temperature below 30°C in its outer packaging to protect from light.

6.5 Nature and contents of container

Transparent PVC/PCTFE and aluminum foil are used as the primary packaging material for our product. Blisters are placed inside cardboard boxes. Blister packs containing 30 capsules per box are provided with a package leaflet.

6.6. Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirement.

7. MARKETING AUTHORISATION HOLDER

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