

Risk Management Plan Summary

Reagila

Cariprazine

1.5 mg/ 3 mg/ 4.5 mg/ 6 mg

Hard capsules

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Marketing Authorization Holder: Recordati AG, Lindenstrasse 8, 6340 Baar

Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimize them.

The RMP summary of Reagila is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Reagila in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic.

Recordati AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of Reagila.

Overview of disease epidemiology

The lifetime morbidity risk for schizophrenia is estimated to be 1.0%. The annual incidence of schizophrenia appears to be 0.22 per 1,000 population¹. One or more negative symptoms are present in about 50 % of patients^{2,3}. About 13 % of the schizophrenic patients are with primary negative symptoms³.

The disorder usually manifests during adolescence or in young adulthood. About 20%–40% of patients experience their first psychotic symptoms before the age of 20 years. For men, the peak incidence of onset of schizophrenia has been determined to be between ages 15 and 25 years; for women, between ages 25 and 35 year¹. The male–female ratio is about 1.4-1.⁴ Men experience more negative symptoms and women more affective symptoms, although acute psychotic symptoms, either in type or severity, do not differ between the two genders¹.

Concerning genetic risks, having a close relative with psychosis or schizophrenia is the biggest risk factor for developing a psychotic disorder⁵. Although more than 80% of patients with schizophrenia have parents who do not have the disorder, the risk of having schizophrenia is greater in persons whose parents have the disorder. The lifetime risk is 13% for a child with one parent with schizophrenia and 35%–40% for a child with two affected parents. The risk increases with the number of affected relatives¹. However, while genetic risk is substantial, it is not due to a single ‘schizophrenia’ gene, but to many genes, each of which makes a small contribution. Therefore, there must also be environmental risks, both biological and psychosocial. Potential biological risks include: complications before or during birth (such as infections, poor nutrition while in the womb, maternal stress or birth trauma); cannabis use, especially in adolescence; older paternal age at birth and seasonality of birth; and exposure to toxoplasma gondii. Potential psychosocial risks include: urban birth and exposure to living in cities; childhood and adult adversity, including poor rearing environments, sexual, physical and emotional abuse, neglect and bullying; and migration, especially when the migrants are from a developing country or a country where the majority of the population is black⁵.

Summary of treatment benefits

Reagila is an atypical antipsychotic indicated for the treatment of schizophrenia in adult patients.

The efficacy of cariprazine for the treatment of schizophrenia was established in three, 6-week trials including altogether 1317 participants. Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impressions-Severity (CGI-S) rating scales were used for assessing psychiatric signs and symptoms in each trial. An active control arm (risperidone or aripiprazole) was included. In all three trials, cariprazine was superior to placebo.

In a long-term clinical study assessing the maintenance of antipsychotic effect, cariprazine (N=200) was more effective than placebo in preventing relapse of schizophrenia.

In a 26-week study designed to assess the effect on negative symptoms of schizophrenia, cariprazine was more effective than risperidone for improving the negative symptoms of patients having persistent predominant negative symptoms (N=461).

Unknowns relating to treatment benefits

There is limited information on how well cariprazine works in elderly patients, in children under 18 years of age and in pregnant and lactating women.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
<p>Movement disorders (Extrapyramidal symptoms including tardive dyskinesia)</p>	<p>Movement disorders (akathisia, parkinsonism, dystonia, dyskinesia) are common undesirable effects in association with antipsychotic treatment including Reagila.</p> <p><i>Akathisia:</i> feeling of inner restlessness manifesting in an inability to sit or remain motionless.</p> <p><i>Dystonia:</i> prolonged abnormal contractions of muscle groups. Symptoms of dystonia include spasm of the neck muscles including muscles around the voice box, swallowing difficulty, tightness of the throat, breathing difficulty, protrusion of the tongue. It can lead to accidental inhalation of food with risk of pneumonia which can be life-threatening condition.</p> <p><i>Parkinson-like symptoms:</i> slow movement, muscle stiffness, uncontrollable twitching or jerking.</p> <p><i>Tardive dyskinesia:</i> an irregular or unusual rapid repetitive muscle movements with slow onset such as grimacing, tongue movements, excessive eye blinking, involuntary movements of</p>	<p>If signs and symptoms of movement disorder appear in a patient treated with Reagila, dose modification (reduction or discontinuation) of antipsychotic treatment and close follow-up or monitoring should be considered. In case of experiencing tardive dyskinesia, medical product discontinuation should be considered. Akathisia develops early in treatment, therefore close monitoring in the first phase of treatment is important.</p> <p>The dose could be modified based on individual response and tolerability.</p> <p>It is also important that patients always inform their doctor if they experienced earlier movement disorders from other antipsychotic drug(s).</p>

	the limbs and fingers, lip smacking or pursing.	
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Important potential risks

Risk	What is known
<p>Life-threatening neurological disorder in reaction to the use of antipsychotic treatment (Neuroleptic malignant syndrome)</p>	<p>Neuroleptic malignant syndrome (NMS) is a known side effect of drugs used to treat schizophrenia. Based on the data from schizophrenia trials, one case of NMS was reported during treatment with Reagila. Patient should consult their doctor immediately or ask professional help if the following signs and symptoms develop while taking Reagila and/or other antipsychotic products:</p> <p><i>Fever, muscle stiffness or other abnormal muscle function, altered mental status or reduced consciousness, faster breathing, sweating, very rapid or irregular heartbeat, sudden changes in blood pressure or if patient presents with unexplained high fever without any other symptoms of NMS.</i></p> <p>Additional signs may occur due to destruction of muscle tissue (called rhabdomyolysis) such as elevated creatine phosphokinase in blood, brown discoloration of the urine due to myoglobinuria/rhabdomyolysis and kidney failure.</p> <p>NMS is a medical emergency condition that may lead to death if not treated appropriately. Consequently, early recognition or diagnosis and immediate aggressive professional treatment are crucial in patients with NMS. In these cases all antipsychotic medicinal products, including Reagila, must be stopped.</p>
<p>Changes to metabolism like high blood sugar, diabetes, weight gain, disorder of the blood fat (lipid) metabolism (Metabolic changes (Hyperglycaemia, Weight gain, Dyslipidaemia))</p>	<p>Slight elevation in blood fat and glucose parameters occurred in the long-term studies with Reagila. Patients treated with any antipsychotic agents, including Reagila, should be observed for signs and symptoms of high blood sugar such as:</p> <ul style="list-style-type: none"> • excessive thirst • passing of large amounts of urine • increase in appetite • feeling weak <p>Patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored with caution and regularly for worsening of blood sugar control while taking Reagila.</p> <p>Weight change has been observed with use of antipsychotics including Reagila. Patients should have their weight monitored.</p>

<p>Ocular changes including lenticular changes and cataract (Ocular changes (lenticular Changes) and cataracts)</p>	<p>A cataract is a clouding of the lens of the eye that leads to a decrease in vision. Cataract can develop as a result of aging, other medical conditions, like diabetes, or exposure to toxic substances, certain drugs (such as corticosteroids or diuretics), ultraviolet light, or radiation. Few cataract cases were experienced in clinical trials, but there is no evidence that Reagila caused the cataract.</p> <p>Patients experiencing visual impairment are advised to visit an ophthalmologist.</p>
<p>Suicidality (Suicidal ideation and behavior)</p>	<p>The occurrence of suicidal behavior is inherent in psychotic illnesses and mood disorders. Some cases have been reported early after initiation or switch of antipsychotic therapy, including Reagila. High-risk patients while taking antipsychotics including Reagila should be handled with caution for the risk of suicidality. If patients are having any thoughts or feelings about hurting themselves, they should contact their doctor immediately.</p>
<p>Condition in which damaged muscle breaks down rapidly (Rhabdomyolysis)</p>	<p>Condition in which damaged muscle breaks down rapidly (rhabdomyolysis) has been reported rarely during clinical development program of Reagila.</p> <p>The creatine phosphokinase test is used to diagnose and evaluate the muscle damage. This test measures the amount of creatine phosphokinase present in the blood. Creatine phosphokinase is a specific enzyme found primarily in the heart, skeletal muscle, and brain tissues. When tissue is damaged, creatine phosphokinase leaks from tissue into the blood, and the level of blood creatine, phosphokinase will be elevated.</p> <p>On rare occasions, muscle breakdown resulting in kidney damage can be serious and may become a potentially life-threatening condition. However, if recognized and treated correctly in time, these reactions often have good outcomes.</p> <p>Therefore, patients should contact their doctors immediately if they experience unexplained muscle pain, tenderness, generalized weakness and darkened urine, as these symptoms can draw the attention to severe muscle injury.</p>
<p>Concomitant use of cariprazine with CYP3A4 inhibitors and inducers (Interaction with CYP3A4 inhibitors and inducers)</p>	<p>Medications like CYP3A4 inhibitors and inducers may influence the level of cariprazine in the blood.</p> <p>Before starting treatment with Reagila, patients should always inform their doctors about their other medications.</p> <p>Do not take Reagila: if you are taking the following medicines:</p>

	<ul style="list-style-type: none"> • boceprevir and telaprevir, medicines used to treat hepatitis caused by hepatitis C virus • clarithromycin, telithromycin, erythromycin and nafcillin, antibiotics used to treat various bacterial infections • rifampicin, a medicine used to treat tuberculosis • cobicistat, indinavir, nelfinavir, ritonavir, saquinavir, efavirenz and etravirine, medicines used to treat HIV infections • itraconazole, ketoconazole, posaconazole, voriconazole and fluconazole, medicines used to treat fungal infections • nefazodone, a medicine and St John's wort (<i>Hypericum perforatum</i>), a herbal remedy, used to treat depression • carbamazepine, phenobarbital and phenytoin medicines used to treat epilepsy and seizures • diltiazem and verapamil, medicines used to treat different heart diseases • modafinil, a medicine used to treat sleepiness • bosentan, a medicine used to treat the high blood pressure in the lungs. <p>Consumption of grapefruit or grapefruit juice should be avoided when taking Reagila.</p>
<p>Possible birth defect and fertility problems (Developmental and reproductive toxicity)</p>	<p>Reproductive toxicity includes adverse effects on fertility, as well as adverse effects on development of the offspring. In animal studies of cariprazine malformations, lower pup survival, and developmental delays was observed in rat. In rat lower fertility rates was observed.</p> <p>There are no sufficient data from human pregnancies which would confirm the safe use of Reagila during human pregnancies, however, the human consequences of the alterations observed during the animal studies are currently not known.</p> <p>Therefore, as a precaution measure, women of childbearing potential must use effective contraception during Reagila treatment. Even after treatment is stopped, contraception must be used for at least 10 weeks after the last dose of Reagila. This is because the medicine will circulate in the body for some time after the last dose was taken. If a patient uses hormonal contraceptives, a so-called barrier method (e.g. condom or diaphragm) should also be used.</p>

Missing information

Risk	What is known
Limited information on the safe use during breastfeeding (Use during lactation)	A drug, which is present in the mother's blood can get into the breast milk to some extent and may cause undesirable effects on the baby. Since it is unknown whether cariprazine is excreted into breast milk, Reagila should not be used in breastfeeding women.
Limited information on use in elderly population (Use in patients > 65 years)	Limited data are available in elderly patients aged 65 years and older treated with Reagila. Doctors should be more cautious in case of treating elderly patients.
Limited information on use in patients with severe renal or hepatic impairment (Use in patients with severe renal or hepatic impairment)	There are currently no recommendations regarding the dosing of Reagila in patients with mild and moderate liver or renal impairment. There are no data on the use of Reagila in patients suffering from severe liver impairment and severe renal impairment. Patient should always inform their doctors about their past or current liver and renal diseases (or they should discuss it when they are not sure about it).

Summary of additional risk minimization measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL) / patient information leaflet (PIL).

In Switzerland, these documents are entitled Information for professionals and Information for the patient, respectively. The measures in these documents are known as routine risk minimization measures.

The safety of this medicine will be appropriately monitored on an ongoing basis; any signals will be evaluated and appropriate measures taken in a timely manner to ensure patient safety.

Planned post authorization development plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Clinical study to investigate the effect of cariprazine on	Confirm that the active substance has no clinically meaningful effect	Concomitant use of cariprazine with CYP3A4	Planned	Final report is planned: Q1 20121

the pharmacokinetics (the changes of the active substance in the body) of combined oral contraceptive pill (Ethinyl Estradiol and Levonorgestrel). Category 3	on the pharmacokinetics (the changes of the active substance in the body) of the selected combined oral contraceptive pill.	inhibitors and inducers		
Clinical study to investigate the concomitant use of cariprazine with moderate CYP3A4 inhibitor (erythromycin) in patients with different genetics of CYP2D6 enzymes. Category 3	Provide dosing recommendations when cariprazine is used concomitantly with moderate CYP3A4 inhibitors. Investigate the effect of different genetics of CYP2D6 enzymes on the exposure of cariprazine	Concomitant use of cariprazine with CYP3A4 inhibitors and inducers	Planned	Final report is planned: Q3 2020
Experimental (non-human) studies on the metabolism of Didesmethyl Cariprazine (DDCAR, a degradation product of cariprazine) to explore contribution of unusual enzymes (CYP2C8, CYP2J2 and other oxidative enzymes) to the elimination of cariprazine. Category 3	Identifying further (not so common) enzymes in the metabolism of DDCAR	Not applicable. No safety concern is raised.	Planned	Final report is planned: Q3 2018

Studies which are condition of the marketing authorization

None of the above studies are conditions of the marketing authorization.

Summary of changes to the risk management plan over time

Not applicable.

References

- ¹ Lehman AF, Lieberman JA et al. Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry 2010
- ² Sicras Mainar A, Maurino J et al Impact of negative symptoms on healthcare resource utilization and associated costs in adult outpatients with schizophrenia: a population-based study. BMC Psychiatry 2014;14:225
- ³ Bobes J, Arango C et al Prevalence of negative symptoms in outpatients with schizophrenia spectrum disorders treated with antipsychotics in routine clinical practice: findings from the CLAMORS study. J Clin Psychiatry 2010;71(3):280-6
- ⁴ Barnes T and the Schizophrenia Consensus Group of the British Association for Psychopharmacology Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. Journal of Psychopharmacology 2011;0(0):1-54
- ⁵ NICE Psychosis and Schizophrenia in adults Treatment and Management Clinical Guideline 178; 2014