GEDEON RICHTER PLC.

RISK MANAGEMENT PLAN

FOR

Cariprazine 1.5 mg, 3 mg, 4.5 mg, 6 mg capsules, hard

and

Cariprazine 1.5 mg, 3 mg, 4.5 mg, 6 mg orodispersible tablets

EU Risk Management Plan for Reagila (cariprazine)

RMP version to be assessed as part of this application:

RMP Version number	5.0
Data lock point for this RMP:	10 May 2023
Date of final sign off	Please see date on digital signature.
Rationale for submitting an updated RMP	Changes presented in parallel procedures (EMEA/H/C/002770/X/0033/G – RMP version 3.0 and EMEA/H/C/002770/II/0034 – RMP version 4.0) were merged in one consolidated RMP (RMP version 5.0).
Summary of significant changes in this RMP	Orodispersible tablet pharmaceutical form was added to the medicinal products which this RMP refers to.
Details of the currently approved RMP:	
Version number	version 4.0
Approved with procedure	EMEA/H/C/002770/II/0034
Date of approval (opinion date):	11 April 2024
QPPV name[1]	**Attila Oláh MD**
QPPV signature	

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

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Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	cariprazine	
Pharmacotherapeutic group(s) (ATC Code)	Nervous system; Psycholeptics; Antipsychotics; Other antipsychotics (ATC Code: N05AX15)	
Marketing Authorisation Holder	Gedeon Richter Plc.	
Medicinal products to which this RMP refers	Reagila 1.5 mg hard capsules Reagila 3 mg hard capsules Reagila 4.5 mg hard capsules Reagila 6 mg hard capsules	Reagila 1.5 mg orodispersible tablet Reagila 3 mg orodispersible tablet Reagila 4.5 mg orodispersible tablet Reagila 6 mg orodispersible tablet
Invented name(s) in the European Economic Area (EEA)	Reagila	
Marketing authorisation procedure	centralised procedure	
Brief description of the product	Chemical class: Cariprazine is an antipsychotic.	
	Summary of mode of action: The therapeutic effect of cariprazine may be mediated through a combination of partial agonist activity at central dopamine D_3, D_2 and serotonin 5-HT_{1A} receptors, and antagonist activity at serotonin 5-HT_{2B} and 5-HT_{2A} receptors.	
	Important information about its composition: **Capsule, hard:** *Capsule contents* Pregelatinized (maize) starch, Magnesium stearate *Capsule shell (1.5 mg capsule)* Titanium dioxide (E 171), Gelatin *Capsule shell (3 mg capsule)* Allura red AC (E 129), Brilliant blue FCF (E 133), Titanium dioxide (E 171), Yellow iron oxide (E 172), Gelatin *Capsule shell (4.5 mg capsule)* Allura red AC (E 129), Brilliant blue FCF (E 133), Titanium dioxide (E 171), Yellow iron oxide (E 172), Gelatin *Capsule shell (6 mg capsule)*	

	Brilliant blue FCF (E 133), Allura red AC (E 129), Titanium dioxide (E 171), Gelatin *Printing ink (black: 1.5 mg, 3 mg and 6 mg capsules)* Shellac, Black iron oxide (E 172), Propylene glycol, Potassium hydroxide *Printing ink (white: 4.5 mg capsule)* Shellac, Titanium dioxide (E 171), Propylene glycol, Simeticone **Orodispersible tablet:** Mixture of mannitol and maize starch (80:20) Sodium starch glycolate Type A Malic acid Sodium stearyl fumarate Silicon dioxide
Hyperlink to the Product Information	Please see eCTD Module 1.3.1
Indication(s) in the EEA	Reagila is indicated for the treatment of schizophrenia in adult patients.
Dosage in the EEA	The recommended starting dose of cariprazine is 1.5 mg once daily. Thereafter the dose can be increased slowly in 1.5 mg increments to a maximum dose of 6 mg/day, if needed. The lowest effective dose should be maintained according to the clinical judgement of the treating physician. 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. Patients should be monitored for adverse reactions and treatment response for several weeks after starting cariprazine and after each dosage change.
Pharmaceutical form(s) and strengths	capsules, hard; 1.5 mg, 3 mg, 4.5 mg, 6 mg orodispersible tablet; 1.5 mg, 3 mg, 4.5 mg, 6 mg
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Treatment of schizophrenia in adult patients

Incidence
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 population.[1] One or more negative symptoms are in present in about 50 % of patients.[2,3] About 13 % of the schizophrenic patients are with primary negative sympoms.[3]

Prevalence
The median values per 1,000 persons (10, 90 percent quintiles) for the distributions for point, period, lifetime, and lifetime morbid risk were 4.6 (1.9, 10.0), 3.3 (1.3, 8.2), 4.0 (1.6, 12.1), and 7.2 (3.1, 27.1), respectively.[4]

Demographics of the population in schizophrenia
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 year.[1] The male–female ratio is about 1.4-1.[5] 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 genders.[1]
Concerning genetic risks, having a close relative with psychosis or schizophrenia is the biggest risk factor for developing a psychotic disorder.[6] 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 relatives.[1] 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 black.[6]

The main existing treatment options
Current guidelines recommend atypical antipsychotics, including aripiprazole, risperidone as first-line treatment for schizophrenia. The blockade of the dopamine D_2 receptor is believed to have a central role in the antipsychotic action (efficacy for positive symptoms) of current schizophrenia medications.[7,8,9] To date no effective therapy is available for negative symptoms of schizophrenia. Some antipsychotics like clozapine, amisulpride, olanzapine, and risperidone have been described to have better efficacy on the negative symptoms than others; however their impact is not sufficient.[10]

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Schizophrenia typically begins with a prodromal period, which precedes first episode psychosis (FEP) and can last from a few days to around 18 months. The prodromal period is often characterized by deterioration in personal functioning. Changes include the emergence of transient and/or attenuated psychotic symptoms, memory and concentration problems, unusual behaviour and ideas, disturbed communication and affect, and social withdrawal, apathy and reduced interest in daily activities.[11] The prodromal period is usually followed by an acute episode marked by hallucinations, delusions, and behavioural disturbances, usually accompanied by agitation and distress. Following resolution of the acute episode, usually after pharmacological, psychological and other interventions, symptoms diminish and often disappear for many people, although sometimes a number of negative symptoms remain. This phase, which can last for many years, may be interrupted by recurrent acute episodes that may need additional pharmacological, psychological and other interventions, as in previous episodes.

Compared with the general population, people with schizophrenia have a 2-2.5 fold increased risk of dying.[12] Although suicide contributes to the increased mortality associated with schizophrenia, individuals with schizophrenia have increased mortality risks due to a wide range of comorbid somatic conditions.[13] Over two-thirds of people with schizophrenia die of coronary heart disease, compared with about a half of the general population.[14] Relevant risk factors, many of which are inter-related, include cigarette smoking, unhealthy diet, exercise, obesity, relative poverty and poor healthcare.

Important co-morbidities

A retrospective analysis was conducted to reveal the medical co-morbidities in patients with schizophrenia. Subjects with schizophrenia were significantly more likely to have one or more chronic conditions compared with controls. Adjusted OR (95% confidence interval [CI]) were 2.62 (2.09 to 3.28) for hypothyroidism, 1.88 (1.51 to 2.32) for chronic obstructive pulmonary disease, 2.11 (1.36 to 3.28) for diabetes with complications, 7.54 (3.55 to 15.99) for hepatitis C, 4.21 (3.25 to 5.44) for fluid/electrolyte disorders, and 2.77 (2.23 to 3.44) for nicotine abuse/dependence.[15]

People with schizophrenia are 2-2.5 times more likely to die earlier than the general population. This is often due to physical illnesses, such as cardiovascular, metabolic and infectious diseases. For example, the prevalence of diabetes in people with schizophrenia is 2-3 times higher than the general population. This is partly due to the lifestyle of people living with schizophrenia and partly due to antipsychotic treatment, both of which can lead to metabolic changes, including weight gain.[12]

Psychiatric co-morbidities in patients with schizophrenia are also common. The most frequent psychiatric co-morbidity is substance abuse with a conservative estimate of 47% lifetime diagnosis. The occurrence of anxiety and depressive symptoms throughout the course of illness is also common, with an estimated prevalence of 15% for panic disorder, 29% for posttraumatic stress disorder, and 23% for obsessive-compulsive disorder. It is estimated that co-morbid depression occurs in 50% of patients.[16]

Part II: Module SII - Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non- clinical studies)	**Relevance to human usage**
Single-dose toxicity Cariprazine has a moderate acute oral toxicity profile in mice and rats. The acute minimum lethal oral dose of RGH-188 free base was considered to lie between 70.0 and 100.0 mg/kg in male and female mice and in female rats (11 and 16 mg/kg human equivalent dose (HED) corresponding to approximately 660 and 960 mg/day human dose, respectively). For male rats the minimum lethal dose is about 200.0 mg/kg. Clinical signs included ataxia, lethargy, hunched posture, palpebral closure, hypothermia, decreased activity, prone posture, and unkempt appearance in mice, and decreased activity in both sexes and palpebral closure, tremors, low gait, chromodacryorrhea and hypothermia in males only in rats.	Adverse effects in animals occurred at dose levels irrelevant to the clinical setting (≥ 100-fold safety multiples based on body surface area). In pre-marketing clinical trials involving cariprazine 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.
Repeat-dose toxicity <u>Effects on the eye</u> 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. The no-observed-adverse-effect-level (NOAEL) for cataract and retinal toxicity in the 1-year dog study is 2 mg/kg/day which is 4.2 times the maximum recommended human dose (MRHD) of 6 mg/day based on AUC of total cariprazine. Cataracts were not observed in other repeat dose studies with pigmented mice and albino rats. Increased incidence of retinal degeneration/atrophy was observed in albino rats in the 2-year study at clinically relevant animal plasma drug concentrations. Retinal degeneration/atrophy was not observed in the 6-month studies in albino rats and pigmented mice. The etiology of the retinal findings is different in rats and dogs. In albino rats that are known	Ophthalmologic testing in 10 of the cariprazine clinical studies included in this application (RGH-MD-01, -03, -04, -05, -06, -11, -17, -18, -36 and RGH-188-005) covering slit lamp examinations revealed no direct causal relationship between human exposure to cariprazine and potential for cataract formation. However, due to the limited amount of data available, the possibility of lenticular changes or cataracts cannot be excluded at this time. Ophthalmologic testing in the cariprazine clinical development program including ocular coherent tomography revealed no evidence for drug-induced retinal toxicity.

Key Safety findings (from non- clinical studies)	Relevance to human usage
to be highly susceptible to retinal injury by light, retinal changes were exacerbation of common background lesions due to behavioural changes and/or increased survival resulting in spending more time exposed to light. In dogs, retinal lesions are secondary to development of hypermature cataracts, and not a direct effect of test article on the retina. The retina is not a target tissue for cariprazine.	
Repeat-dose toxicity <u>Phospholipidosis</u> Phospholipidosis was observed in the lungs of rats, dogs, and mice (with or without inflammation) and in the adrenal 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 no-observed-effect-level (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.	The systematic analysis of the clinical database with regard to respiratory/pulmonary symptoms did not yield a pulmonary safety signal associated with exposure to cariprazine.
Repeat-dose toxicity <u>Adrenal hypertrophy/hyperplasia</u> 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.	No specific assessments of adrenocorticotrophic hormones were performed in the cariprazine clinical program; however, a search of the clinical database did not reveal a pattern indicative of adrenal dysfunction.

Key Safety findings (from non- clinical studies)	Relevance to human usage
Reproductive toxicity Fertility Cariprazine was administered by oral gavage to male or female rats before mating, through mating and up to day 7 of gestation at doses of 1, 3, and 10 mg/kg/day. In female rats, lower fertility and conception indices were observed at all dose levels (less than 1.6 times the MRHD of 6 mg/day based on mg/m2 body surface area). No effects on male fertility were noted at any dose (up to 4.8 times the MRHD of 6 mg/day based on AUC). Developmental toxicity: Administration of cariprazine to rats during the period of organogenesis caused malformations at maternally toxic doses, 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 neither teratogenic nor foetotoxic in rabbits at doses up to 5.8 times the MRHD of 6 mg/day. Pre- and postnatal toxicity: Administration of cariprazine to pregnant rats during the period of organogenesis, throughout pregnancy and lactation at oral doses up to 1 mg/kg/day (0.4 times the MRHD of 6 mg/day based on AUC) decreased postnatal survival, birth weight, and post-weaning body weight of first-generation pups. In addition, pale, cold bodies and developmental delays (renal papillae not developed/underdeveloped and decreased auditory startle response in males) were observed in the absence of significant maternal toxicity at this dose. Reproductive performance of the first-generation pups was unaffected; however, second generation pups also had similar clinical signs and lower body weight. Cariprazine and its metabolites were excreted in milk of rats during lactation.	The effect of cariprazine on human fertility has not been evaluated. Women of childbearing potential must be advised to avoid pregnancy while on Reagila. Female patients of child-bearing potential must use highly effective contraceptive methods during treatment and for at least 10 weeks following the last dose of Reagila. There is limited amount of data from the use of cariprazine in pregnant women. Animal studies have shown reproductive toxicity. Reagila is not recommended during pregnancy and women of childbearing potential not using reliable contraception. After discontinuation of cariprazine treatment contraception should be used up to 10 weeks due to the long acting metabolites. It is unknown whether cariprazine or its major active metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with cariprazine.
Nephrotoxicity No overt toxic effect on the kidneys were revealed by the non-clinical toxicity studies.	None.

Key Safety findings (from non- clinical studies)	Relevance to human usage
Hepatotoxicity No overt toxic effect on the liver were revealed by the non-clinical toxicity studies.	None.
Genotoxicity Cariprazine demonstrated small but statistically significant increases in mutant frequency at cytotoxic concentrations in the mouse lymphoma assay under conditions of metabolic activation. Based on negative findings in the bacterial reverse mutation, chromosome aberrations, and in vivo mouse micronucleus assays, the weight of evidence suggests a negligible mutagenic potential for cariprazine. Didesmetyl-cariprazine (DDCAR), a major active metabolite of cariprazine was tested in two in vitro genetic toxicity assays. A chromosomal aberrations test using human lymphocytes showed that DDCAR met the criteria for a positive test in the presence of metabolic activation at a cytotoxic dose. Given the negative results in the bacterial reverse mutation assay and the mouse carcinogenicity study, the weight of evidence also suggests a negligible mutagenic potential for this major active metabolite.	None.
Carcinogenicity No increases in tumours were noted in a 6-month carcinogenicity study in transgenic mice. In a two-year rat carcinogenicity assay, a slightly increased incidence of benign and malignant tumours of the adrenal gland (pheochromocytoma) was observed in high dose females. To further clarify this observation, a Pathology Working Group (PWG) was convened. A Pathology Working Group (PWG) reviewed these findings and concluded that the slightly higher incidence in this dose group was due to incidental biological variation of a spontaneous background lesion and is unrelated to cariprazine treatment. Supporting evidence included the absence of a clear dose response in the incidence of adrenal medullary neoplasms and lack of a dose-related increase in medullary hyperplasia.	None.

Key Safety findings (from non- clinical studies)	Relevance to human usage
General safety pharmacology Cardiovascular system The in vitro cardiovascular studies indicate that cariprazine and its major active metabolites have low potential for inhibiting hERG channel activity and affecting cardiac action potential duration (IC_{50} values~ 55-75-fold over the C_{max} at the MRHD of 6 mg/day). The potency of cariprazine and its major active metabolites for inhibiting hERG channel activity is approximately 10-fold lower than other antipsychotics. Cariprazine showed only minor effects on heart rate and blood pressure in conscious dogs (exposure margin of ~ 16 relative to the C_{max} (~23 ng/mL) at the MRHD of 6 mg). It produced no QTc prolongation in any of the cardiovascular safety studies.	Cariprazine did not result in clinically significant QTc prolongation following supratherapeutic dose (9 mg/day and 18 mg/day).
General safety pharmacology Nervous system In the CNS safety pharmacology studies (Irwin test) cariprazine at pharmacologically-effective doses (> 0.4 mg/kg PO) produced overt CNS-related symptoms that may be attributed to the exaggerated primary pharmacological activity of this compound. Cariprazine did not produce significant pro- or anticonvulsive activity or effects on sleep duration at doses that were at least 3-fold its ED50 value for antipsychotic-like effects. Cariprazine and its major active metabolite DDCAR showed low cataleptogenic potential as compared to the reference atypical antipsychotics. They showed no catalepsy at doses up to at least 50-fold their antipsychotic-like potencies.	Despite the lack of cataleptogenic effects up to a dose of 85 mg/kg which is 100-700-fold the ED50 value of cariprazine for antipsychotic-like efficacy in non-clinical studies and with an exposure margin of 140 at the MRHD of 6 mg/day, extrapyramidal symptoms were among the most frequently reported adverse drug reactions (≥10%) with cariprazine in the dose range (1.5 – 6 mg) in clinical studies in patients with schizophrenia treated for up to 72 weeks.
General safety pharmacology Endocrine system Cariprazine induced hyperprolactinemia in both male and female rats at doses ≥ 0.5 mg/kg PO (HED = 0.08 mg/kg or 4.8 mg).	This finding seems to be of limited or no relevance to human use, since hyperprolactinemia was not observed in the clinical studies.
General safety pharmacology Other systems Cariprazine did not have any major effects on respiratory, renal or gastrointestinal system.	None.

Key Safety findings (from non- clinical studies)	Relevance to human usage
Mechanisms for drug interactions CYP3A4 and, to a lesser extent, CYP2D6 appear to be the two major enzymes involved in the metabolism of cariprazine and its metabolites based on studies with human recombinant CYP enzymes and/or human liver microsomes (Study RGD:72359/E, 2009).	In a drug-drug interaction study, cariprazine C_{max} and $AUC_{0-\tau}$ following coadministration of cariprazine with ketoconazole increased by 3.42-fold and 3.88-fold, respectively; DDCAR C_{max} and $AUC_{0-\tau}$ increased by 1.43-fold while DCAR C_{max} and $AUC_{0-\tau}$ decreased by 35% and 32%, respectively (Study RGH-PK-07, 2010). However, the study length was relatively short and the exposure has not reached steady state. The results suggest that CYP3A4 is a major enzyme responsible for the metabolism of cariprazine. (See Section SVII.4.2; Important identified and potential interactions.)
In vitro metabolism studies of DDCAR was required by the EMA to explore contribution of unusual CYP (CYP2C8, CYP2J2) and other oxidative enzymes with the objective of identifying further (not so common) enzymes in the metabolism of DDCAR. The intrinsic clearance (CL_{int}) of DDCAR was measured in human liver microsomes, S9 fractions, cytosols and hepatocytes using 'substrate depletion' approach. The data of the performed study indicate clearly that the metabolic clearance of DDCAR is low. It is most probably mediated only by microsomal enzymes, perhaps exclusively by CYPs with a predominant (91.2%) contribution of CYP3A4. The role of other individual CYPs in the metabolism of DDCAR is probably minor involving CYP2C8, CYP2B6, CYP2D6 and perhaps CYP3A5 sum up not more than 3-4 percent contribution. The contribution of CYP2C9 is less than 5.2%. DDCAR is not a substrate for CYP2J2 or CYP1A2, CYP2A6, CYP2C19, CYP2E1, FMO1, FMO3 and FMO5 either. No safety concern is raised.	No safety finding has been raised. Since the study had been finalised, it has been removed from the Pharmacovigilance plan.

Conclusions on non-clinical data

Based on the non-clinical data the following safety concerns have been identified:

Important potential risks (not refuted by clinical data or which are of unknown significance): Ocular changes (Lenticular changes and cataracts) Developmental and reproductive toxicity
Missing information: Use during lactation

Part II: Module SIII - Clinical trial exposure

Safety data gained was analysed according to modal daily doses, to better assess potential dose-response relationships. Modal daily doses were moreover grouped into 3 subgroups (cariprazine modal daily dose 1.5-3 mg/day, modal daily dose 4.5-6 mg/day and modal daily dose 9-12 mg/day).
8 completed Phase 2/3 studies in schizophrenia form the basis for the primary safety assessment of cariprazine. For safety analyses, studies in schizophrenia that were of similar design (such as the short term or long-term, open-label studies) were grouped together; whereas unsimilar studies that had special designs or were performed on a special subpopulation were treated separately (maintenance of effect, negative symptom study). Based on study design, dosage, and patient populations, the clinical studies in schizophrenia have been categorized into distinct groupings: Data from 6-week controlled schizophrenia studies (RGH-MD-03, RGH-MD-04, RGH-MD-05, RGH-MD-16) were pooled to Group 1A (1317 patients). Data from long-term safety studies (RGH-MD-11 and RGH-MD-17) were grouped to Group 1B [679(461) patients]. Data from studies RGH-MD-06 (765 patients) and RGH-188-005 (230 patients) were not pooled with any other data. Table below summarizes the safety groups.

Phase 2/3 Cariprazine Clinical Studies in Schizophrenia Safety Population

Study No.	***Study Title (Treatment Groups)***	***Placebo N***	***Cariprazine N***	***Active Comparator N***
Group 1A: 6-Week, Double-blind, Placebo-Controlled Schizophrenia Studies				
RGH-MD-03	A double-blind placebo-controlled evaluation of the safety and efficacy of RGH-188 in the acute exacerbation of schizophrenia (Placebo; Cariprazine 1.5-4.5 mg/day or 6-12 mg/day)	129	260	—
RGH-MD-04	A double-blind, placebo and active-controlled evaluation of the safety and efficacy of cariprazine in the acute exacerbation of schizophrenia (Placebo; Cariprazine 3 mg/day or 6 mg/day; Aripiprazole 10 mg/day)	153	312	Aripiprazole152
RGH-MD-05	A double-blind, placebo-controlled evaluation of the safety and efficacy of cariprazine in the acute exacerbation of schizophrenia (Placebo; Cariprazine 3-6 mg/day or 6-9 mg/day)	151	307	—
RGH-MD-16	Evaluation of the safety and efficacy of RGH-188 in the acute exacerbation of schizophrenia (Placebo; Cariprazine 1.5 mg/day, 3 mg/day, or 4.5 mg/day; Risperidone 4 mg/day)	151	438	Risperidone 140
Overall exposure in Group 1A			1317	
Group 1B: 48-Week, Long-term, Open-label Schizophrenia Studies				
RGH-MD-11 [a]	Evaluation of the long-term safety, tolerability, and pharmacokinetics of cariprazine in patients with schizophrenia (Cariprazine 3-9 mg/day)	—	586	—
RGH-MD-17	A long-term, open-label extension study of the safety and tolerability of RGH-188 (cariprazine) in patients with schizophrenia (Cariprazine 1.5-4.5 mg/day)	—	93	—
Overall exposure in Group 1B			679 (416)*	

Study No.	*Study Title (Treatment Groups)*	*Placebo N*	*Cariprazine N*	*Active Comparator N*
RGH-MD-06: Maintenance of Effect Study				
RGH-MD-06 [b]	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of cariprazine (RGH-188) in the Prevention of Relapse in Patients with Schizophrenia (Placebo; Cariprazine 3-9 mg/day)	99	765	—
RGH-188-005: Negative Symptom Study				
RGH-188-005	A Randomized, Double-blind, Parallel-group Study to Investigate the Efficacy, Safety, and Tolerability of Cariprazine in Patients with Predominant Negative Symptoms of Schizophrenia (Cariprazine 3-6 mg/day; Risperidone 3-6 mg/day)	—	230	Risperidone 230

*=In Study RGH-MD-11, 416 patients were randomized newly to cariprazine, who were either newly enrolled (235) or received placebo or active comparator in the lead-in study. For the total of patients receiving cariprazine 416 patients were counted (Appendix 120-SUR, Table 1.1.5)

Exposure in Schizophrenia

A total of 2728 patients were treated with cariprazine in the schizophrenia Phase 2/3 studies, of which 1317 patients were treated with cariprazine in 6-week controlled studies, 679 patients were treated with cariprazine in 48-week, long-term, open-label studies (of which 416 patients newly received cariprazine – 235 patients were newly enrolled, and 181 received placebo or active comparator in the lead-in study), 765 patients were treated with cariprazine in Study RGH-MD-06, and finally 230 patients were treated with cariprazine in Study RGH-188-005.
Table below lists the overall exposure to the drug in the schizophrenia program by treatment time.

Table SIII.1: Duration of exposure in All Schizophrenia Studies (All Groups/studies)—Safety Population

Exposure	*All patients in schizophrenia phase 2/3 trials (N = 2991[a])*	*Group 1A*	*Group 1B*	*RGH-MD-06*	*RGH-188-005*
		Cariprazine (N = 1317)	**Cariprazine (N = 679)**	**Cariprazine (N = 765)**	**Cariprazine (N = 230)**
Treatment duration, n (%)[b]					
≥ 1 day	2991 (100.0)	1317	679	765	230
≥ 3 weeks	2421 (80.9)	994	592	615	214
≥ 6 weeks	1874 (62.7)	676	511	474	211
≥ 12 weeks	969 (32.4)	—	449	329	184[d]
≥ 24 weeks	614 (20.5)	—	346	90	178[d]
≥ 48 weeks	268 (9.0)	—	211	57	—
Patient-years exposure[c]	**795.4**	**117.9**	**350.3**	**158.6**	**97.6**

a) Roll-over patients from short term studies into long-term safety extensions are counted only once in the total
b) Treatment duration for cariprazine-treated patients was calculated as the number of days from the date of first dose of cariprazine taken to the date of last dose of cariprazine taken (inclusive of the gap in dosing between lead-in and extension studies for patients who took cariprazine in both).
c) Patient-years = (total treatment duration in days)/365.25.
d) ≥ 14 weeks and ≥ 26 weeks for RGH-188-005

Source: Module 2.7.4 Table 1.2.1-1

Table SIII.2: Age group and gender

	Group 1A (1317)*	Group 1B (679) **	RGH-MD-06 (765)***	RGH-188-005(230)****	Overall
Age					
< 55 years	1232	623	723	207	2785
⩾ 55 years	85	56	42	23	206
Gender					
male	945	471	544	124	2084
female	372	208	221	106	907

Source:*2.7.4 Table 1.3.1.2-1; **NDA-R-VI Tbale 3-1-2;***Study report MD 06 Table 11.2.1-1;**** M 2.7.4.Table 1.3.4.2-1

Table SIII.3: Dose (Modal daily dose)

	Persons			
Dose of exposure modal daily dose	***Group 1A(1317)****	***Group 1B(679)****	***RGD-MD-06(765) *****	***RGH-188-005********
1.5 -3mg	539	170	4	0
3.0 mg			99	6
4.5 mg	575	361	18	209
6.0 mg			236	6
9 mg	203	148	408	0
12 mg			0	0
total	1317	679	765	221

Source:*M 2.7.4Table 1.2.1.1-4; ** NDA-R: Table 5.1.3; ***Study report MD-06 Table 14.3.1.2B, Table 14.1.3c; **** Study report MD-005 Table 12.1

Table SIII.4: Ethnic origin

Race	Persons
Group 1A*	1317
White	574
All Other Races	709
Black/African American	440
Asian	232
Other	37
Missing[a]	34
Group 1B**	679
White	302
All Other Races	362
Black/African American	240

Asian	98
Other	24
Missing[a]	15
Group 06 total (double-blind phase)* **	765
White	299
All Other Races	466
Black/African American	313
Asian	149
Other	4
Missing[a]	0
Group 005	230
White	221
All Other Races	0
Black/African American	0
Asian	0
Other	0
Missing[b]	9

a Race data are missing for patients enrolled at RGH-MD-04 study centers in Romania per local regulations
b Race data were not collected for patients enrolled at study centers in France, per local regulations.
Source:*2.7.4 Table 1.3.1.2-1; **NDA-R-VI Tbale 3-1-2;***Study report MD 06 Table 11.2.1-1;**** M 2.7.4.Table 1.3.4.2-1

Part II: Module SIV - Populations not studied in clinical trials

SIV.1Exclusion criteria in pivotal clinical studies within the development programme

History of intolerance or hypersensitivity to other drugs of the same class as cariprazine or to rescue medications, or any history of severe drug allergy or hypersensitivity
Reason for exclusion: to avoid hypersensitivity reactions.
Is it considered to be included as missing information?: No.
Rationale: The expected effect should be avoided. Hypersensitivity to the active substance or to any of the excipients became a contraindication.

Pregnant, breast-feeding, and/or planning to become pregnant and/or breast-feed during the study, not using reliable method of contraception
Reason for exclusion: Animal studies have shown reproductive toxicity.
Is it considered to be included as missing information?: Initially "lactation" was classified as missing information, since no data is available for human. In rat cariprazine was excreted to breast milk, therefore breastfeeding is not recommended. Since no additional PV action is planned to investigate the effect in human, this missing information is recommended to be deleted based on the principles of GVP Module V Rev 2. See Part II SVII.
Rationale: See above.

SIV.2Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme has some limitations.
More than 6000 patients received at least 1.5 mg/day for at least 6 weeks. ADRs with a frequency greater than 1 in 2000 could be detected if there were no background incidence.
Prolonged exposure was investigated only in schizophrenia studies. In completed studies, more than 600 subjects were exposed to treatment lasting more than 24 weeks with at least 1.5 mg/day dose and more than 250 subjects were exposed for 48 weeks.
No cumulative effect is expected. The most frequent treatment emergent adverse events (TEAEs), such as akathisia were analysed regarding the cumulative effect of the drug. For the first occurrence of akathisia and EPS decreased after 2-3 weeks of cariprazine treatment in the 6-week controlled schizophrenia trials. In long-term, open-label schizophrenia studies, most akathisia and extrapyramidal symptoms (EPS) were reported for the first time within the first 6 weeks of treatment, and the number of new cases decreases dramatically thereafter.
Tardive dyskinesia is a late-onset form of EPS, can occur usually from 3 months to years after treatment.[17] The incidence of this adverse reaction has been defined based on the data of the clinical trials and found to be similar with the other members of the class.

SIV.3Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Pregnant women	Not included in the clinical development program.
Breastfeeding women	
Use in patients > 65 years	50 patients.
Patients with relevant comorbidities: • Patients with hepatic impairment	16 patients. Patients with liver enzyme tests >2x the upper limit were excluded in Phase 2/3 clinical trials. RGH PK 04, an open-label, parallel-group study, was designed to assess the pharmacokinetics of cariprazine and its desmethyl and didesmethyl metabolites in healthy subjects and patients with hepatic impairment after a single dose (Part A) and multiple doses (Part B) of cariprazine. In Part A, 24 subjects (8 patients with mild hepatic impairment, 8 patients with moderate hepatic impairment, and 8 healthy subjects) were enrolled and received a single oral dose of 1.0 mg cariprazine under fed conditions. In Part B, 24 subjects (8 patients with mild hepatic impairment, 8 patients with moderate hepatic impairment, and 8 healthy subjects) were enrolled and received a daily oral dose of 0.5 mg cariprazine for 14 days under fed conditions.
Patients with relevant comorbidities: • Patients with renal impairment	The population PK analysis included data from 2844 patients with renal impairment. Among these patients, 520 (18%) had mild renal impairment, 24 (1%) had moderate renal impairment, and 2300 (81%) had normal renal function.
Patients with relevant comorbidities: • Patients with cardiovascular impairment	Patient with cardiac impairment were excluded
Patients with relevant comorbidities: • Immunocompromised patients	Not included in the clinical development program
Patients with relevant comorbidities: • Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin	See Table S III.4.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Other	Not included in the clinical development program.

Part II: Module SV - Post-authorisation experience

Cariprazine was first approved in the United States (US) on 17 September 2015. Gedeon Richter's partner, Allergan Sales, LLC. [an AbbVie company] holds the marketing authorisation for cariprazine in the US.
Gedeon Richter Plc.'s products containing cariprazine as an active ingredient were first approved in the EU under the centralised procedure EMEA/H/C/002770. The end date of the procedure was 13 July 2017. In Western Europe, Recordati S.p.a acts as distributor. In the Swiss Confederation from 01 July 2018 Recordati AG is the Marketing Authorisation Holder. Since 2017 the product has been authorised in several other countries in non-EEA territory by Gedeon Richter and Partner companies of Gedeon Richter.

For the presentation of post-authorisation exposure a Data Lock Point of 05 October 2022 was used.

Cariprazine is currently marketed worldwide by Gedeon Richter Plc. and Gedeon Richter's Partner companies in 63 countries.

Data presented in the following sections cover all cariprazine containing products that are already authorised and/or marketed with the following strengths and formulations:

- 1,5 mg capsules, hard
- 3 mg capsules, hard
- 4.5mg capsules, hard
- 6 mg capsules, hard

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

Worldwide cariprazine exposure is estimated from sales data based on own Intercontinental Medical Statistics (IMS) data, IMS sales data from the Company's European partner Recordati S.p.a., and IMS sales data from the Company's US partner Allergan Sales LLC (an AbbVie company).

Patient-treatment-days are calculated from IMS National Prescription Audit (NPA) Weekly or Monthly Extended Unit Total Dispensed Prescriptions (EUTRx) data for cariprazine and are based on the defined daily dose of cariprazine (3 mg).

It is to be noted that calculated patient-treatment-days may overestimate actual patient treatment days since some of the drug may not have reached patients yet, and some of the drug that reached patients, may not have been taken for various reasons.

The post-authorisation exposure data is grouped in this section based on the source of the data:

- Patient exposure in territories where Gedeon Richter or partner Companies of Glosarij doo Podgorica, Dexcel Ltd., Hikma Pharmaceutical LLC or Mitsubishi Tanabe Pharma Corporation is the marketing authorisation holder is presented in Table SV.2.1
- Patient exposure in territories where partner company Recordati S.p.a. is the marketing authorisation holder or distributor is presented in Table SV.2.2
- Patient exposure in the US where partner Company Allergan Sales LLC (an AbbVie company) is the Marketing Authorization Holder is presented in Table SV.2.3

Total cumulative patient exposures for all territories are calculated as about **230 988 139** patient treatment-days meaning **632 844** patient treatment-years.

SV.1.2 Exposure

The following table shows the cumulative patient exposure according to the different regions:

Table SV.2: Exposure table by region

Table SV.2.1. **Post-Marketing Cumulative Patient Exposure to Cariprazine in Eastern Europe and non-EEA countries by Gedeon Richter and its partner companies**

	No. of Capsules Dispensed					Exposure (Patient-Treatment-Days)[a]
	1.5 mg of Cariprazine[f]	3.0 mg of Cariprazine[f]	4.5 mg of Cariprazine[f]	6.0 mg of Cariprazine[f]	Amount of Cariprazine (mg)	
EEA[b]	**2 880 396**	**3 297 366**	**1 588 095**	**1 320 736**	**29 283 537**	**9 761 179**
[redacted]						
EAEU[c]	**877 632**	**901 040**	**326 760**	**326 536**	**7 449 204**	**2 483 068**
[redacted]						
ROW[d]	**1 013 994**	**754 831**	**336 369**	**293 899**	**7 062 539**	**2 354 180**
Total[e]	**4 772 022**	**4 953 237**	**2 251 224**	**1 941 172**	**43 795 280**	**14 598 427**

Key: EEA = European Economic Area, EAEU = Eurasian Economic Union, ROW = Rest of the world, No. = Number.

[a]The exposure (amount of cariprazine and patient-treatment-days) of EEA, EAEU and ROW countries does not add up to the exact sum of total exposure, as the values are rounded to the nearest whole number.

[b]Countries under the European Economic Area.

[c] Countries under the Eurasian Economic Union.

[d] Countries outside of the European Economic Area and the Eurasian Economic Union.

[d]Total = EEA + EAEU + ROW.

[e] Source = GR., Dexcel Ltd., Glosarij doo Podgorica, Hikma Pharmaceutical LLC, Mitsubishi Tanabe Pharma Corporation and Seqirus Pty Ltd

Note: Includes data with cut-off date 30 September 2022.

Table SV.2:2 Post-Marketing Cumulative Patient Exposure to Cariprazine in EEA and non-EEA (Western Europe) by partner company Recordati S.p.a

Countries	No. of Capsules Dispensed					Exposure (Patient-Treatment-Days)[a]
	1.5 mg of Cariprazine[e]	3.0 mg of Cariprazine[e]	4.5 mg of Cariprazine[e]	6.0 mg of Cariprazine[e]	Amount of Cariprazine (mg)	
EEA[b]	**11 346 944**	**8 389 839**	**3 401 535**	**2 913 714**	**74 979 125**	**24 993 042**
[redacted]						
Non-EEA[c]	**637 280**	**499 492**	**233 408**	**170 212**	**4 526 004**	**1 508 668**
[redacted]						
Total[d]	**11 984 224**	**8 889 331**	**3 634 943**	**3 083 926**	**79 505 129**	**26 501 710**

Key: EEA = European Economic Area, No. = Number. IMS = Intercontinental Medical Statistics, EUTRx = Extended Unit Total Dispensed Prescriptions.

[a]The exposure (amount of cariprazine and patient-treatment-days) of EEA and Non-EEA countries does not add up to the exact sum of total exposure, as the values are rounded to the nearest whole number.

[b]Countries under the European Economic Area.

[c]Countries outside the European Economic Area.

[d]Total = EEA + Non-EEA.

[e] Source = IMS NPA monthly EUTRx metric, Recordati S.p.a.

Note: Includes data with cut-off date 30 September 2022.

Table SV.2.3. Exposure in the US territory

Doses	Capsules Dispensed[a]	Amount of Cariprazine (mg)	Exposure (Patient-Treatment-Days)
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Key: EUTRx = Extended Unit Total Dispensed Prescriptions, IMS = Intercontinental Medical Statistics, NPA = National Prescription Audit, US = United States.

[a]*Source = Quintiles IMS NPA Weekly EUTRx metric.*

[b]*Patient-years calculation uses the defined daily dose of cariprazine (3 mg).*

[c]*Titration pack.*

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Cariprazine did not demonstrate abuse potential in animal models of cocaine addiction. The anti-abuse potential of cariprazine was investigated in rats, in cocaine self-administration paradigms in comparison with aripiprazole. Cariprazine and aripiprazole were able to reduce the rewarding effect of cocaine (minimum effective doses were 0.17 and 1.0 mg/kg, respectively) in the continuous self-administration regimen (Module 4.2.1.2 Study RGD 74326/E). Cariprazine, similar to aripiprazole, dose dependently attenuated relapse to cocaine-seeking with median effective oral dose of 0.2 and 4.0 mg/kg (Module 4.2.1.2 Study RGD 71976). The potency of cariprazine in these paradigms was approximately 6 to 20-fold greater than that of aripiprazole. So overall misuse for illegal purposes is not expected.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

'Interaction with CYP3A4 inhibitors and inducers' previously classified as an important potential risk is removed from the list of safety concerns based on the Guideline on good pharmacovigilance practices (GVP) Module V (EMA/838713/2011 Rev 2), since all additional pharmacovigilance activities (Study RGH-188-301 and RGH-188-302) has been finalized and no further pharmacovigilance activity is needed to characterize the risk.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Safety Concern #1-Important identified risk- Extrapyramidal symptoms including tardive dyskinesia

Potential mechanisms

Antagonism of the dopamine D_2 receptor is believed to mediate both AP activity and the occurrence of EPS. Positron emission tomography studies have revealed that approximately 60–70% of D_2 blockade is needed for FGAs to be efficacious; however, more than 75–80% D_2 blockade results in acute EPS.[17]

Evidence source(s) and strength of evidence

Medical literature/Database

Characterisation of the risk

Most events of akathisia and EPS were mild or moderate in severity in short-term controlled schizophrenia studies. By severity, altogether 12 patients (0.44%) in the cariprazine group had severe EPS-related TEAEs from schizophrenia safety studies.

The proportions of patients who had akathisia that was severe or led to discontinuation are consistent with what has been reported in the literature for aripiprazole (< 10% and 0.3%, respectively, in short-term schizophrenia trials).[18] Although akathisia and EPS were among the most common AEs observed, study discontinuation for these AEs was low.

In accordance with the protocols, the investigators used propranolol and antiparkinson medications (e.g. benztropine and trihexyphenidyl) to manage symptoms of akathisia and EPS. The use of medication for akathisia and EPS appeared to correlate generally with the severity of the reported AEs.

For the first occurrence of akathisia and EPS decreased after 2-3 weeks of cariprazine treatment in the 6-week controlled schizophrenia trials. In long-term, open-label schizophrenia studies, most akathisia and EPS events were reported for the first time within the first 6 weeks of treatment, and the number of new cases decreases dramatically thereafter.

To address the potential for severe outcomes associated with the presence of akathisia, the clinical data was examined for suicidality in patients with akathisia. A relationship between akathisia and suicidal tendency was not observed in the cariprazine clinical program. There was no suicidal behaviour reported among patients who had akathisia or restlessness in the controlled schizophrenia studies.

Tardive dyskinesia is a special form of EPS which is a potentially irreversible type of dyskinesia that develops later in therapy (after 3 month or years) and persists even if therapy is stopped. Altogether 4 patients experienced tardive dyskinesia, none of them were severe.

Risk factors and risk groups

Akathisia: Patient risk factors for akathisia have not been well established, but increasing age, female sex, negative symptoms, cognitive dysfunction, iron deficiency, prior akathisia, concomitant Parkinsonism, and mood disorders may entail greater risk.[19]

The risk of drug-induced Parkinsonism has been associated with increasing age, female gender, dementia, HIV infection, and pre-existing extrapyramidal disease or family history of Parkinson's disease[19].

Patient risk factors for dystonia include age, male sex, race, previous dystonic reactions, and family history of dystonia, cocaine use, mood disorders, hypocalcaemia, hypoparathyroidism, hyperthyroidism and dehydration. Children and young adults are highly vulnerable, whereas drug-induced dystonia is rare over 45 years of age.[19]
Previous studies of TD risk have suggested an association with increasing age, female gender, psychiatric diagnosis, longer duration of antipsychotic treatment, higher cumulative drug doses, concomitant drug treatments, higher ratings of negative symptoms and thought disorder, greater cognitive impairments, presence of acute EPS, and diabetes.[19]

Preventability
To prevent EPS it is recommended to use conservative doses opting for lower potency agents, inform patients and caregivers of risk, assess on a regular basis for incipient signs, consider differential diagnosis and reconsider drug treatment if symptoms emerge. In high-risk patients prophylactic anticholinergic medications can be considered.[19]

Impact on the risk-benefit balance of the product
EPS are serious, sometimes debilitating and stigmatizing adverse effects, and require additional pharmacotherapy. EPS develop into two phases. Early, acute EPS most often develop up on the beginning of treatment with antipsychotics or when the dose is increased. The later-onset EPS usually occur after prolonged treatment and present as TD. Acute EPS are one of the main causes of poor adherence to antipsychotic treatment due to the reversibility of symptoms, while late-onset TD has the most serious impact on patients and caregivers with respect to quality of life. [20]

Public health impact
The occurrence of EPS generally does not induce hospitalisation.

Safety Concern #2 -Important identified risk- Weight gain

Potential mechanisms
Lifestyle factors such as increased food intake, high calorific content of meals, and lack of exercise have been implicated. Stimulation of 5-HT_{1a} is associated with increase in food intake and maybe partly responsible. Multiple other receptors in the brain including H_1, 5-HT_{2c}, 5-HT_6 and muscarinic anticholinergic receptors can have a role in developing weight gain. Other receptor mechanisms may have additive or synergistic effects; dopamine D_2 receptor antagonism can enhance 5-HT_{2C}-mediated effects on food intake. Elevated leptin secretion in the absence of a decrease in food intake indicates drug-induced leptin insensitivity in the hypothalamus.[21]

Evidence source(s) and strength of evidence
Medical literature/Database

Characterisation of the risk
The increased rates of both overweight and obesity reported in mentally-ill patients are prevalently due to the use of second-generation antipsychotics.[22] The magnitude of weight gain can be associated with the antipsychotic used for the management. Little weight gain has been reported with aripiprazole and ziprasidone followed by risperidone and quetiapine. Clozapine and olanzapine are associated with the greatest increase in weight.[23]

Most events related to weight increased were mild to moderate in severity. Of the TEAEs of weight increased 2 were severe in intensity. No serious adverse event related to weight increased were reported from schizophrenia studies.
In the short-term studies, there were slightly greater mean increases in body weight in the cariprazine group compared to the placebo group; 1 kg and 0.3 kg, respectively. In the long-term maintenance of effect study, there was no clinically relevant difference in change of body weight from baseline to end of treatment (1.1 kg for cariprazine and 0.9 kg for placebo). In the open-label phase of the study during 20 weeks cariprazine treatment 9.0% of patients developed potentially clinically significant (PCS) weight gain (defined as increase ≥ 7%) while during the double-blind phase, 9.8 % of the patients who continued with cariprazine treatment had PCS weight gain versus 7.1% of the patients who were randomized to placebo after the 20 week open-label cariprazine treatment. In the negative symptom study, the mean change of body weight was -0.3 kg for cariprazine and +0.6 kg for risperidone and PCS weight gain was observed in 6% of the cariprazine group while 7.4% of the risperidone group.[24]

Risk factors and risk groups
General risk for weight gain include a calorific diet and low physical activity. Risk of antipsychotic induced weight gain is associated with lower body weight (low/normal body mass index) at the beginning of antipsychotic treatment and the diagnosis of undifferentiated schizophrenia.[22,25] A systematic appraisal of the literature concluded that young non-overweight women with an acute psychotic episode were particularly high risk of antipsychotic-induced weight gain.[23]

Preventability
Changes of weight should be monitored as part of a standard of clinical care. Patients should also have their weight monitored.

Impact on the risk-benefit balance of the product
Significant weight gain is usually the most distressing issue among patients. Weight gain associated with antipsychotic treatment may compromise a patient's health by contributing to comorbid conditions such as hypertension and coronary artery disease.

Public health impact
For people with psychiatric illness, obesity (weight gain) is an additional health burden with problematic sequelae, adversely affecting compliance, quality of life and cardiovascular morbidity and mortality.[26] More than two third of patients with schizophrenia compared with approximately one half of the general population die in coronary heart disease.[27]

Safety Concern #3 -Important potential risk- Neuroleptic Malignant Syndrome

Potential mechanisms
The most widely accepted mechanism by which antipsychotics cause neuroleptic malignant syndrome is that of dopamine D_2 receptor antagonism. In this model, central D_2 receptor blockade in the hypothalamus, nigrostriatal pathways, and spinal cord leads to increased muscle rigidity and tremor via extrapyramidal pathways.
Hypothalamic D_2 receptor blockade results in an elevated temperature set point and impairment of heat-dissipating mechanisms (e.g. cutaneous vasodilation, sweating), while nigrostriatal blockade results in muscular rigidity. Peripherally, antipsychotics lead to increased calcium release from the sarcoplasmic reticulum, resulting in increased contractility, which can contribute to hyperthermia, rigidity, and muscle cell breakdown.[28]

Evidence source(s) and strength of evidence
Medical literature/Database.

Characterisation of the risk
Neuroleptic Malignant Syndrome (NMS) represents an extremely rare but potentially lethal form of EPS combining features of advanced Parkinsonism and catatonia. Classic signs are elevated temperatures from moderate to life-threatening hyperthermia, generalized rigidity with tremors, altered consciousness with catatonia, and autonomic instability. In extreme form, NMS presents as a hypermetabolic crisis with muscle enzyme elevations (creatine phosphokinase, median elevations 800 IU/L), myoglobinuria, leukocytosis, metabolic acidosis, hypoxia, elevated serum catecholamines, and low serum iron levels.[18] The incidence of NMS is about 0.02% among patients treated with antipsychotic drugs.[18]
Only one related TEAE of NMS was reported in schizophrenia safety studies. The incidence of NMS was 0.05% based on schizophrenia safety studies in the therapeutic dose-range. This TEAE was non-serious and the outcome was resolved.

Risk factors and risk groups
Potential risk factors have been investigated in small case control studies, and include dehydration, exhaustion, agitation, catatonia, previous episodes, and high doses of high-potency drugs given parenterally at a rapid rate[18].

Preventability
The lowest effective dose should be used. Monitoring early signs (rigidity, hyperthermia, and changes of consciousness).

Impact on the risk-benefit balance of the product
NMS is potentially life-threatening. After recovery there is no impact on quality of life.

Public health impact
NMS is rare, often self-limited after drug discontinuation, but potentially fatal due to renal failure, sudden cardiorespiratory arrest, disseminated intravascular coagulation, pulmonary emboli, or aspiration pneumonia.

Safety Concern #4-Important potential risk-Ocular changes (lenticular changes and cataracts)

Potential mechanisms
Lens opacities associated with psychotropic drugs are an accumulation of pigment usually located in the anterior subcapsular layers. Changes in the anterior surface of the lens and the posterior cornea imply alterations in aqueous humour. The lens and cornea are avascular and dependent upon diffusion for oxygen and nutrition. Photosensitizing agents like chlorpromazine and its metabolites denature proteins, which become opacified when exposed to sunlight and are deposited in the lens, cornea, and skin. Melanin is also considered a probable cause of lens discoloration because it traps free radicals produced by e.g. chlorpromazine. Melanin and chlorpromazine have a strong bonding affinity. When chlorpromazine interacts with ultraviolet-B light, it produces purple or bluish coloured free-radical metabolites. This phototoxic reaction creates the cataract cellular changes.[30]

In the case of cariprazine the suspected pathomechanism is the decreased level of serum cholesterol, based on preclinical finding, however it seems to have no clinical relevance.

Evidence source(s) and strength of evidence
Medical literature/Database.

Characterisation of the risk
Global prevalence of cataract in European adults over 50 years of age was estimated at 47.8%. Crude prevalence of cataract in European adults in 2007 was 19.3%. The prevalence of cataract in Europe increased with age from 5% for the 52–62 and 30% for 60–69 years of age to 64% for the population over 70 years.[29] People with schizophrenia are documented to be at a higher risk for ocular pathologies, since they often have many contributory factors, such as smoking, poor health, and concomitant illnesses or pharmaceutical exposures.[30] In a cohort study the incidence rate of a clinical diagnosis of cataract in patients with a psychotic disorder, schizophrenia (n=4209) was established and compared with the rate in the general population (n=10 000). The incidence of cataracts was 4.5 per 1,000 person-years among the general population and 3.5 in the schizophrenia population. Overall, antipsychotic drug use was not associated with the occurrence of cataracts. Nevertheless, among long-term users of chlorpromazine at daily doses of 300 mg or greater, and among users of prochlorperazine, the relative risks were 8.8 (95% confidence interval 5 3.1–25.1) and 4.0 (95% confidence interval 5 0.8 –20.7), respectively.[31] As observed with quetiapine, a species-specific nonclinical finding does not necessarily correlate with clinical risk in humans. Although preclinical investigations of quetiapine identified a risk of cataract in dogs, a randomized, long-term clinical trial showed no cataractogenic potential relative to risperidone.[32]
Development of cataracts was observed in cariprazine non clinical studies. Therefore, cataract formation was closely monitored with slit lamp examinations in the clinical studies and patients with existing cataracts were excluded. During the schizophrenia clinical development program of cariprazine, few cataract cases were reported, characterized with minor lens opacities with no visual impairment (13/3192; 0.4%). Some of these patients had confounding factors. The most commonly reported ocular adverse event was blurred vision (placebo: 1/683; 0.1%, cariprazine: 22/2048; 1.1%).[24]

Risk factors and risk groups
Age is the most common cause. Lens proteins denature and degrade over time, and this process is accelerated by diseases such as diabetes mellitus and hypertension. Environmental factors, including toxins, radiation, and ultraviolet light, have cumulative effects, which are worsened by the loss of protective and restorative mechanisms due to alterations in gene expression and chemical processes within the eye. Risk factors for the development of cataract include poor general health, smoking, alcoholism, a high-fat diet and comorbidities such as diabetes and hypertension which are common in patients with schizophrenia.[32]

Preventability
Avoiding the risk factors such as smoking, high fat diet and treating the co-morbidities.

Impact on the risk-benefit balance of the product
Cataract manifests as impairment of vision which has a negative subjective impact on quality of life.

Public health impact

Cataract is responsible for 51% of world blindness, which represents about 20 million people (2010). Although cataracts can be surgically removed, in many countries' barriers exist that prevent patients to access surgery. Cataract remains the leading cause of blindness. As people in the world live longer, the number of people with cataract is anticipated to grow. Cataract is also an important cause of low vision in both developed and developing countries. [33]

Safety Concern #5-Important potential risk- Suicidal ideation and behaviour

Potential mechanisms
In the background of the mechanism is the disease itself.

Evidence source(s) and strength of evidence
Medical literature/Database.

Characterisation of the risk
Schizophrenia is a major cause of suicide and APs are mainly used to control the disease and prevent suicide.[34] When compared to the general population, patients with the disease have 8.5-fold greater risk of suicide.[35] It is estimated that approximately 40 percent of patients diagnosed with schizophrenia will attempt suicide, with 10 percent of patients succeeding.[36]
The cariprazine development program laid special focus on the monitoring of suicidality and suicidal behaviour. Initially this was done by assessing AE data only, followed by the administration of the Suicidality Tracking Scale (study RGH-MD-17 only) and finally from 2009 onwards by the administration of the Columbia–Suicide Severity Rating Scale.
The following table shows the TEAEs of the suicidality category of cariprazine in schizophrenia studies in the therapeutic dose-range.

	Cariprazine Overall (N = 2048) n (%)
Suicidality related TEAEs	**18(0.88)**
Completed suicide	2(0.1)
Suicide attempt	1(0.05)
Suicidal ideation	13(0.63)
Intentional overdose	1(0.05)
Intentional self-injury	1(0.05)

The incidence of suicidality related TEAEs was 0.88% in schizophrenia safety studies in the therapeutic dose-range. From the 18 TEAEs, 5 cases were related to cariprazine based on Investigator assessment. Events of completed suicide were assessed as not related to cariprazine by the Investigator.
From this 18 TEAEs 8 were serious event. Outcome of completed suicide were death in both cases. All other patients experiencing suicidality related TEAEs recovered.

Risk factors and risk groups
Risk factors with a strong association with later suicide included being young, male, and with a high level of education. Illness-related risk factors were important predictors, with number of prior suicide attempts, depressive symptoms, active hallucinations and delusions, and the presence of insight all having a strong evidential basis. A family history of suicide, and comorbid substance

misuse were also positively associated with later suicide. The only consistent protective factor for suicide was delivery of and adherence to effective treatment.[37]

Preventability
Close observation at the beginning of therapy, especially the high-risk patients.

Impact on the risk-benefit balance of the product
Suicidality has a substantial impact not only for the patient's quality of life but also for the family.

Public health impact
The risk is not considered to have a public health impact. It has a relevant impact on the schizophrenic population.

Safety Concern #6-Important potential risk-Developmental and reproductive toxicity

Potential mechanisms
Not known.

Evidence source(s) and strength of evidence
Own study/Database.

Characterisation of the risk
The human risk cannot be established.
Administration of cariprazine to rats during the period of organogenesis caused malformations at maternally toxic doses, 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 neither teratogenic nor foetotoxic in rabbits at doses up to 5.8 times the MRHD of 6 mg/day.
Administration of cariprazine to pregnant rats during the period of organogenesis, throughout pregnancy and lactation at oral doses up to 1 mg/kg/day (0.4 times the MRHD of 6 mg/day based on AUC) decreased postnatal survival, birth weight, and post-weaning body weight of first generation pups. In addition, pale, cold bodies and developmental delays (renal papillae not developed/underdeveloped and decreased auditory startle response in males) were observed in the absence of significant maternal toxicity at this dose. Reproductive performance of the first generation pups was unaffected; however, second generation pups also had similar clinical signs and lower body weight.
In rat studies lower female fertility and conception indices were observed, no effects on male fertility were noted at any dose.
In the human safety database no sign of reproductive toxicity was detected.
A total of 22 pregnancies were reported during the cariprazine schizophrenia clinical development program; 15 of these occurred in cariprazine-treated patients. From 15 cases of pregnancy during cariprazine use 5 cases reported healthy delivery, 6 elective abortion, 2 spontaneous abortion and the outcome of 2 cases is unknown.

Risk factors and risk groups
Women of childbearing potential.

Preventability

Women of childbearing potential must be advised to avoid pregnancy while on Reagila. Female patients of child-bearing potential must use highly effective contraceptive methods during treatment and for at least 10 weeks following the last dose of Reagila.

Impact on the risk-benefit balance of the product

The quality of life of an individual who has a baby born with any birth defect cannot be assessed; the burden depends on the congenital anomaly and the attitude of the environment (mother, family).

Public health impact

If the product is used in line with the Product information (applying reliable contraception in women of childbearing potential) no relevant public health concern is suspected.

SVII.3.2. Presentation of the missing information

Safety Concern #7-Missing information-Use in patients >65 years

Elderly patients are a vulnerable population and sometimes need careful treatment. Elderly patients with dementia often need to be treated with antipsychotics, however it is well known that in this case the mortality increases as well as cerebrovascular morbidity. In the cariprazine development program insufficient number of patients older than 65 years were treated, therefor no data is available how this population behaves when cariprazine is administered. Follow-up of adverse events is needed to further characterise this patient population.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	#1. Extrapyramidal symptoms including tardive dyskinesia
	#2. Weight gain
Important potential risks	#3. Neuroleptic Malignant Syndrome
	#4. Ocular changes (Lenticular changes and cataracts)
	#5. Suicidal ideation and behaviour
	#6. Developmental and reproductive toxicity
Missing information	#7. Use in patients > 65 years

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for

- safety concern #4 "Ocular changes (Lenticular changes and cataracts)" and
- safety concern #7 "Use in patients >65 years"

These specific questionnaires are used for the collection of relevant data and proper medical assessment of spontaneously reported individual case safety reports (ICSRs) related to ocular changes and in connection with cariprazine use in patients above 65 years.

Other forms of routine pharmacovigilance activities:

- Half yearly trend analysis for safety concern #4 "Ocular changes (Lenticular changes and cataracts)"

This trend-analysis is proposed to show any unusual patterns or accumulations of cataracts that occurred and any public health concerns if they emerged.
For the overall safety analysis, all those ICSR are used, which are recorded in the MAH's validated electronic safety database regarding the concerned period.
For the identification of cataract event, Lens disorders SMQ [20000155] is used.

During the trend analysis the following risk factors are also assessed in connection with the event and also cariprazine:

- age over 50 years
- cataract in family history
- diabetes mellitus
- smoking
- alcohol
- previous eye injury or trauma
- previous eye inflammation
- previous eye surgery

III.2 Additional pharmacovigilance activities

Not applicable, since no additional pharmacovigilance studies/activities are conducted or planned.

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Not applicable, since no additional pharmacovigilance studies/activities are conducted or planned.

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
#1. Extrapyramidal symptoms including tardive dyskinesia *(Important identified risk)*	Routine risk communication: Akathisia, parkinsonism, dystonia, other extrapyramidal diseases and abnormal movement disorders, dyskinesia, tardive dyskinesia and drug withdrawal syndrome neonatal are included in section 4.8. of the Summary of Product Characteristics (SmPC) and in section 2 and 4 of the PL(package leaflet). Routine risk minimisation activities recommending specific clinical measures to address the risk: The following warnings are stated in section 4.4: Slow up and down-titration of cariprazine in the first phase of treatment is needed because of akathisia. Dose modification is also needed depending on individual response. Discontinuation should be considered in case of tardive dyskinesia. Recommendation in section 4.6 regarding neonates exposed to antipsychotics experiencing extrapyramidal or withdrawal symptoms. Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to medical prescription.
#2. Weight gain *(Important identified risk)*	Routine risk communication: Weight increased is included in section 4.8 of the SmPC and in section 2 and 4 of the PL. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for monitoring weight is stated in section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to medical prescription.
#3. Neuroleptic Malignant Syndrome *(Important potential risk)*	Routine risk communication: Neuroleptic malignant syndrome is included in section 4.8 of the SmPC and in section 2 and 4 of the PL. Routine risk minimisation activities recommending specific clinical measures to address the risk:

Safety concern	Routine risk minimisation activities
	Several warnings and precaution measures (including discontinuation in case of NMS) in section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to medical prescription.
#4. Ocular changes (Lenticular changes and cataracts) *(Important potential risk)*	Routine risk communication: Cataract is listed in section 4.8 of the SmPC and in section 2 and 4 of the PL. Routine risk minimisation activities recommending specific clinical measures to address the risk: Ophtalmologic examination and re-evaluation of treatment continuation are proposed in section 4.4 in case of development of symptoms related to cataract. Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to medical prescription.
#5. Suicidal ideation and behaviour *(Important potential risk)*	Routine risk communication: Suicidal behaviour is listed in section 4.8 of the SmPC and in section 2 and 4 of the PL. Routine risk minimisation activities recommending specific clinical measures to address the risk: The need for close supervision of high-risk patients is highlighted in section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to medical prescription.
#6. Developmental and reproductive toxicity *(Important potential risk)*	Routine risk communication: SmPC (section 4.6 and in section 5.3) and PL (section 2) lists adequate information on the possibility of developmental and reproductive toxicity. Routine risk minimisation activities recommending specific clinical measures to address the risk: Warning in section 4.4, 4.5 and 4.6 regarding women of childbearing potential. It is suggested to use highly effective contraception. Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to medical prescription.
#7. Use in patients > 65 years	Routine risk communication:

Safety concern	Routine risk minimisation activities
(Missing information)	It is mentioned in section 4.4 of SmPC that cariprazine has not been studied in patients with dementia-related disturbances. Section 3 of PIL contains information regarding cariprazine use in elderly patients. Routine risk minimisation activities recommending specific clinical measures to address the risk: Cautious dose selection is suggested in section 4.2. Warning in section 4.4 regarding patients with dementia that there is an increased risk of mortality in patient using antipsychotic medicinal products. Other routine risk minimisation measures beyond the Product Information: Legal status: Medicinal product subject to medical prescription.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
#1. Extrapyramidal symptoms including tardive dyskinesia *(Important identified risk)*	Routine risk minimisation measures: SmPC sections 4.4; 4.6; 4.8 PL sections 2; 4. Medicinal product subject to medical prescription. Additional risk minimisation measures: No additional risk minimisation measures are proposed.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
#2. Weight gain *(Important identified risk)*	Routine risk minimisation measures: SmPC sections 4.4; 4.8. PL sections 2; 4. Medicinal product subject to medical prescription. Additional risk minimisation measures: No additional risk minimisation measures are proposed.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
#3. Neuroleptic Malignant Syndrome *(Important potential risk)*	Routine risk minimisation measures: SmPC sections 4.4; 4.8. PL sections 2; 4. Medicinal product subject to medical prescription. Additional risk minimisation measures: No additional risk minimisation measures are proposed.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
#4. Ocular changes (Lenticular changes and cataracts) *(Important potential risk)*	Routine risk minimisation measures: SmPC sections 4.4; 4.8. PL sections 2; 4. Medicinal product subject to medical prescription. Additional risk minimisation measures: No additional risk minimisation measures are proposed.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Specific adverse reaction follow-up questionnaire • Half yearly trend analysis Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
#5. Suicidal ideation and behaviour *(Important potential risk)*	Routine risk minimisation measures: SmPC sections 4.4; 4.8. PL sections 2; 4. Medicinal product subject to medical prescription. Additional risk minimisation measures: No additional risk minimisation measures are proposed.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
#6. Developmental and reproductive toxicity *(Important potential risk)*	Routine risk minimisation measures: SmPC sections 4.4; 4.5; 4.6; 5.3. PL section 2. Medicinal product subject to medical prescription. Additional risk minimisation measures: No additional risk minimisation measures are proposed.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
#7. Use in patients > 65 years *(Missing information)*	Routine risk minimisation measures: SmPC sections 4.2; 4.4. PL section 2. Medicinal product subject to medical prescription. Additional risk minimisation measures: No additional risk minimisation measures are proposed.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific adverse reaction follow-up questionnaire Additional pharmacovigilance activities: None

Part VI: Summary of the risk management plan

Summary of risk management plan for Reagila (cariprazine)

This is a summary of the risk management plan (RMP) for Reagila. The RMP details important risks of Reagila, how these risks can be minimised, and how more information will be obtained about Reagila's risks and uncertainties (missing information).
Reagila's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Reagila should be used.
This summary of the RMP for Reagila should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).
Important new concerns or changes to the current ones will be included in updates of Reagila's RMP.

I. The medicine and what it is used for

Reagila is indicated for the treatment of schizophrenia in adult patients.
It contains cariprazine as the active substance and it is given orally once a day.

Further information about the evaluation of Reagila's benefits can be found in Reagila's EPAR, including its plain-language summary, available on the EMA website, under the medicine's webpage (https://www.ema.europa.eu/en/medicines/human/EPAR/reagila).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Reagila, together with measures to minimise such risks and the proposed studies for learning more about Reagila's risks, are outlined below.
Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.
If important information that may affect the safe use of Reagila is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Reagila are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Reagila. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Summary of safety concerns	
Important identified risks	#1. Extrapyramidal symptoms including tardive dyskinesia
	#2. Weight gain
Important potential risks	#3. Neuroleptic Malignant Syndrome
	#4. Ocular changes (Lenticular changes and cataracts)
	#5. Suicidal ideation and behaviour
	#6. Developmental and reproductive toxicity
Missing information	#7. Use in patients > 65 years

II.B Summary of important risks

Safety Concern #1 - Important identified risk - Extrapyramidal symptoms including tardive dyskinesia	
Evidence for linking the risk to the medicine	Medical literature/Database
Risk factors and risk groups	Akathisia: Patient risk factors for akathisia have not been well established, but increasing age, female sex, negative symptoms, cognitive dysfunction, iron deficiency, prior akathisia, concomitant parkinsonism, and mood disorders may entail greater risk. The risk of drug-induced parkinsonism has been associated with increasing age, female gender, dementia, HIV infection, and pre-existing extrapyramidal disease or family history of Parkinson's disease. Patient risk factors for dystonia include age, male sex, race, previous dystonic reactions, family history of dystonia, cocaine use, mood disorders, hypocalcaemia, hypoparathyroidism, hyperthyroidism and dehydration. Children and young adults are highly vulnerable, whereas drug-induced dystonia is rare over 45 years of age.19

	Previous studies of TD risk have suggested an association with increasing age, female gender, psychiatric diagnosis, longer duration of antipsychotic treatment, higher cumulative drug doses, concomitant drug treatments, higher ratings of negative symptoms and thought disorder, greater cognitive impairments, presence of acute EPS, and diabetes.[19]
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4; 4.6; 4.8 PL sections 2; 4. Medicinal product subject to medical prescription. Additional risk minimisation measures: No additional risk minimisation measures are proposed.

Safety Concern #2 - Important identified risk - Weight gain	
Evidence for linking the risk to the medicine	Medical literature/Database
Risk factors and risk groups	General risk for weight gain include a calorific diet and low physical activity. Risk of antipsychotic induced weight gain is associated with lower body weight (low/normal body mass index) at the beginning of antipsychotic treatment and the diagnosis of undifferentiated schizophrenia.[22] A systematic appraisal of the literature concluded that young non-overweight women with an acute psychotic episode were particularly high risk of antipsychotic-induced weight gain.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4; 4.8. PL sections 2; 4. Medicinal product subject to medical prescription. Additional risk minimisation measures: No additional risk minimisation measures are proposed.

Safety Concern #3 - Important potential risk - Neuroleptic malignant syndrome	
Evidence for linking the risk to the medicine	Medical literature/Database
Risk factors and risk groups	Dehydration, exhaustion, agitation, catatonia, previous episodes, and high doses of high-potency drugs given parentally at a rapid rate.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4; 4.8. PL sections 2; 4. Medicinal product subject to medical prescription. Additional risk minimisation measures: No additional risk minimisation measures are proposed.

Safety Concern #4 - Important potential risk - Ocular changes (Lenticular changes and cataracts)	
Evidence for linking the risk to the medicine	Medical literature/Database
Risk factors and risk groups	Age is the most common cause. Lens proteins denature and degrade over time, and this process is accelerated by diseases such as diabetes mellitus and hypertension. Environmental factors, including toxins, radiation, and ultraviolet light, have cumulative effects, which are worsened by the loss of protective and restorative mechanisms due to alterations in gene expression and chemical processes within the eye. Risk factors for the development of cataract include poor general health, smoking, alcoholism, a high-fat diet and comorbidities such as diabetes and hypertension which are common in patients with schizophrenia
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4; 4.8. PL sections 2; 4. Medicinal product subject to medical prescription. Additional risk minimisation measures: No additional risk minimisation measures are proposed.

Safety Concern #5 - Important potential risk - Suicidal ideation and behaviour	
Evidence for linking the risk to the medicine	Medical literature/Database
Risk factors and risk groups	Risk factors with a strong association with later suicide included being young, male, and with a high level of education. Illness-related risk factors were important predictors, with number of prior suicide attempts, depressive symptoms, active hallucinations and delusions, and the presence of insight all having a strong evidential basis. A family history of suicide, and comorbid substance misuse were also positively associated with later suicide. The only consistent protective factor for suicide was delivery of and adherence to effective treatment.
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4; 4.8. PL sections 2; 4. Medicinal product subject to medical prescription. Additional risk minimisation measures: No additional risk minimisation measures are proposed.

Safety Concern #6 - Important potential risk - Developmental and reproductive toxicity-	
Evidence for linking the risk to the medicine	Database
Risk factors and risk groups	Women of childbearing potential

Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.4; 4.6; 4.5; 5.3. PL section 2. Medicinal product subject to medical prescription. Additional risk minimisation measures: No additional risk minimisation measures are proposed.

Safety Concern #7 - Missing information – Use in patients > 65 years	
Risk minimisation measures	Routine risk minimisation measures: SmPC sections 4.2; 4.4. PL section 2. Medicinal product subject to medical prescription. Additional risk minimisation measures: No additional risk minimisation measures are proposed.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Reagila.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Reagila.

Annex 4 - Specific adverse drug reaction follow-up forms

TARGETED FOLLOW UP FORM
for Cataract related events

Reporter Details:

Name:	**e-mail:**	☐ Medical doctor ☐ Pharmacist ☐ Nurse ☐ Other
Date of report *(dd/Mm/yyyy):*	**phone:**	
	Signature:	

Patient details:

Initials:	**Year of birth:**	**Ethnic origin:** ☐ Caucasian ☐ Asian ☐ Black ☐ Australian ☐ Other
Gender: ☐ **Male /** ☐ **Female**	**Age at time of the event:**	
Height: …….. cm	**Weight: ……… kg**	

Adverse reactions:

(Seriousness means that the event results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect, or is an important medical event)

(The following options can be selected for outcome: Fatal: Event resulted in death; Not recovered/Not resolved: Event is ongoing or worsened; Recovered/Resolved: Event is reported to have resolved, with no reported sequel; Recovered/resolved with sequel: Event is reported to have resolved, but the patient has sequel (e.g., paralysis following a stroke); Recovering/resolving: Event is reported to be improved or improving, but has not resolved entirely; Unknown: Reporter states that the outcome is not known)

Event	**Dates** *dd/Mm/yyyy*	**Outcome** (Please choose the appropriate one)	**Serious?**
	Onset date: ………………… **End date:** …………………	☐Recovered ☐Not recovered ☐Recovered with sequela ☐Recovering ☐Fatal ☐Unknown	☐Yes/☐No
	Onset date: ………………… **End date:** …………………	☐Recovered ☐Not recovered ☐Recovered with sequela ☐Recovering ☐Fatal ☐Unknown	☐Yes/☐No
	Onset date: ………………… **End date:** …………………	☐Recovered ☐Not recovered ☐Recovered with sequela ☐Recovering ☐Fatal ☐Unknown	☐Yes/☐No
	Onset date: ………………… **End date:** …………………	☐Recovered ☐Not recovered ☐Recovered with sequela ☐Recovering ☐Fatal ☐Unknown	☐Yes/☐No

Medications:

Brand name	Active substance(s)	Route and form of administration	Daily dose (mg)	Start date *dd/Mm/yyyy*	Stop date *dd/Mm/yyyy*	Indication	Suspected drug?
							☐Yes/☐No
							☐Yes/☐No
							☐Yes/☐No
							☐Yes/☐No

Please provide more related information below, if the above fields do not cover all:

……
……
……
……..

SPECIFIC QUESTIONS RELATED TO CATARACT/LENS OPACITIES

1. Please, clarify the location of cataract/ lens opacities:

a) right eye ☐ yes ☐ no
If yes, please specify:
☐ posterior subcapsular cataract
☐ cortical cataract
☐ nuclear cataract
☐ other If yes, please specify: ……

b) left eye ☐ yes ☐ no
If yes, please specify:
☐ posterior subcapsular cataract
☐ cortical cataract
☐ nuclear cataract
☐ other If yes, please specify: ……

2. Does the patient experience reduction in visual acuity?

a) right eye ☐ yes ☐ no If yes, please specify: ……
b) left eye ☐ yes ☐ no If yes, please specify: ……

3. Does the patient have any of the following risk factors (Please indicate the duration)

1) ☐ age over 50 years
2) ☐ cataract in family history If yes, please specify: ……
3) ☐ diabetes mellitus If yes, please specify: ……
4) ☐ smoking If yes, please specify: ……
5) ☐ alcohol If yes, please specify: ……
6) ☐ previous eye injury or trauma If yes, please specify: ……
7) ☐ previous eye inflammation If yes, please specify: ……
8) ☐ previous eye surgery If yes, please specify: ……

4. Please provide the patient's past medications and how long has the patient been treated with these medications?

……
……
……
……..…

5. Please provide the sign and symptoms which were experienced related to ocular event.

……
……
……
……

6. Please provide in a short description all available ocular examination data or results. These documents could be attached to the questionnaire. (Please take special care for data privacy)

……
……
……
……

7. Action taken with cariprazine:

a) ☐ discontinued ☐ temporarily For how long?.....
b) ☐ discontinued ☐ permanently Date……..
c) ☐ dose reduced Date…….. In this case, follow-up is needed 6 month later.
d) ☐ dose increased Date…….. In this case, follow-up is needed 6 month later.
e) ☐ unchanged Date…….. In this case, follow-up is needed 6 month later.

TARGETED FOLLOW UP FORM
for adverse events in elderly patients > 65 years

Reporter Details:

Name:	**e-mail:**	☐ Medical doctor ☐ Pharmacist ☐ Nurse ☐ Other
Date of report *(dd/Mm/yyyy):*	**phone:**	
	Signature:	

Patient details:

Initials:	**Year of birth:**	**Ethnic origin:** ☐ Caucasian ☐ Asian ☐ Black ☐ Australian ☐ Other
Gender: ☐ **Male /** ☐ **Female**	**Age at time of the event:**	
Height: …….. cm	**Weight: ……… kg**	

Adverse reactions:

(Seriousness means that the event results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect, or is an important medical event)

(The following options can be selected for outcome: Fatal: Event resulted in death; Not recovered/Not resolved: Event is ongoing or worsened; Recovered/Resolved: Event is reported to have resolved, with no reported sequel; Recovered/resolved with sequel: Event is reported to have resolved, but the patient has sequel (e.g., paralysis following a stroke); Recovering/resolving: Event is reported to be improved or improving, but has not resolved entirely; Unknown: Reporter states that the outcome is not known)

Event	**Dates** *dd/Mm/yyyy*	**Outcome** (Please choose the appropriate one)	**Serious?**
	Onset date: **…………………** **End date:** **………………….**	☐Recovered ☐Not recovered ☐Recovered with sequela ☐Recovering ☐Fatal ☐Unknown	☐Yes/☐No
	Onset date: **…………………** **End date:** **………………….**	☐Recovered ☐Not recovered ☐Recovered with sequela ☐Recovering ☐Fatal ☐Unknown	☐Yes/☐No
	Onset date: **…………………** **End date:** **………………….**	☐Recovered ☐Not recovered ☐Recovered with sequela ☐Recovering ☐Fatal ☐Unknown	☐Yes/☐No
	Onset date: **…………………** **End date:** **………………….**	☐Recovered ☐Not recovered ☐Recovered with sequela ☐Recovering ☐Fatal ☐Unknown	☐Yes/☐No

Medications:

Brand name	Active substance(s)	Route and form of administration	Daily dose (mg)	Start date *dd/Mm/yyyy*	Stop date *dd/Mm/yyyy*	Indication	Suspected drug?
							☐Yes/☐No
							☐Yes/☐No
							☐Yes/☐No
							☐Yes/☐No

Please provide more related information below, if the above fields do not cover all:

……
……
……
……..

1. **Please provide previous medication and duration of treatment with these medications:**

……
……
……
……..…

2. **Please provide medical history (former diseases, operations) of the patient:**

……
……
……
……

3. **Please provide any relevant medical finding, laboratory parameter or outcome of examinations performed:**

……
……
……
……

4. **Action taken with cariprazine:**

a) ☐ discontinued ☐ temporarily For how long?.....
b) ☐ discontinued ☐ permanently Date……..
c) ☐ dose reduced Date…….. In this case, follow-up is needed in 6 month.
d) ☐ dose increased Date…….. In this case, follow-up is needed in 6 month.
e) ☐ unchanged Date…….. In this case, follow-up is needed in 6 month..

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.