NAME OF THE MEDICINAL PRODUCT Reagila 1.5 mg - 3 mg - 4.5 mg - 6 mg, hard capsules **QUALITATIVE AND QUANTITATIVE COMPOSITION** Each hard capsule contains cariprazine hydrochloride corresponding to 1.5 mg – 3 mg – 4.5 mg – 6 mg cariprazine. Excipient with known effect: Reagila 3 mg hard capsules Each hard capsule contains 0.0003 mg Allura red AC (E 129). Reagila 4.5 mg hard capsules Each hard capsule contains 0.0008 mg Allura red AC (E 129). Reagila 6 mg hard capsules Each hard capsule contains 0.0096 mg Allura red AC (E 129). **PHARMACEUTICAL FORM** Hard capsule. Reagila 1.5 mg hard capsules 'Size 4' (approximately 14.3 mm in length) hard gelatin capsule with white opaque cap and white opaque body imprinted with "GR 1.5" on the capsule body with black ink. Reagila 3 mg hard capsules 'Size 4' (approximately 14.3 mm in length) hard gelatin capsule with green opaque cap and white opaque body imprinted with "GR 3" on the capsule body with black ink. Reagila 4.5 mg hard capsules 'Size 4' (approximately 14.3 mm in length) hard gelatin capsule with green opaque cap and green opaque body imprinted with "GR 4.5" on the capsule body with white ink. Reagila 6 mg hard capsules 'Size 3' (approximately 15.9 mm in length) hard gelatin capsule with purple opaque cap and white opaque body imprinted with "GR 6" on the capsule body with black ink. The capsules are filled with white to yellowish white powder mixture. The capsules are filled with white to yellowish white powder mixture. **THERAPEUTIC INDICATIONS** Reagila is indicated for the treatment of schizophrenia in adult patients. **POSOLOGY AND METHOD OF ADMINISTRATION** Posology 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 dose change. *Switching from other antipsychotics to cariprazine* When switching from another antipsychotic to cariprazine gradual cross-titration should be considered, with gradual discontinuation of the previous treatment while cariprazine treatment is initiated. *Switching to another antipsychotic from cariprazine* When switching to another antipsychotic from cariprazine, no gradual cross-titration is needed, the new antipsychotic should be initiated in its lowest dose while cariprazine is discontinued. It should be considered that plasma concentration of cariprazine and its active metabolites will decline by 50% in ~1 week. *Missed dose* If the patient misses a dose, the patient should take the missed dose as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped and the next dose should be taken according to the regular schedule. It is not recommended to take a double dose to make up for the forgotten dose. Special population *Renal impairment* No dose adjustment is required in patients with mild to moderate renal impairment (Creatinine Clearance (CrCl) $\geq$ 30 mL/min and < 89 mL/min). Safety and efficacy of cariprazine have not been evaluated in patients with severe renal impairment (CrCl < 30 mL/min). Use of cariprazine is not recommended in patients with severe renal impairment. *Hepatic impairment* No dose adjustment is required in patients with mild to moderate hepatic impairment (Child-Pugh score between 5-9). Safety and efficacy of cariprazine have not been evaluated in patients with severe hepatic impairment (Child-Pugh score between 10 and 15). Use of cariprazine is not recommended in patients with severe hepatic impairment. *Elderly* Available data in elderly patients aged $\geq$ 65 years treated with cariprazine are not sufficient to determine whether or not they respond differently from younger patients. Dose selection for an elderly patient should be more cautious. *Paediatric population* The safety and efficacy of cariprazine in children and adolescents aged less than 18 years have not been established. No data are available. Method of administration Reagila is for oral use, to be taken once daily at the same time of the day with or without food. Alcohol should be avoided when taking cariprazine. **CONTRAINDICATIONS** Hypersensitivity to the active substance or to any of the excipients. Concomitant administration of strong CYP3A4 inhibitors. Concomitant administration of strong or moderate CYP3A4 inducers. **SPECIAL WARNINGS AND PRECAUTIONS FOR USE** Suicidal ideation and behaviour The possibility of suicidality (suicidal ideation, suicide attempt and completed suicide) is inherent in psychotic illnesses and, generally, it is reported early after initiation or switch of antipsychotic therapy. Close supervision of high-risk patients should accompany antipsychotic therapy. Akathisia, restlessness Akathisia and restlessness are frequently occurring adverse reactions of antipsychotics. Akathisia is a movement disorder characterized by a feeling of inner restlessness and a compelling need to be in constant motion, as well as by actions such as rocking while standing or sitting, lifting the feet as if marching on the spot, and crossing and uncrossing the legs while sitting. As cariprazine causes akathisia and restlessness, it should be used cautiously in patients who are prone to or already exhibit symptoms of akathisia. Akathisia develops early in treatment. Therefore close monitoring in the first phase of treatment is important. Prevention includes slow up-titration; treatment measures include slight down-titration of cariprazine or anti-EPS medicinal product The dose can be modified based on individual response and tolerability. Tardive dyskinesia Tardive dyskinesia is a syndrome consisting of potentially irreversible, rhythmical, involuntary movements, predominantly of the tongue and/or face that can develop in patients treated with antipsychotics. If signs and symptoms of tardive dyskinesia appear in a patient treated with cariprazine, discontinuation should be

considered. Parkinson's disease If prescribed to patients with Parkinson's disease, antipsychotic medicinal products may exacerbate the underlying disease and worsen symptoms of Parkinson's disease. Physicians should, therefore, weigh the risks versus the benefits when prescribing cariprazine to patients with Parkinson's disease. Ocular symptoms/cataract In the preclinical studies of cariprazine lens opacity/cataract was detected in dogs. However, a causal relationship between lenticular changes / cataracts observed in human studies and cariprazine use has not been established. Nevertheless, patients who would develop symptoms potentially related to cataract should be advised to ophthalmologic examination and re-evaluated for treatment continuation. Neuroleptic malignant syndrome (NMS) A potentially fatal symptom complex referred to as NMS has been reported in association with antipsychotic treatment. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, elevated serum creatine phosphokinase levels, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, cariprazine must be discontinued immediately. Seizures and convulsions Cariprazine should be used cautiously in patients with history of seizures or with conditions that potentially lower the seizure threshold. Elderly patients with dementia Cariprazine has not been studied in elderly patients with dementia and is not recommended to treat elderly patients with dementia due to increased risk of overall mortality. Risk of cerebrovascular accidents (CVA) An approximately 3-fold increased risk of CVA has been seen in randomised placebo-controlled clinical studies in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Cariprazine should be used with caution in patients with risk factors for stroke. Cardiovascular disorders *Blood pressure changes* Cariprazine can cause orthostatic hypotension as well as hypertension. Cariprazine should be used with caution in patients with known cardiovascular disease predisposing to blood pressure changes. Blood pressure should be monitored. *Electrocardiogram (ECG) changes* QT prolongation can develop in patients treated with antipsychotics. With cariprazine no QT interval prolongation was detected compared to placebo in a clinical study designed to assess QT prolongation. In clinical studies, only a few, non-serious, QT-prolongations have been reported with cariprazine. Therefore, cariprazine should be used cautiously in patients with known cardiovascular disease or in patients with a family history of QT prolongation and in patients treated with medicinal products that might cause QT prolongation. *Venous thromboembolism (VTE)* Cases of VTE have been reported with antipsychotic medicinal products. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with cariprazine and preventive measures undertaken. Hyperglycaemia and diabetes mellitus Patients with an established diagnosis of diabetes mellitus or patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should be monitored for serum glucose levels. In clinical studies, glucose-related adverse reactions have been reported with cariprazine. Weight change Significant weight gain has been observed with the use of cariprazine. Patients should have their weight monitored regularly. Concomitant treatment with moderate CYP3A4 inhibitors Co-administration of cariprazine with moderate inhibitors of CYP3A4 may lead to increased total cariprazine exposure. Monitoring of the individual response and tolerability is recommended and, if needed, the cariprazine dose should be (temporarily) reduced to account for the potential increase in exposure. Excipients Reagila 3 mg, 4.5 mg and 6 mg hard capsules contain Allura red AC (E 129), which may cause allergic reactions. **UNDESIRABLE EFFECTS** Summary of the safety profile The most frequently reported adverse drug reactions (ADRs) with cariprazine in the dose range (1.5-6 mg) were akathisia (19%) and parkinsonism (17.5%). Most events were mild to moderate in severity. List of adverse reactions ADRs based upon pooled data from cariprazine schizophrenia studies are shown by system organ class and by preferred term. Adverse reactions are ranked by frequency, the most frequent first, using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000) very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. ***Adverse drug reactions occurring in patients with schizophrenia.*** **Blood and Lymphatic system disorders:** Uncommon: Anaemia, Eosinophilia. Rare: Neutropenia. **Immune system disorders:** Rare: Hypersensitivity. **Endocrine disorders:** Uncommon: Blood thyroid stimulating hormone decreased. Rare: Hypothyroidism. **Metabolism and nutrition disorders:** Common: Dyslipidaemia, Weight increased, Decreased appetite, Increased appetite. Uncommon: Blood sodium abnormal, Diabetes mellitus, Blood glucose increased. **Psychiatric disorders:** Common: Sleep disorders[1], Anxiety. Uncommon: Suicidal behaviour, Delirium, Depression, Libido decreased, Libido increased, Erectile dysfunction. **Nervous system disorders:** Very common: Akathisia[2], Parkinsonism[3]. Common: Sedation, Dizziness, Dystonia[4], Other extrapyramidal diseases and abnormal movement disorders[5]. Uncommon: Tardive dyskinesia, Dyskinesia[6], Dysaesthesia, Lethargy. Rare: Seizures/Convulsion, Amnesia, Aphasia. Very rare: Neuroleptic malignant syndrome. **Eye disorders:** Common: Vision blurred. Uncommon: Intraocular pressure increased, Accommodation disorder, Visual acuity reduced, Eye irritation. Rare: Cataract,

Photophobia. **Ear and labyrinth disorders:** Uncommon: Vertigo. **Cardiac disorders:** Common: Tachyarrhythmia. Uncommon: Cardiac conduction disorders, Bradyarrhythmia, Electrocardiogram QT prolonged, Electrocardiogram T wave abnormal. **Vascular disorders:** Common: Hypertension. Uncommon: Hypotension. **Respiratory, thoracic and mediastinal disorders:** Uncommon: Hiccups. **Gastrointestinal disorders**: Common: Vomiting, Nausea, Constipation. Uncommon: Gastrooesophageal reflux disease. Rare: Dysphagia. **Hepatobiliary disorders:** Common: Hepatic enzymes increased. Uncommon: Blood bilirubin increased. Very rare: Toxic hepatitis. **Skin and subcutaneous tissue disorders:** Uncommon: Pruritus, Rash. **Musculoskeletal and connective tissue disorders:** Common: Blood creatine phosphokinase increased. Rare: Rhabdomyolysis. **Renal and urinary disorders:** Uncommon: Dysuria, Pollakisuria. **Pregnancy, puerperium and perinatal conditions:** Very rare: Drug withdrawal syndrome neonatal. **General disorders and administration site conditions:** Common: Fatigue. Uncommon: Thirst. [1]Sleep disorders: Insomnia, Abnormal dreams/nightmare, Circadian rhythm sleep disorder, Dyssomnia, Hypersomnia, Initial insomnia, Middle insomnia, Nightmare, Sleep disorder, Somnambulism, Terminal insomnia. [2]Akathisia: Akathisia, Psychomotor hyperactivity, Restlessness. [3]Parkinsonism: Akinesia, Bradykinesia, Bradyphrenia, Cogwheel rigidity, Extrapyramidal disorder, Gait disturbance, Hypokinesia, Joint stiffness, Tremor, Masked facies, Muscle rigidity, Musculoskeletal stiffness, Nuchal rigidity, Parkinsonism. [4]Dystonia: Blepharospasm, Dystonia, Muscle tightness, Oromandibular dystonia, Torticollis, Trismus. [5]Other extrapyramidal diseases and abnormal movement disorders: Balance disorder, Bruxism, Drooling, Dysarthria, Gait deviation, Glabellar reflex abnormal, Hyporeflexia, Movement disorder, Restless legs syndrome, Salivary hypersecretion, Tongue movement disturbance. [6]Dyskinesia: Choreoathetosis, Dyskinesia, Grimacing, Oculogyric crisis, Protrusion tongue. Reporting of suspected adverse reactions Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via: **Belgium:** Federaal agentschap voor geneesmiddelen en gezondheidsproducten, www.fagg.be, Afdeling Vigilantie, Website: www.eenbijwerkingmelden.be, e-mail: adr@fagg-afmps.be **Luxemburg**: Centre Régional de Pharmacovigilance de Nancy ou Division de la pharmacie et des médicaments de la Direction de la santé Site internet : www.guichet.lu/pharmacovigilance **Nederland**: Nederlands Bijwerkingen Centrum Lareb Website : www.lareb.nl. **PHARMACODYNAMIC PROPERTIES** Pharmacotherapeutic group: Psycholeptics, other antipsychotics, ATC code: N05AX15. **MARKETING AUTHORISATION HOLDER** Gedeon Richter Plc. Gyömrői út 19-21. 1103 Budapest Hungary. **MARKETING AUTHORISATION NUMBERS** Reagila 1.5 mg (28 hard capsules): EU/1/17/1209/003. Reagila 3 mg (28 hard capsules): EU/1/17/1209/013. Reagila 4.5 mg (28 hard capsules): EU/1/17/1209/021. Reagila 1.5 mg (28 hard capsules): EU/1/17/1209/029. **GENERAL CLASSIFICATION FOR SUPPLY** Prescription only. **DATE OF REVISION OF THE TEXT** 04/2024