30 May 2024
EMA/CHMP/152859/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Reagila

International non-proprietary name: Cariprazine

Procedure No. EMEA/H/C/002770/X/0033

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE adverse event

AUC area under the concentration-time curve

CI confidence interval

Cmax maximum concentration

CPK creatine phosphokinase

DAD Diode-Array Detector

DCAR desmethyl cariprazine

DDCAR didesmethyl cariprazine

EPS extrapyramidal symptom

GCP Good Clinical Practice

ICH International Conference on Harmonisation

MedDRA Medical Dictionary for Regulatory Activities

PD pharmacodynamic

Ph.Eur. European Pharmacopoeia

PK pharmacokinetic

QbD Quality by design

QC Quality Control

SAE serious adverse event

SD standard deviation

SmPC Summary of products characteristics

SOC system organ class

TEAE treatment-emergent adverse event

T_{max} time for maximum concentration

1. Background information on the procedure

1.1. Submission of the dossier

Gedeon Richter Plc. submitted on 22 June 2023 an extension of the marketing authorisation.

Extension application to introduce a new pharmaceutical form (orodispersible tablets).
The RMP (version 5.0) is updated in accordance.

The MAH applied for the following indication for Reagila new pharmaceutical form:

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

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point(s) (d) - Extensions of marketing authorisations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0162/2023 on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver.

At the time of submission of the application, the PIP EMEA-001652-PIP01-14-M05 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder Co-Rapporteur: N/A

The application was received by the EMA on	22 June 2023
The procedure started on	13 July 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	02 October 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	06 October 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	06 October 2023
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	09 November 2023
The MAH submitted the responses to the CHMP consolidated List of Questions on	19 January 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	20 February 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	07 March 2024
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	21 March 2024
The MAH submitted the responses to the CHMP List of Outstanding Issues on	30 April 2024
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	15 May 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Reagila on	30 May 2024

2. Scientific discussion

2.1. Problem statement

Reagila (cariprazine) is indicated for the treatment of schizophrenia in adult patients.

The approved pharmaceutical form of cariprazine is hard capsule, 1.5, 3, 4.5, and 6 mg.

In addition to this existing approved formulation, a new pharmaceutical form i.e., orodispersible tablet has been developed. This new formulation may be preferred in the indicated population which may experience potential difficulties swallowing capsules and it may contribute to improved compliance.

2.1.1. Disease or condition

Schizophrenia is one of the most frequent and debilitating psychotic disorders with worldwide lifetime morbidity risk of about 1 percent. The age of onset of the first psychotic episode is typically in the late teens but can be as late as into the mid-thirties. Onset prior to adolescence is rare.

The symptoms of schizophrenia are classified as positive (delusions, hallucinations, disorganised speech, and disorganised or catatonic behaviours) and negative (affective flattening, restriction in the fluency and productivity of thought and speech and in the initiation of goal directed behaviour). In addition, cognitive deficits are common. The positive symptoms appear to reflect an excess or distortion of normal functions, whereas negative symptoms reflect a diminution or loss of normal function.

Primary negative symptoms are outstanding and insistent in up to a quarter of the patients with schizophrenia, and approximately half of the first-episode acute schizophrenia and up to two thirds of all chronic outpatients might experience negative symptoms at any given time.

2.1.2. Epidemiology

Schizophrenia typically begins in late adolescence or early adulthood. Its lifetime prevalence is about 1% globally. It is equally prevalent in men and women and affects more than 21 million people worldwide. Incidence rates per year of schizophrenia in adults within a quite narrow range between 0.1 and 0.4 per 1000 population (WHO).

2.1.3. Biologic features

Dopamine hypothesis as simplified posits that schizophrenia results from too much dopaminergic activity. Efficacy of antipsychotic medications correlates with their ability to antagonize dopamine type 2 (D2) receptors. In addition, several other neurotransmitters and receptor types are involved.

An enlargement of cerebral ventricles, reduced brain symmetry, deficits in prefrontal cortex and decrease in size of hippocampus and amygdala have been all observed in patients with schizophrenia.

2.1.4. Clinical presentation, diagnosis

A patient usually gradually recovers from the first episode of schizophrenia. However, relapses are common, and pattern of the illness during the first 5 years indicates generally the course. In general, deterioration in the patient’s baseline functioning happens after each relapse. Positive symptoms tend to ease with time, but the socially debilitating negative and deficit symptoms may increase and become more severe. Only 10-20% of schizophrenia patients have been described to achieve a good outcome. It has been estimated that 20-30% continue to experience moderate symptoms and 40-60% remain significantly impaired. This means that patients with schizophrenia often have great difficulties in integrating in society and to normal life, for example through the loss of an acquired capability to earn a livelihood or the disruption of studies. In addition, comorbidity with other somatic diseases, such as obesity, cardiovascular diseases and diabetes mellitus, as well as with substance abuse is common. People with schizophrenia have a 40-60% higher rate of dying prematurely than general population due to physical health problems and suicide.

2.1.5. Management

Antipsychotic medications are the mainstay treatment for schizophrenia in addition to psychosocial interventions. Antipsychotics diminish symptoms and reduce relapse rates. Antipsychotics have a wide variety of pharmacological properties, but all have a capacity to antagonize postsynaptic dopamine receptors in the brain.

Acute psychotic symptoms require immediate attention and focuses to alleviating of severe symptoms with an adequate trial of medication. If no adequate response is followed by a few weeks trial, treatment should be changed to another type of antipsychotic. Side effects are very common with antipsychotics.

These include extrapyramidal side effects, tardive dyskinesia, sexual side effects, sedation, just a few to mention.

2.2. About the product

Cariprazine (RGH-188) is an atypical antipsychotic, an orally active and potent dopamine D2 and D3 receptor partial agonist with preferential binding to D3 receptors and partial agonist at serotonin 5-HT1A receptors.

Reagila (cariprazine) is intended for the treatment of schizophrenia in adult patients.

The approved pharmaceutical form of cariprazine is hard capsule, in doses of 1.5, 3, 4.5, and 6 mg.

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.

A new pharmaceutical form i.e., orodispersible tablet, 1.5 mg, 3 mg, 4.5 mg, and 6 mg, has now been developed.

2.3. Type of Application and aspects on development

No scientific advice has been given by the EMA or Member states for the new formulation orodispersible tablet.

To support the line extension application, the Applicant carried out a 2 single dose fasting bioequivalence studies with the 1.5 mg orodispersible tablet: pivotal study EU-KIFO-CAR-01-2020 (with the orodispersible tablet taken without water) and study EU-KIFO-CAR-02-2020 (with the orodispersible tablet taken dispersed in a glass of water). Biowaiver of in vivo studies was submitted for the 3, 4.5 and 6 mg orodispersible tablet strengths.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as orodispersible tablets (ODTs) containing cariprazine hydrochloride corresponding to 1.5 mg, 3 mg, 4.5 mg and 6 mg cariprazine as active substance.

Other ingredients are: mannitol (E 421), maize starch, sodium starch glycolate Type A, malic acid (E 296), sodium stearyl fumarate (E 485), and silicon dioxide (E 551).

The product is available in blisters made of PA/Al/PVC foil (forming foil) and Paper/PET/Al blister lidding foil with peelable functionality (sealing foil) packaged in a folded carton box as described in section 6.5 of the SmPC.

2.4.2. Active Substance

The active substance used to manufacture the new pharmaceutical form, orodispersible tablets, is the same as that used in the manufacture of the currently authorised Reagila hard capsules (EU/1/17/1209/001-42).

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as follows:

1.5 mg: white or almost white, triangle, biconvex orodispersible tablet. Engraving on one side is "C2", the other side is without engraving. The diameter of the tablet is approx. 8 mm and thickness is approx. 3-4 mm.

3 mg: white or almost white, round, biconvex orodispersible tablet. Engraving on one side is "C3", the other side is without engraving. The diameter of the tablet is 7 mm and thickness is approx. 3-4 mm.

4.5 mg: white or almost white, square, biconvex orodispersible tablet. Engraving on one side is "C4", the other side is without engraving. The diameter of the tablet is approx. 7 mm and thickness is approx. 3-4 mm.

6 mg: white or almost white, oval, biconvex orodispersible tablet. Engraving on one side is "CI", the other side is without engraving. The width of the tablet is 5 mm, length is 8.5 mm and thickness is approx. 3-4 mm.

The ODTs have been developed as a new oral dosage form of cariprazine as a line extension to the approved hard capsules for patients with swallowing difficulties. The ODTs tablets are formulated in four tablet strengths differentiated with shape, dimensions and engraving, as described above.

The tablet strengths can be considered as having proportional compositions since the amount of active substance is below 5% (1.2 – 4.7%) and the amounts of excipients are the same except for the filler which is a ready-to-use, co-processed excipient (mannitol and maize starch), physical mixture of two components of Ph. Eur. quality in the ratio of 78-82% and 15-19%, which compensate for the change in active substance. This was considered acceptable.

Compatibility studies were conducted at different stages of product development by testing the physical and chemical stability of the active substance with excipients in their binary mixtures and as complete tablet systems as well. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. A mixture of mannitol and maize starch is used. The separate ingredients comply with respectively Ph. Eur. monograph and a specification is provided for the mixture including relevant test parameters such as particle size. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

In vivo equivalence between the ODTs and the already authorised capsule dosage form is demonstrated by a bioequivalence study using the lowest strength (1.5 mg). Dissolution profiles are provided for 1.5 mg ODTs and 1.5 mg capsules used in the study (biobatches) at pH 1, 4.5 and 5.0 (QC media). The dissolution profiles are similar with more than 85% dissolved within 15 minutes for

both formulations at all three pHs. Dissolution tests in support of a biowaiver of strength are provided. More than 85% is dissolved within 15 minutes for all four strengths (1.5 mg, 3 mg, 4.5 mg and 6 mg) of the ODTs at all tested pHs (1, 4.5 and 5.0). In addition, according to *Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr), comparative dissolution data of four tablets of 1.5 mg strength versus one tablet of 6 mg strength at pH 6.8 has been provided as requested during evaluation, and they were comparable. Due to the pH dependent solubility of cariprazine, about 70% is dissolved within 120 minutes.

The finished product is manufactured by direct compression. It was considered the most advantageous as due to the absence of a granulation step it provides the required fast tablet disintegration and smooth mouthfeel.

Criticality / non-criticality of the manufacturing process steps or parameters were established based on the failure mode, effects and criticality analysis (FMECA).

A design of experiments (DoE) was set up for the optimization of the compression step. Process parameter ranges were determined based on previous tablet compression experiences. The experimental results were evaluated for the quality attributes (dependent variables) which may be impacted by the process parameters: tablet mass, resistance to crushing, thickness, friability, disintegration. The results were subjected to statistical analysis to determine the criticality of process parameters and their acceptable range. In addition, dissolution profiles were measured at least at the extreme process parameter settings. The optimization of tablet compression was carried out on one batch per strength. The ranges of process parameters covered in the compression DoE have been accepted as the set ranges.
The primary packaging is blisters made of PA/Al/PVC foil (forming foil) and Paper/PET/Al blister lidding foil with peelable functionality (sealing foil). The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site.

The manufacturing process consists of four main steps: homogenization, final blending, compression and packaging

Process validation has been performed on four commercial scale batches of the lowest 1.5 mg strength and three pilot scale batches each of the other strengths (3 mg, 4.5 mg and 6 mg). The commercial scale batch size for the 3 mg, 4.5 mg and 6 mg strengths will be validated prior to marketing in line with the process validation scheme provided. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: characters/appearance (visual), identity (HPLC, DAD), related substances (HPLC), microbiological purity (Ph. Eur.), assay (HPLC), disintegration (Ph. Eur.), dissolution (Ph. Eur.), uniformity of dosage units-content uniformity (Ph. Eur.).

A risk analysis following the recommendations of ICH Q3D has been performed for elemental impurities. The risk assessment covers 7 elements expected to be evaluated as per the guideline for

oral administration. Overall, based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for 3 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 commercial scale batches per strength of the finished product stored for up to 12 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for characters/appearance, related substances, microbiological purity, assay, disintegration, and dissolution.

All results of the tested quality attributes for all tablet strengths complied with acceptance criteria throughout the stability studies performed so far under long term and accelerated conditions.

In addition, one batch per strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant degradation could be detected indicating that the product is not sensitive to light.

Bulk stability data are provided demonstrating that ODTs stored in plastic bags prior to packaging are stable for up to 12 months at 25°C / 60% RH. It is confirmed that start of shelf-life is set based on the first manufacturing step according to CPMP/QWP/072/96, EMEA/CVMP/453/01 CPMP/CVMP and EMA Q&A on stability issues of pharmaceutical bulk products use in manufacture of the finished product. This is accepted.

As the active substance is moisture-sensitive, the finished product should be protected from moisture.

Based on available stability data, the proposed shelf-life of 2 years with no special temperature restriction and to be stored in the original package to protect from moisture as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

This line extension is introducing ODT as a new oral dosage form of cariprazine for patients with swallowing difficulties. Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process the finished product.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

No new non-clinical data was submitted in this line extension application. This is acceptable.

2.5.2. Toxicology

Impurities

One degradation product of cariprazine has a proposed shelf-life specification of 1.0 %. As this limit is above the qualification threshold (0.8%), further justification has been provided.

According to the Applicant this degradation product was tested for potential mutagenic activity using the Bacterial Reverse Mutation Assay. The experiments were carried out using strains of Salmonella typhimurium and strain of Escherichia coli. Based on the results of the preliminary concentration range finding test (informatory toxicity test), in accordance with the OECD 471 guideline, the various concentrations of degradation product were prepared and investigated in the main experiments.

The reported data of this mutagenicity assay show that under the experimental conditions applied, degradation product did not induce gene mutations in the genome of the examined strains of Salmonella typhimurium and Escherichia coli. It is concluded that degradation product has no mutagenic activity on the applied bacterium tester strains under the test conditions.

2.5.3. Ecotoxicity/environmental risk assessment

The present application concerns a change to existing marketing authorization, i.e. addition of a new pharmaceutical form. Therefore, the products containing the above-mentioned active substance are

the extension of other products (Cariprazine 1.5 mg, 3 mg, 4.5 mg and 6 mg hard capsules) of similar active substance content already existing on the market.

The orodispersible tablets (Cariprazine 1.5 mg, 3 mg, 4.5 mg and 6 mg) are intended to substitute for other similar products on the market. The products do not contain any component which result is additional hazard to the environment during storage, distribution, use and disposal.

The approval of the referred products will not result in increase of the total quantity of Cariprazine HCI released into the environment, therefore will not result in increase of risk to the environment.

2.5.4. Discussion on non-clinical aspects

No new non-clinical data was submitted in this application. This is acceptable.

Cariprazine is already used in existing marketed products and no significant increase in environmental exposure is anticipated as the present application concerns addition of a new pharmaceutical form. Therefore, cariprazine is not expected to pose a risk to the environment.

2.5.5. Conclusion on the non-clinical aspects

There are no objections to approval of Reagila orodispersible tablets from a non-clinical point of view.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

No issues regarding GCP have been identified.

- **Tabular overview of clinical studies**

Table 1: Overview of cariprazine bioequivalence studies to support the development of the new formulation orodispersible tablets.

Type of Study	*Study Identifier*	*Module Location of Study Report*	*Objective(s) of the Study*	*Study Design and Type of Control*	*Test Product(s); Dose Regimen; Route of Administration*	*Number of Subjects*[a]	*Healthy Subjects or Diagnosis of Patients*	*Duration of Treatment*[b]	*Study Status; Type of Report*
BE	EU-KIFO-CAR-01-2020 A single-dose, two-period, two-treatment, two-sequence, cross-over bioequivalence study of Cariprazine 1.5 mg orodispersible tablets and Cariprazine 1.5 mg capsules, hard under fasting conditions	5.3.1.2	(1) Primary: Assessment of bioequivalence of cariprazine 1.5 mg orodispersible tablets and cariprazine 1.5 mg capsules, hard in healthy, adult volunteers after single dose administration under fasting conditions determined by use of $AUC_{0\text{-}72h}$ and C_{max} of cariprazine (2) Secondary: Assessment of safety and tolerability of the study treatments	Single centre, open-label, randomised (order of treatments), balanced, 2-period, 2-sequence, single dose cross-over trial with administration under fasting conditions	Test: Cariprazine 1.5 mg orodispersible tablet; oral Reference: Cariprazine 1.5 mg capsule, hard oral	54	Healthy subjects	Two (2) treatment periods with oral single dose administration each separated by a washout period of at least 55 treatment free days, i.e., 8 weeks	Complete; Full
BE	EU-KIFO-CAR-02-2020 A single-dose, two-period, two-treatment, two-sequence, cross-over bioequivalence study of Cariprazine 1.5 mg orodispersible tablets dispersed in a glass of water and Cariprazine 1.5 mg capsules, hard under fasting conditions	5.3.1.2	(1) Primary: Assessment of bioequivalence of cariprazine 1.5 mg orodispersible tablets dispersed in a glass of water and cariprazine 1.5 mg capsules, hard in healthy, adult volunteers after single dose administration under fasting conditions determined by use of $AUC_{0\text{-}72h}$ and C_{max} of cariprazine (2) Secondary: Assessment of safety and tolerability of the study treatments	Single centre, open-label, randomised (order of treatments), balanced, 2-period, 2-sequence, single dose cross-over trial with administration under fasting conditions	Test: Cariprazine 1.5 mg orodispersible tablet dispersed in a glass of water; 1.5 mg; oral Reference: Cariprazine 1.5 mg capsule, hard oral	64	Healthy subjects	Two (2) treatment periods with oral single dose administration each separated by a washout period of at least 55 treatment free days, i.e., 8 weeks	Complete; Full

To support this line extension application, the MAH submitted one pivotal and one additional study.

Study EU-KIFO-CAR-01-2020 (pivotal), a single-dose, two-period, two-treatment, two-sequence, cross-over bioequivalence study of Cariprazine 1.5 orodispersible tablets and Cariprazine 1.5 mg capsules, hard under fasting conditions.

Study EU-KIFO-CAR-02-2020, a single-dose, two-period, two-treatment, two-sequence, cross-over bioequivalence study of Cariprazine 1.5 orodispersible tablets dispersed in a glass of water and Cariprazine 1.5 mg capsules, hard under fasting conditions.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The development of the new cariprazine formulation (orodispersible tablets) is supported by a pivotal single-dose bioequivalence study in the fasting state comparing the new orodispersible tablet 1.5 mg with the approved hard capsules (EU-KIFO-CAR-01-2020). A strength biowaiver is sought for the other cariprazine orodispersible tablets strengths (3, 4.5 and 6 mg). The method of administration used in the pivotal bioequivalence study is in line with the proposed method of administration in the SmPC. Furthermore, the MAH has submitted an additional bioequivalence study comparing the cariprazine

orodispersible tablet 1.5 mg dispersed in a glass of water with the cariprazine hard capsule under fasting conditions (EU-KIFO-CAR-02-2020).

The currently approved hard capsules of cariprazine can be administered with or without food.

Methods

- *Bioanalysis*

Plasma concentrations of cariprazine and its metabolites Desmethyl and Didesmethyl Cariprazine were determined with LC-MS/MS methods.

- *Non-compartmental analysis*

Standard methods were used in the non-compartmental analysis.

- *Statistical analysis*

Standard statistical methods were used and bioequivalence between the hard capsule and the orodispersible tablets was established if the 90 % CI of the ratios of adjusted geometric means of cariprazine $AUC_{0\text{-}72h}$ and C_{max} were within the conventional acceptance limits of 80.00 % - 125.00 %.

Bioequivalence

The pivotal study EU-KIFO-CAR-01-2020 was an open-label, randomized, two-period, two-sequence, single dose cross-over study in 54 healthy volunteers. The study was conducted with the lowest strength of 1.5 mg of cariprazine for tolerability reasons. The study periods were separated by a washout period of at least 55 treatment free days.

The orodispersible tablets were administered in the fasting state without water. Bioequivalence was demonstrated for $AUC_{0\text{-}72h}$ and C_{max} when compared to the approved hard capsules administered as indicated.

- *Waiver of in vivo studies for the 3, 4.5 mg and 6 mg orodispersible tablet strengths*

A waiver of bioequivalence studies for the strengths 3, 4.5 and 6 mg is acceptable from a pharmacokinetic point of view since cariprazine exhibit linear pharmacokinetics in the therapeutic dose range.

The additional study EU-KIFO-CAR-02-2020 was an open-label, randomised, two-period, two-sequence, single dose cross-over study in 64 healthy volunteers. The study was conducted with the lowest strength of 1.5 mg of cariprazine for tolerability reasons. The study periods were separated by a washout period of at least 55 treatment free days.

The orodispersible tablets were administered dispersed in a glass of 240 mL water in the fasting state. Bioequivalence was demonstrated for $AUC_{0\text{-}72h}$ when compared to the approved hard capsules administered as indicated, but C_{max} was below the lower limit of the conventional 90% confidence interval.

2.6.2.2. Pharmacodynamics

Not applicable.

2.6.3. Discussion on clinical pharmacology

No issues regarding GCP have been identified, but some clarification and additional information was warranted. Therefore, the applicant was requested to provide information on inspections and inspection outcomes for the clinical and bioanalytical sites. In conclusion, the provided information was considered acceptable and no concerns are raised regarding GCP.

The bioanalysis methods used for the clinical studies included the application were adequately validated. The methods performed satisfactorily during study sample analysis.

Bioequivalence was demonstrated for $AUC_{0\text{-}72h}$ and C_{max} comparing the cariprazine 1.5 mg orodispersible tablet administered without water with the approved hard capsules administered as indicated in the Reagila SmPC.

For substances with linear pharmacokinetics and low solubility, a study with the highest strength would normally be required. As cariprazine has linear pharmacokinetics in the therapeutic range and single doses of more than 2 mg per day are not well tolerated in healthy volunteers, a study at the lowest dose strength is acceptable for safety reasons.

Waiver of *in vivo* studies for the additional orodispersible tablets strengths 3, 4.5 and 6 mg is acceptable.

The determination of bioequivalence was made based on parent only in the pivotal as well as in the non-pivotal bioequivalence study. This is considered acceptable.

The additional method of administration investigated in the non-pivotal bioequivalence study did not demonstrate bioequivalence for C_{max}, which was slightly below the conventional 90% CI range. As this is a line extension application where demonstrating strict bioequivalence is not considered necessary, and considering that additional methods of administration may provide clinical benefits, the applicant was invited to critically discuss the clinical relevance of a C_{max} below the conventional acceptance limits and whether the results of study EU-KIFO-CAR-02-2020 could support the inclusion of the additional method of administration (orodispersible tablets dispersed in a glass of water) in the SmPC. The applicant provided a discussion supporting that a slightly lower C_{max} for orodispersible tablets dispersed in a glass of water has low clinical impact since the effect of cariprazine is driven by the total exposure of the parent compound and the two active metabolites. However, a question was raised regarding the proposed instruction in SmPC (Method of administration section 4.2) regarding dispersion of the orodispersible tablet in water and the applicant was asked to discuss if there was a need for the instruction to be more specified. The final wording proposed by the applicant was "*Alternatively, disperse the tablet in water and drink the resulting suspension. In this case, the contents of the glass should be thoroughly stirred to avoid settling down of undissolved residues* ". This is considered acceptable.

2.6.4. Conclusions on clinical pharmacology

The applied cariprazine orodispersible tablets formulation is bioequivalent with the cariprazine hard capsule formulation when the orodispersible tablets are administered without water. The additional method of administration investigated in the non-pivotal bioequivalence study did not demonstrate bioequivalence for C_{max}, which was slightly below the conventional 90% CI range. However, the applicant provided a discussion supporting that a slightly lower C_{max} for orodispersible tablets dispersed in a glass of water has low clinical impact which was considered acceptable, including the proposed update of the method of administration in the SmPC.

Approval is recommended for the cariprazine 1.5 mg orodispersible tablet strength from a pharmacokinetic point of view.

Biowaiver of in vivo studies for the 3 mg, 4.5 mg and 6 mg orodispersible tablet strengths is adequately justified.

2.6.5. Clinical efficacy

No new clinical efficacy data was submitted in this line extension application.

The efficacy of cariprazine was previously documented in five pivotal trials, three short-term trials, one long-term maintenance of effect study, and a long-term study in patients with predominant negative symptoms of schizophrenia. The short-term trials (RGH-MD-16, RGH-MD-04, and RGH-MD-05) were 6-week, double-blind, placebo- and active-controlled, with fixed or fixed/flexible doses of cariprazine in the range 1.5-9 mg/day, performed in adult patients with acute exacerbation of schizophrenia at European, US and other study centers. The active controls were 10 mg aripiprazole and 4 mg risperidone (in study RGH-MD-04 and GH-MD-16, respectively).

The long-term maintenance of effect study, (RGH-MD-06), was a double-blind, placebo-controlled, randomized-withdrawal study in order to assess prevention of relapse, with fixed cariprazine doses of 3 mg/day to 9 mg/day, for 20 weeks (open-label phase), followed by a placebo-controlled double-blind phase of 26 weeks. Patients came from European countries (Ukraine, Slovakia, Romania), India and the US.

The long-term study in patients with predominant negative symptoms of schizophrenia (RGH-188-005) had a randomized, 26-week, double-blind, risperidone-controlled design in patients with predominant negative symptoms, treated with fixed/flexible cariprazine doses of 3 to 6 mg/day, with a target dose of 4.5 mg/day. All patients were from Europe.

The results of the short-term studies have shown clinically relevant effect of cariprazine in the treatment of psychotic symptoms of schizophrenia. Maintenance of effect in long-term use was confirmed in the randomised withdrawal study. The study RGH-188-005 was designed to evaluate the effect on negative symptoms and has shown significant symptom improvement for both cariprazine and risperidone groups.

2.6.6. Discussion on clinical efficacy

No new clinical efficacy data was submitted in this line extension application, which is considered acceptable.

2.6.7. Conclusions on the clinical efficacy

The benefit/risk profile of cariprazine is unchanged. There are no concerns with Reagila orodispersible tablets from an efficacy point of view.

2.6.8. Clinical safety

No new safety data from clinical trials in patients was submitted in this line extension application.

The unfavourable effects of cariprazine are comparable to those of other atypical antipsychotics. In the previously conducted clinical schizophrenia studies, up to 81.7% of cariprazine treated patients treated with 1.5-6 mg /day had TEAEs, 6.6% had SAEs, 12.1% discontinued their treatment due to adverse events and there were 3 deaths. The most frequent AEs were akathisia (14.6%), insomnia (14.0%),

and headache (12.1%). Other common AEs were restlessness (6.2%), weight increase (5.1%), dizziness (4.5%), and CPK increase (2.6%).

Extrapyramidal symptoms, dominated by akathisia, were among the most frequent TAEs in the cariprazine development program (14.6% in the claimed posology and 3.4% in placebo). Akathisia was mostly reported within the initial 5-6 weeks of the cariprazine treatment, however, longer time to onset was observed up to week 36 in the long-term studies and with the majority judged as mild to moderate in severity. Akathisia was mainly managed with anti-EPS medications (propranolol, benztropine and trihexyphenidyl) in cariprazine treated patients while with dose reductions in risperidone treated patients during the comparison studies. Time to resolution of EPS-related TEAEs tended to be shorter with lower doses of cariprazine (measured by days to resolve 50th percentile around 14 days for 1.5 mg, up to 43 days for 6 mg). Akathisia was the second most frequent adverse event (following exacerbation of underlying disease) that led to treatment discontinuation. Therefore, individual up-titration based on the observed effect and tolerance as well as the lowest effective maintenance dose according to the judgement of the treating physician is recommended.

To support the current application, the MAH submitted two BA/BE studies in healthy volunteers.

Study EU-KIFO-CAR-01-2020, a single-dose, two-period, two-treatment, two-sequence, cross-over bioequivalence study of Cariprazine 1.5 orodispersible tablets and Cariprazine 1.5 mg hard capsules, under fasting conditions; and

Study EU-KIFO-CAR-02-2020, a single-dose, two-period, two-treatment, two-sequence, cross-over bioequivalence study of Cariprazine 1.5 orodispersible tablets dispersed in a glass of water and Cariprazine 1.5 mg hard capsules, under fasting conditions.

2.6.8.1. Patient exposure

Study EU-KIFO-CAR-01-2020

Fifty-three (53) of 54 subjects received the investigational product at least once. All 54 subjects randomised were evaluated for safety following single-dose administration of the test product (cariprazine 1.5 mg orodispersible tablet) and the reference product (cariprazine 1.5 mg hard capsule).

Study EU-KIFO-CAR-02-2020

Sixty-four (64) male and female subjects (8 female, 56 male) were randomized in the course of this trial. Sixty-two (62) of 64 subjects received the investigational product at least once. Two (2) subjects were randomized but withdrew their consent prior to administration of study drug. Both subjects were still included in the FAS.

2.6.8.2. Adverse events

Study EU-KIFO-CAR-01-2020

In total 98 TEAEs were reported by 41 subjects. Fifty-four (54) TEAEs in 29 subjects occurred after Test treatment and 44 TEAEs in 26 subjects after Reference treatment. The most frequently reported TEAEs (PT) were fatigue (N = 18), nausea (N = 13) and headache (N = 12). The intensity of all TEAEs was mild in 74 out of 98 cases (75.51 %) and moderate in 24 out of 98 cases (24.49 %). No TEAEs with severe intensity occurred.

Study EU-KIFO-CAR-02-2020

In total 157 TEAEs were reported by 56 subjects. Ninety-six (96) TEAEs in 43 subjects occurred after Test treatment and 61 TEAEs in 36 subjects after Reference treatment. The most frequently reported TEAEs (PT) were: fatigue (N = 41), headache (N = 18), nausea (N = 17) and increased blood pressure (N = 17).

2.6.8.3. Serious adverse event/deaths/other significant events

No deaths, SAEs or other significant events were reported in Study EU-KIFO-CAR-01-2020.

In Study EU-KIFO-CAR-02-2020, one subject experienced an SAE of tendon rupture, considered not related to study drug treatment.

2.6.8.4. Laboratory findings

There were no new or unexpected findings observed with regards to clinical laboratory investigations.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Not applicable.

2.6.8.7. Immunological events

No new data were reported.

2.6.8.8. Safety related to drug-drug interactions and other interactions

No new data were reported.

2.6.8.9. Discontinuation due to adverse events

Study EU-KIFO-CAR-01-2020

Ten subjects discontinued from the study. One subject dropped out due to a pre-treatment adverse event. Seven subjects discontinued due to TEAEs: Five (5) subjects dropped out due to "vomiting", which was in all cases assessed as study drug related and was of mild intensity. One subject dropped out due to "increased blood pressure", which was assessed as unrelated to investigational product intake and of mild intensity. One (1) subject dropped out due to "tonsillitis", which was also assessed as unrelated to study drug and of moderate intensity.

In addition, 2 subjects withdrew their consent in the course of the trial.

Study EU-KIFO-CAR-02-2020

Thirteen subjects were discontinued due to TEAEs. One due to tendon rupture, six due to vomiting, 5 due to clinical laboratory values, and one subject due to Lyme disease. All clinical laboratory

abnormalities recovered without sequelae except for one mild gamma-glutamyltransferase increased, considered not related to study drug.

In addition, 5 subjects withdrew their consent in the course of the trial and one subject was discontinued due to non-adherence.

2.6.8.10. Post marketing experience

There is no post-marketing experience with the orodispersable tablet.

2.6.9. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

No clinical safety issues were identified in the submitted comparative BA/BE studies.

2.6.10. Conclusions on the clinical safety

The benefit/risk profile of cariprazine is unchanged. There are no concerns with Reagila orodispersible tablets from a safety point of view.

2.7. Risk Management Plan

2.7.1. 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

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

2.7.4.

Table 2: 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
#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

Safety concern	Risk minimisation measures	Pharmacovigilance activities
#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

2.7.5. Conclusion

The CHMP considered that the risk management plan version 5.0 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Reagila hard capsules. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

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

Schizophrenia is one of the most frequent and debilitating psychotic disorders with worldwide lifetime morbidity risk of about 1 percent. The age of onset of the first psychotic episode is typically in the late teens but can be as late as into the mid-thirties. Onset prior to adolescence is rare.

The symptoms of schizophrenia are classified as positive (delusions, hallucinations, disorganised speech, and disorganised or catatonic behaviours) and negative (affective flattening, restriction in the fluency and productivity of thought and speech and in the initiation of goal directed behaviour). In addition, cognitive deficits are common. The positive symptoms appear to reflect an excess or distortion of normal functions, whereas negative symptoms reflect a diminution or loss of normal function.

Primary negative symptoms are outstanding and insistent in up to a quarter of the patients with schizophrenia, and approximately half of the first-episode acute schizophrenia and up to two thirds of all chronic outpatients might experience negative symptoms at any given time.

3.1.2. Available therapies and unmet medical need

The approved pharmaceutical form of cariprazine is hard capsule, 1.5, 3, 4.5, and 6 mg.

In addition to this existing approved formulation, a new pharmaceutical form i.e., orodispersible tablet has been developed. This new formulation may be preferred in the indicated population which may experience potential difficulties swallowing capsules and it may contribute to improved compliance.

3.1.3. Main clinical studies

The development of the new formulation (orodispersible tablets) is supported by a pivotal single-dose bioequivalence study in the fasting state comparing the new orodispersible tablet 1.5 mg with the approved cariprazine hard capsules (EU-KIFO-CAR-01-2020). A strength biowaiver is sought for the other strengths (3 mg, 4.5 mg and 6 mg). The method of administration used in the pivotal bioequivalence study is in line with the proposed method of administration in the Reagila SmPC.

In addition, the MAH has submitted a bioequivalence study comparing the new orodispersible tablet 1.5 mg dispersed in a glass of water, with the cariprazine hard capsule under fasting conditions (EU-KIFO-CAR-02-2020).

3.2. Favourable effects

In the pivotal study EU-KIFO-CAR-01-2020, bioequivalence was demonstrated for $AUC_{0\text{-}72h}$ and C_{max} when comparing the cariprazine 1.5 mg orodispersible tablet administered without water with the approved hard capsules administered as indicated in the Reagila SmPC.

3.3. Uncertainties and limitations about favourable effects

None.

3.4. Unfavourable effects

No clinical safety concerns were raised by the submitted BA/BE studies.

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Not applicable.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the pivotal study EU-KIFO-CAR-01-2020, bioequivalence was demonstrated for AUC_{0-72h} and C_{max} comparing the lowest dose strength (1.5 mg) cariprazine orodispersible tablet administered without water with the approved hard capsules administered as indicated in the Reagila SmPC.

For substances with linear pharmacokinetics and low solubility, a study with the highest strength would normally be required. As cariprazine has linear pharmacokinetics in the therapeutic range and single doses of more than 2 mg per day are not well tolerated in healthy volunteers, a study at the lowest dose strength is acceptable for safety reasons.

The determination of bioequivalence was made based on parent only in both bioequivalence studies. This is considered acceptable.

The additional method of administration investigated in the non-pivotal bioequivalence study EU-KIFO-CAR-02-2020 did not demonstrate bioequivalence for C_{max}, which was slightly below the conventional 90% CI range. As this is a line extension application where demonstrating strict bioequivalence is not considered necessary, and considering that additional methods of administration may provide clinical benefits, the applicant was invited to critically discuss the clinical relevance of a C_{max} below the conventional acceptance limits and whether the results of study EU-KIFO-CAR-02-2020 could support the inclusion of the additional method of administration (orodispersible tablets dispersed in a glass of water) in the SmPC. It was concluded that a slightly lower C_{max} for orodispersible tablets dispersed in a glass of water has low clinical impact since the effect of cariprazine is driven by the total exposure of the parent compound and the two active metabolites.

Biowaiver of in vivo studies for the 3, 4.5 and 6 mg orodispersible tablet strengths is adequately justified.

The bioequivalence studies EU-KIFO-CAR-01-2020 and EU-KIFO-CAR-02-2020 in healthy volunteers did not reveal any new concerns with Reagila orodispersible tablets from a safety point of view.

3.7.2. Balance of benefits and risks

The overall B/R of Reagila new pharmaceutical form orodispersible tablet is positive.

3.8. Conclusions

The overall benefit/risk balance of Reagila is positive, subject to the conditions stated in section ‘Recommendations’.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus

that the benefit-risk balance of, Reagila orodispersible tablets is favourable in the following indication(s):

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

The CHMP therefore recommends the extension(s) of the marketing authorisation for Reagila subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.