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Public Assessment Report

Name of the Product:

Agartha DUO

50 mg/850 mg and 50 mg/1000 mg

film-coated tablets

(vildagliptin/metformin hydrochloride)

Procedure number: HU/H/0673/001-002/DC

Marketing authorisation holder: Gedeon Richter Plc.

Date 2nd February 2021

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Agartha DUO 50 mg/850 mg and 50 mg/1000 mg film-coated tablets. The holder of the marketing authorisation is Gedeon Richter Plc.

The active substances are vildagliptin/metformin hydrochloride.

- Each Agartha DUO 50 mg/850 mg film-coated tablet contains 50 mg vildagliptin and 850 mg metformin hydrochloride (corresponding to 660 mg of metformin).
- Each Agartha DUO 50 mg/1000 mg film-coated tablet contains 50 mg vildagliptin and 1000 mg metformin hydrochloride (corresponding to 780 mg of metformin).

The other ingredients are:

- Agartha DUO 50 mg/850 mg film-coated tablet: Hydroxypropylcellulose, Magnesium stearate, Hypromellose 2910 (E464), Titanium dioxide (E171), Iron oxide yellow (E172), Macrogol 4000 (E1521) and Talc (E553b).
- Agartha DUO 50mg/1000mg film-coated tablet: Hydroxypropylcellulose, Magnesium stearate, Hypromellose 2910 (E464), Titanium dioxide (E171), Iron oxide yellow (E172), Iron oxide red (E172), Iron oxide black (E172), Macrogol 4000 (E1521) and Talc (E553b).

The appearance of the tablets is:

- Agartha DUO 50 mg/850 mg film-coated tablets are yellow, oblong shaped, biconvex film-coated tablets of about 18.0 mm length and 9.0 mm width, with a yellow bordered white or almost white coloured fracture surface, engraved with “AB3” on one side and a median line on the other side. The fracture surface of the tablets is white with yellow margins.

- Agartha DUO 50 mg/1000 mg film-coated tablets are brown, oblong shaped, biconvex film-coated tablets of about 17.7 mm length and 10.0 mm width, with a brown bordered white or almost white coloured fracture surface, engraved with “AB4” on one side and a median line on the other side. The fracture surface of the tablets is white with brown margins.

- The median line is intended only to facilitate breaking for ease of swallowing and not to divide the tablet into equal doses.

- Agartha DUO 50mg/850mg film-coated tablets are packaged in oriented PA/Al /PVC//Al cold-blisters.
- Available in packs containing 30 or 60 film-coated tablets and in multi-packs containing 120 (2 packs of 60) or 180 (3 packs of 60) film-coated tablets.

- Agartha DUO 50mg/1000mg film-coated tablets are packaged in oriented PA/Al /PVC//Al cold-blisters.
- Available in packs containing 30 or 60 film-coated tablets and in multi-packs containing 120 (2 packs of 60) or 180 (3 packs of 60) film-coated tablets.

– Not all pack sizes may be marketed.

The active substances of Agartha DUO, vildagliptin and metformin, belong to a group of medicines called "oral antidiabetics". Agartha DUO is used to treat adult patients with type 2 diabetes. This type of diabetes is also known as noninsulin-dependent diabetes mellitus. Type 2 diabetes develops if the body does not make enough insulin or if the insulin that the body makes does not work as well as it should. It can also develop if the body produces too much glucagon. Both insulin and glucagon are made in the pancreas. Insulin helps to lower the level of sugar in the blood, especially after meals. Glucagon triggers the liver to make sugar, causing the blood sugar level to rise.

Both active substances, vildagliptin and metformin, help to control the level of sugar in the blood. The substance vildagliptin works by making the pancreas produce more insulin and less glucagon. The substance metformin works by helping the body to make better use of insulin. This medicine has been shown to reduce blood sugar, which may help to prevent complications from your diabetes.

What patients need to know before taking Agartha DUO

Patients must not take Agartha DUO
- if the patients are allergic to vildagliptin, metformin or any of the other ingredients of this medicine (see above). If the patients think they may be allergic to any of these, they should talk to their doctor before taking Agartha DUO.
- if the patients have uncontrolled diabetes, with, for example, severe hyperglycaemia (high blood glucose), nausea, vomiting, diarrhoea, rapid weight loss, lactic acidosis (see "Risk of lactic acidosis" below) or ketoacidosis. Ketoacidosis is a condition in which substances called ketone bodies accumulate in the blood and which can lead to diabetic pre-coma. Symptoms include stomach pain, fast and deep breathing, sleepiness or their breath developing an unusual fruity smell.
- if the patients have recently had a heart attack or if they have heart failure or serious problems with their blood circulation or difficulties in breathing which could be a sign of heart problems.
- if the patients have severely reduced kidney function.
- if the patients have a severe infection or are seriously dehydrated (have lost a lot of water from their body).
- if the patients are going to have a contrast x-ray (a specific type of x-ray involving an injectable dye).
  Please also see information about this in section "Warnings and precautions".
- if the patients have liver problems.
- if the patients drink alcohol excessively (whether every day or only from time to time).
- if the patients are breast-feeding (see also "Pregnancy and breast-feeding").

Warnings and precautions

<u>Risk of lactic acidosis</u>
Agartha DUO may cause a very rare, but very serious side effect called lactic acidosis, particularly if the patient's kidneys are not working properly. The risk of developing lactic acidosis is also increased with uncontrolled diabetes, serious infections, prolonged fasting or alcohol

intake, dehydration (see further information below), liver problems and any medical conditions in which a part of the body has a reduced supply of oxygen (such as acute severe heart disease). If any of the above apply to the patients, they should talk to their doctor for further instructions.

Patients should stop taking Agartha DUO for a short time if they have a condition that may be associated with dehydration (significant loss of body fluids) such as severe vomiting, diarrhoea, fever, exposure to heat or if patients drink less fluid than normal. Patients should talk to their doctor for further instructions.

Patients should stop taking Agartha DUO and contact a doctor or the nearest hospital immediately if they experience some of the symptoms of lactic acidosis, as this condition may lead to coma.
Symptoms of lactic acidosis include:
- vomiting
- stomach ache (abdominal pain)
- muscle cramps
- a general feeling of not being well with severe tiredness
- difficulty in breathing
- reduced body temperature and heartbeat

Lactic acidosis is a medical emergency and must be treated in a hospital.

Agartha DUO is not a substitute for insulin. Therefore, patients should not receive Agartha DUO for the treatment of type 1 diabetes.

Patients should talk to their doctor, pharmacist or nurse before taking Agartha DUO if they have or have had a disease of the pancreas.

Patients should talk to their doctor, pharmacist or nurse before taking Agartha DUO if they are taking an anti-diabetic medicine known as a sulphonylurea. Their doctor may want to reduce their dose of the sulphonylurea when they take it together with Agartha DUO in order to avoid low blood glucose (hypoglycaemia).

If the patients have previously taken vildagliptin but had to stop taking it because of liver disease, they should not take this medicine.

Diabetic skin lesions are a common complication of diabetes. Patients are advised to follow the recommendations for skin and foot care that they are given by their doctor or nurse. The patients are also advised to pay particular attention to new onset of blisters or ulcers while taking Agartha DUO. Should these occur, they should promptly consult their doctor.

If the patients need to have major surgery they must stop taking Agartha DUO during and for some time after the procedure. Their doctor will decide when they must stop and when to restart their treatment with Agartha DUO.

A test to determine the patients liver function will be performed before the start of Agartha DUO treatment, at three-month intervals for the first year and periodically thereafter. This is so that signs of increased liver enzymes can be detected as early as possible.

During treatment with Agartha DUO, the patients' doctor will check their kidney function at least once a year or more frequently if they are elderly and/or have worsening renal function.

The patients' doctor will test their blood and urine for sugar regularly.

Children and adolescents

The use of Agartha DUO in children and adolescents up to 18 years of age is not recommended.

Other medicines and Agartha DUO

If the patients need to have an injection of a contrast medium that contains iodine into their bloodstream, for example in the context of an X-ray or scan, they must stop taking Agartha DUO before or at the time of the injection. Their doctor will decide when they must stop and when to restart their treatment with Agartha DUO.

Patients should tell their doctor if they are taking, have recently taken or might take any other medicines. Patients may need more frequent blood glucose and kidney function tests, or their doctor may need to adjust the dosage of Agartha DUO. It is especially important to mention the following:
- glucocorticoids generally used to treat inflammation
- beta-2 agonists generally used to treat respiratory disorders
- other medicines used to treat diabetes
- medicines which increase urine production (diuretics)
- medicines used to treat pain and inflammation (NSAID and COX-2-inhibitors, such as ibuprofen and celecoxib)
- certain medicines for the treatment of high blood pressure (ACE inhibitors and angiotensin II receptor antagonists)
- certain medicines affecting the thyroid, or
- certain medicines affecting the nervous system.

Agartha DUO with alcohol

Avoid excessive alcohol intake while taking Agartha DUO since this may increase the risk of lactic acidosis (please see section "Warnings and precautions").

Pregnancy and breast-feeding

If the patients are pregnant, think they may be pregnant or are planning to have a baby, they should ask their doctor for advice before taking this medicine. Their doctor will discuss with them the potential risk of taking Agartha DUO during pregnancy.

Patients should not use Agartha DUO if they are breast-feeding.

Patients should ask their doctor or pharmacist for advice before taking any medicine.

Driving and using machines

If patients feel dizzy while taking Agartha DUO, they should not drive or use any tools or machines.

When and how to take Agartha DUO

Patients should swallow the tablets whole with a glass of water. Patients should take one tablet in the morning and the other in the evening with or just after food. Taking the tablet just after food will lower the risk of an upset stomach.

Patients should continue to follow any advice about diet that their doctor has given them. In particular, if they are following a diabetic weight control diet, they should continue with this while they are taking Agartha DUO.

What to do if more Agartha DUO was taken that it should have been?

If a patient takes too many Agartha DUO tablets, or if someone else takes their tablets, he/she should talk to a doctor or pharmacist immediately. Medical attention may be necessary. If they have to go to a doctor or hospital, they should take the pack and the leaflet with them.

What to do if taking Agartha DUO was forgotten?

If a patient forgets to take a tablet, he/she should take it with his/her next meal unless they are due to take one then anyway. No double dose to make up for a forgotten tablet must be taken!

May patients stop taking Agartha DUO?

Patients should continue to take this medicine as long as their doctor prescribes it so that it can continue to control their blood sugar. Patients should not stop taking Agartha DUO unless their doctor tells them to. If patients have any questions about how long to take this medicine, they should talk to their doctor.

If patients have any further questions on the use of this medicine, they should ask their doctor, pharmacist or nurse.

Possible side effects

Like all medicines, Agartha DUO can cause side effects, although not everybody gets them.

Patients must stop taking the medicinal product and see a doctor immediately, if experiencing any of the following side effects:

- Lactic acidosis (very rare: may affect up to 1 user in 10,000):

Agartha DUO may cause a very rare, but very serious side effect called lactic acidosis (see section “Warnings and precautions”). If this happens, patients must stop taking Agartha DUO and contact a doctor or the nearest hospital immediately, as lactic acidosis may lead to coma.

- Angioedema (rare: may affect up to 1 in 1,000 people):

Symptoms include swollen face, tongue or throat, difficulty swallowing, difficulty breathing, sudden onset of rash or hives, which may indicate a reaction called “angioedema”.

- Liver disease (hepatitis) (rare):

Symptoms include yellow skin and eyes, nausea, loss of appetite or dark-coloured urine, which may indicate liver disease (hepatitis).

- Inflammation of the pancreas (pancreatitis) (frequency not known):

Symptoms include severe and persistent pain in the abdomen (stomach area), which might reach through to the patient's back, as well as nausea and vomiting.

Other side effects
Some patients have experienced the following side effects while taking Agartha DUO:

- Very common (may affect more than 1 in 10 people): nausea, vomiting, diarrhoea, pain in and around the stomach (abdominal pain), loss of appetite.
- Common (may affect up to 1 in 10 people): dizziness, headache, trembling that cannot be controlled, metallic taste, low blood glucose.
- Uncommon (may affect up to 1 in 100 people): joint pain, tiredness, constipation, swollen hands, ankle or feet (oedema).
- Very rare (may affect up to 1 in 10,000 people): sore throat, runny nose, fever; signs of a high level of lactic acid in the blood (known as lactic acidosis) such as drowsiness or dizziness, severe nausea or vomiting, abdominal pain, irregular heart beat or deep, rapid breathing; redness of the skin, itching; decreased vitamin B12 levels (paleness, tiredness, mental symptoms such as confusion or memory disturbances).

Some patients have experienced the following side effects while taking Agartha DUO and a sulphonylurea:

- Common: dizziness, tremor, weakness, low blood glucose, excessive sweating.

Some patients have had the following side effects while taking Agartha DUO and insulin:

- Common: headache, chills, nausea (feeling sick), low blood glucose, heartburn.
- Uncommon: diarrhoea, flatulence.

Since this product has been marketed, the following side effects have also been reported:

- Frequency not known (cannot be estimated from the available data): itchy rash, inflammation of the pancreas, localised peeling of skin or blisters, muscle pain.

How to store Agartha DUO?

This medicine should be stored below 25 °C. It should be stored in the original package in order to protect from light.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Agartha DUO 50 mg/850 mg and 50 mg/1000 mg film-coated tablets. The procedure was finalised at 22nd November 2020. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for **Agartha DUO 50 mg/850 mg, 50 mg/1000 mg film-coated tablets** (Gedeon Richter Plc).
The products is indicated for treatment of type 2 diabetes mellitus in adults.
A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC and therefore contained no new clinical or preclinical data, other than supporting literature where necessary. The Applicant has adequately demonstrated bioequivalence between the product applied for and the reference product.

The originator products are Eucreas 50 mg/850 mg film-coated tablets and Eucreas 50 mg/1000 mg film-coated tablets by Novartis Europharm Ltd., registered since 14 November 2007 throughout the European Union.

II. QUALITY ASPECTS

II.1 Introduction

The chemical-pharmaceutical assessment report concerns the application of Agartha DUO 50 mg/850 mg and 50 mg/1000 mg film-coated tablets via a decentralized procedure according to Article 10.1 of Directive 2001/83/EC (i.e a generic application). The products have been developed by Richter Gedeon Romania, S.A.

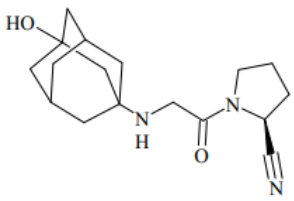
Reference products are Eucreas 50 mg/850 mg and 50 mg/1000 mg film-coated tablets (containing 50 mg vildagliptin and 850 mg or 1000 mg metformin hydrochloride as active ingredients, respectively) which were the original products of Novartis Europharm Limited.

II.2 Drug substances

II.2.1 Vildagliptin

Full 3.2.S part on the quality and manufacture of the active substance were provided in the applicant's submission with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: Vildagliptin
Chemical name: (2S)-1-[2-[(3-hydroxy-1-adamantyl)amino]acetyl]pyrrolidine-2-carbonitrile
Structure:



The active substance is white to yellowish-white or greyish-white crystalline powder, freely soluble in dichloromethane, ethanol (96 per cent), methanol and deionized water, soluble in acetone, sparingly soluble in 2-propanol and practically insoluble in cyclohexane. Vildagliptin has one asymmetric carbon atom, the active substance is the S configuration. Only crystalline Form A of the compound exists, the manufacturer consistently produces this form.

Complete details of the manufacturing process has been presented. Description of the manufacturing process of the active pharmaceutical ingredient (API) is adequate.

Evidence of the structure has been confirmed by UV, NMR, MS and IR analysis as well as TGA, DSC, FT-IR and X-Ray powder diffraction spectroscopy. The impurity profile of the API contains detailed information about genotoxic impurities, residual solvents and catalysts.

Vildagliptin is not official in the Ph.Eur. Therefore, an in-house specification has been set for the active substance, which includes the following tests: characters, particle size distribution, identification, loss on drying, related substances, residual solvents, assay and microbiological purity. The presented specification is in accordance with the Ph.Eur. general monograph on *Substances for Pharmaceutical Use* and the ICH Q6A guideline. The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.
The substance complies with the requirements of the EMA guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

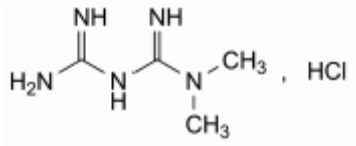
Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period is acceptable when the API is stored below 30 °C in the original packaging.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

II.2.2 Metformin hydrochloride

Data on the quality and manufacture of the active substance were provided in the applicant's submission using CEP procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: Metformin hydrochloride
Chemical name: 1,1-Dimethylbiguanide hydrochloride
Structure:



The active substance is white or almost white crystals, freely soluble in water, slightly soluble in ethanol (96 per cent), practically insoluble in acetone and in methylene chloride.
The impurity profile of the API contains detailed information about organic impurities, genotoxic impurities, residual solvents and elemental impurities.

The substance is specified according to the requirements of the current Ph.Eur. monograph and the CEP (residual solvents), additional specification has been set for bulk and tapped density, requirement for NDMA (NMT 0.032 ppm) and NDEA (0.009 ppm). The Ph. Eur. specification includes the following tests for metformin hydrochloride: appearance, solubility, identification, appearance of solution, related substances, loss on drying, sulphated ash and assay.
Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterized.
The substance complies with the requirements of the EMA guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented stability data the proposed re-test period is acceptable if the API is preserved in tight containers at below 30° C.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim was to develop film-coated tablets containing vildaglipin and metformin hydrochloride as drug substances in 50 mg and 850 mg /1000 mg doses, respectively; which are bioequivalent and pharmaceutically equivalent to the reference medicinal product Eucreas 50 mg /850 mg and 50 mg /1000 mg film-coated tablets, the branded original products of Novartis Europharm Ltd.
A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.
As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance and composition was obtained.
50 mg/850 mg strength: Yellow, oblong shaped, biconvex film-coated tablet of about 18.0 mm length and 9.0 mm width, with a yellow bordered white or almost white coloured fracture surface, engraved with "AB3" on one side, and a median line on the other side.
50 mg/1000 mg strength: Brown, oblong shaped, biconvex film-coated tablet of about 17.7 mm length and 10.0 mm width, with a brown bordered white or almost white coloured fracture surface, engraved with "AB4" on one side, and a median line on the other side.
The median line is intended only to facilitate breaking for ease of swallowing and not to divide the tablet into equal doses.

The excipients used in the finished product are hydroxypropylcellulose, magnesium stearate and film-coating containing hypromellose 2910, titanium dioxide (E171), iron oxide yellow/red/black, macrogol 4000 and talc. All excipients used comply with their respective European Pharmacopoeia monograph. Compliance of the product with the general monograph of the European Pharmacopoeia *on the Products with the risk of TSE* has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph.Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is OPA/Al/PVC//Al blister. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a **shelf-life of 18 months** is approved **with the following storage restriction: "Store below 25 °C. Store in the original package in order to protect from light."**

The Summary of Product Characteristics, patient Information Leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From chemical-pharmaceutical points of view the product is approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of vildagliptin and metformin hydrochloride are well known. As vildagliptin and metformin hydrochloride are widely used, well-known active substances, no further studies are required and the Applicant provides none. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to the active ingredients.

III.2 Pharmacology

Vildagliptin, a member of the islet enhancer class, is a potent and selective DPP-4 inhibitor. Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose via three mechanisms, by reduction of hepatic glucose production, modestly increasing insulin sensitivity in muscle and delaying intestinal glucose absorption.

The active substances are well-known compounds. No further information was provided regarding the pharmacology of vildagliptin and metformin hydrochloride.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the Applicant.

III.4 Toxicology

No new toxicity studies were submitted by the Applicant for the product, which is acceptable for this type of application.

III.5 Ecotoxicology/environmental risk assessment

Since Agartha DUO is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Pharmacodynamics, pharmacokinetics and toxicology of vildagliptin and metformin hydrochloride are well-known. As Agartha DUO is a generic product there is no need for further excessive non-clinical studies. The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of vildagliptin and metformin hydrochloride are well known.

The application is submitted in accordance with Article 10(1) of Directive 2001/83/EC as amended.

To support the application, the applicant has submitted 2 pivotal (2018-4496, 2019-4604) bioequivalence studies in fed conditions.
The two strengths (50/850 mg and 50/1000 mg) of Vildagliptin+Metformin film-coated tablets were investigated in separate bioequivalence studies due to their not quantitatively proportional compositions, in accordance with the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/ Corr. London, 20 January 2010).

The application contains an adequate review of published clinical data.

IV.2 Pharmacokinetics

Vildagliptin possesses several desirable pharmacokinetic properties that contribute to its lower variability and low potential for drug interaction. Following oral administration, vildagliptin is rapidly and well absorbed with an absolute bioavailability of 85%. An approximately dose-proportional increase in exposure to vildagliptin over the dose range of 25–200 mg has been reported. Food does not have a clinically relevant impact on the pharmacokinetics of vildagliptin, and it can be taken without regard to food. Vildagliptin is minimally bound to plasma proteins (9.3%) and, on the basis of a volume of distribution of 71 L, it is considered to distribute extensively into extravascular spaces. Renal clearance of vildagliptin (13 L/h) accounts for 33% of the total body clearance after intravenous administration (41 L/h). The primary elimination pathway is hydrolysis by multiple tissues/organs. The DPP-4 enzyme contributes to the formation of the major hydrolysis metabolite; therefore, vildagliptin is also a substrate of DPP-4.

After an oral dose of metformin, Tmax is reached in 2.5 h. Absolute bioavailability of a 500 mg metformin tablet is approximately 50-60 % in healthy subjects. After an oral dose, the nonabsorbed fraction recovered in faeces was 20-30 %.
After oral administration, metformin absorption is saturable and incomplete. It is assumed that the pharmacokinetics of metformin absorption is non-linear. At the usual metformin doses and dosing schedules, steady state plasma concentrations are reached within 24-48 h and are generally less than 1 μg/mL. In controlled clinical trials, maximum metformin plasma levels (Cmax) did not exceed 5 μg/mL, even at maximum doses.
Food decreases the extent and slightly delays the absorption of metformin. Following administration of a dose of 850 mg, a 40 % lower plasma peak concentration, a 25 % decrease in AUC and a 35 min prolongation of time to peak plasma concentration was observed. The clinical relevance of this decrease is unknown.

Plasma protein binding is negligible. Metformin partitions into erythrocytes. The blood peak is lower than the plasma peak and appears at approximately the same time. The red blood cells most likely represent a secondary compartment of distribution. The mean volume of distribution (Vd) ranged between 63 – 276 L.

Metformin is excreted unchanged in the urine. No metabolites have been identified in humans. Renal clearance of metformin is > 400 mL/min, indicating that metformin is eliminated by glomerular filtration and tubular secretion. Following an oral dose, the apparent terminal elimination half-life is approximately 6.5 h. When renal function is impaired, renal clearance is decreased in proportion to that of creatinine and thus the elimination half-life is prolonged, leading to increased levels of metformin in plasma.

IV.2.1 Bioequivalence studies

Study No. 2018-4496
The study was an open-label, randomised, two-treatment, two-period, two-sequence single-dose crossover study with the 50 mg/1000 mg film-coated tablets conducted in 34 healthy volunteers under fed conditions, with a 7-day wash out period used between treatment periods.

Results:
Vildagliptin:

Pharmacokinetic Parameter	Contrast	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV% [1]
AUC_t	A vs B	102.52	100.66 - 104.41	4
C_{max}	A vs B	100.54	95.15 - 106.24	13
[1] *Estimated from the Residual Mean Squares.*				

Metformin:

Pharmacokinetic Parameter	Contrast	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV% [1]
AUC_t	A vs B	102.40	99.40 - 105.50	7
C_{max}	A vs B	98.53	94.85 - 102.35	9
[1] *Estimated from the Residual Mean Squares.*				

The 90% confidence intervals of the ratios of LSM derived from analyses on the ln-transformed PK parameters AUC0-t and Cmax for vildagliptin and metformin in plasma were within the predefined protocol limits (80% to 125%) indicating bioequivalence with the reference product.

Study No. 2019-4604
The study was a randomised, two-treatment, two-period, two-sequence single-dose crossover study with the 50 mg/850 mg film-coated tablets conducted in 34 healthy volunteers under fed conditions, with a 7-day wash out period used between treatment periods. Pharmacokinetic parameters were determined based on 33 subjects' data.

Results:

Vildagliptin:

Pharmacokinetic Parameter	Contrast	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV% [1]
AUC_t	A vs B	100.99	99.29 - 102.72	4
C_{max}	A vs B	103.11	96.63 - 110.02	16

Metformin:

Pharmacokinetic Parameter	Contrast	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV% [1]
AUC_t	A vs B	98.36	95.29 - 101.54	8
C_{max}	A vs B	101.00	97.53 - 104.60	8

The 90% confidence intervals of the ratios of LSM derived from analyses on the ln-transformed PK parameters AUC0-t and Cmax for vildagliptin and metformin in plasma were within the predefined protocol limits (80% to 125%) indicating bioequivalence with the reference product.

Pharmacokinetic conclusion:

Based on the submitted bioequivalence study No. 2018-4496 the Vildagliptin + Metformin hydrochloride 50 mg/1000 mg film-coated tablets (manufactured by Richter Gedeon S.A., Romania, batch number: F81802) (Test) is considered to be bioequivalent with the Reference Eucreas® 50 mg/1000 mg film-coated tablets (manufactured by Novartis Pharma GmbH, Germany Lot number: WY257) in healthy adult volunteers in fed conditions.

Based on the submitted bioequivalence study No. 2019-4604 the Vildagliptin + Metformin hydrochloride 50 mg/850 mg film-coated tablets (Richter Gedeon S.A., Romania, batch number: F7B886) (Test) is considered to be bioequivalent with the Reference Eucreas® 50 mg/850 mg film-coated tablets (Novartis Pharma GmbH, Germany Lot number: WY255) in healthy adult volunteers in fed conditions.

IV.3 Pharmacodynamics

Clinical pharmacology studies to evaluate the pharmacodynamics of Agartha DUO were not performed and none are required.

IV.4 Clinical efficacy

No new efficacy data have been submitted and none are required. The Applicant has provided an adequate literature review to describe the efficacy profile of vildagliptin and metformin hydrochloride.

IV.5 Clinical safety

The Applicant has provided an adequate literature review to describe the safety profile of vildagliptin and metformin hydrochloride.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The Applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant GVP module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

The applicant has submitted a Risk Management Plan in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Agartha DUO film-coated tablets.

The applicant has identified the following safety concerns:

Summary of safety concerns	
Important identified risks	- Transaminase elevation and drug-induced liver injury (DILI) - Angioedema - Acute pancreatitis - Lactic acidosis - Skin lesions - Hypoglycaemia
Important potential risks	- Serious infections - Cardiac events in congestive heart failure (NYHA functional class III) patients - Muscle events/myopathy/rhabdomyolysis, in particular with current statin use - Neuropsychiatric events - Breast cancer - Pancreatic cancer
Missing information	- Gender incidence/frequency differences - Patients with severe hepatic impairment - Patients with compromised cardiac function (NYHA functional class IV)

Summary of safety concerns	
	- Pregnancy

Pharmacovigilance Plan: Routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Richter's product containing vildagliptin-metformin combination.

As routine pharmacovigilance activity, targeted follow-up questionnaires ("checks lists") are in place the following safety concerns:

- Transaminase elevations and Drug-induced liver injury (DILI)
- Angioedema
- Acute pancreatitis
- Lactic acidosis
- Skin lesions
- Hypoglycaemia
- Muscle events/ myopathy/rhabdomyolysis, in particular with current statin use
- Pancreatic cancer

No additional activities are proposed.

Risk Minimisation Measures: Routine risk minimisation measures (i.e. wording in SmPC, PL and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to Richter's product containing vildagliptin-metformin combination.

No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

IV.6.3 Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for these medicinal products 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.

IV.7 Discussion on the clinical aspects

The application concerns a generic product.

The products is indicated for treatment of type 2 diabetes mellitus in adults.

To support the application the Applicant has adequately demonstrated bioequivalence between Agartha DUO and the reference product Eucreas.

There is no objection against granting the marketing authorization from a clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The application for Agartha DUO contains an adequate review of published nonclinical and clinical data.
The applicant demonstrated bioequivalence between Agartha DUO and Eucreas products.

Safety and efficacy profile of the active ingredients of Agartha DUO are well-known and widely documented.

Based on the review of the non-clinical and clinical data on safety and efficacy, the RMS considers that the application for Agartha DUO in the treatment of type 2 diabetes mellitus is approvable.

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and user consultation

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Eucreas 50 mg/850 mg film-coated tablets and Eucreas 50 mg/1000 mg film-coated tablets. The bridging report submitted by the applicant has been found acceptable.

VI. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached