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Public Assessment Report

Name of the Product:

Agartha
50 mg tablets

(vildagliptin)

Procedure number: HU/H/0622/001/DC

Marketing authorisation holder: Gedeon Richter Plc.

Date: 4 May 2020

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 50 mg tablets. The holder of the marketing authorisation is Gedeon Richter Plc.

The active substance is vildagliptin. Each tablet contains 50 mg vildagliptin.

The other ingredients are lactose, microcrystalline cellulose, sodium starch glycolate (type A) and magnesium stearate.

Vildagliptin, belongs to a group of medicines called "oral antidiabetics". Agartha 50 mg tablet (further on: Agartha) is used to treat adult patients with type 2 diabetes. It is used when diabetes cannot be controlled by diet and exercise alone. It helps to control the level of sugar in the blood. The doctor will prescribe Agartha either alone or together with certain other antidiabetic medicines which the patient already takes if these have not proved sufficiently effective to control diabetes.

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.

Insulin is a substance which helps to lower the level of sugar in the blood, especially after meals. Glucagon is a substance which triggers the production of sugar by the liver, causing the blood sugar level to rise. The pancreas makes both of these substances.

Agartha works by making the pancreas produce more insulin and less glucagon. This helps to control the blood sugar level. This medicine has been shown to reduce blood sugar, which may help to prevent complications from your diabetes. Even though the patient is now starting a medicine for the diabetes, it is important continuing to follow the diet and/or exercise which has been recommended.

What patients need to know before taking Agartha

Those who are allergic to vildagliptin or any of the other ingredients of this medicine or think they may be allergic to vildagliptin or any of the other ingredients, *should not take this medicine* and should consult their doctor.

Warning and precautions

Patients should talk to their doctor, pharmacist or nurse before taking Agartha if:

- they have type 1 diabetes (i.e. the body does not produce insulin) or if they have a condition called diabetic ketoacidosis,
- they are taking an anti-diabetic medicine known as a sulphonylurea (the doctor may want to reduce the dose of the sulphonylurea when taking it together with Agartha in order to avoid low blood glucose [hypoglycaemia]),

- if having moderate or severe kidney disease (the patient will need to take a lower dose of Agartha),
- if being on dialysis,
- if having liver disease,
- if suffering from heart failure,
- if having or having had a disease of the pancreas.

Those who have previously taken vildagliptin but had to stop taking it because of liver disease, 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 the doctor or nurse. Patients are also advised to pay particular attention to new onset of blisters or ulcers while taking Agartha. Should these occur, the doctor must be consulted promptly.

A test to determine the liver function will be performed before the start of Agartha 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.

Children and adolescents

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

Other medicines and Agartha

If the patient is taking, has recently taken or might take any other medicines, the doctor should be informed. The doctor may wish to alter the patient's dose of Agartha if other medicines are taken such as:

- thiazides or other diuretics (also called water tablets),
- corticosteroids (generally used to treat inflammation),
- thyroid medicines,
- certain medicines affecting the nervous system.

Pregnancy and breast-feeding

Those who are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, consult their doctor for advice before taking this medicine.

You should not use Agartha during pregnancy. It is not known if vildagliptin (the active substance) passes into breast milk. Consequently, patients should not use Agartha if they are breast-feeding or plan to breast-feed.

Driving and using machines

Those who feel dizzy while taking Agartha, ahould not drive or use machines.

Agartha contains lactose

Those who have been told by their doctor that they have an intolerance to some sugars, contact the doctor before taking this medicinal product.

How to take Agartha

This medicine must be taken exactly as the doctor prescribed.

The recommended dose of Agartha varies depending on the general condition of the patients. The doctor will tell the patient exactly how many tablets of Agartha to take. The maximum daily dose is 100 mg.

The recommended dose of Agartha is either:

- if the patient takes Agartha with another medicine called a sulphonylurea: 50 mg daily taken as one dose in the morning,
- if the patient takes Agartha alone, with another medicine called metformin or a glitazone, with a combination of metformin and a sulphonylurea, or with insulin: 100 mg daily taken as 50 mg in the morning and 50 mg in the evening,
- if the patient has moderate or severe kidney disease or if he/she is on dialysis: 50 mg daily in the morning.

The tablet should be swallowed whole with some water.

How long to take Agartha?
- The patient should take Agartha every day for as long as the doctor prescribes it. This treatment may last over a long period of time.
- The doctor will regularly monitor the patient's condition to check that the treatment is having the desired effect.

What to do if more Agartha has been taken than it should have been?

If the patient takes too many Agartha tablets, or if someone else has taken the patient's medicine, the doctor must be consulted straight away**.** Medical attention may be needed. If the person needs to see a doctor or go to the hospital, he/she must take the pack with him/her.

What to do if taking Agartha has been forgotten?

If taking a dose of this medicine has been forgotten, it should be taken as soon as it is remembered. Then the next dose should be taken at the usual time. If it is almost time for the next dose, the missed dose is to be skipped. No double dose must be taken to make up for a forgotten tablet.

May patients stop taking Agartha?

Patients should not stop taking Agartha unless the doctor orders it.

Possible side effects

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

Certain symptoms need immediate medical attention. Patients should stop taking Agartha and see the doctor immediately if experiencing the following side effects.

- Angioedema (rare: may affect up to 1 in 1,000 people). Its symptoms include swollen face, tongue or throat, difficulty swallowing, difficulties breathing, sudden onset 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 back, as well as nausea and vomiting.

Other side effects

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

- Common (may affect up to 1 in 10 people): trembling, headache, dizziness, nausea, low blood glucose.
- Uncommon (may affect up to 1 in 100 people): tiredness.

Agartha and a sulphonylurea:

- Common: trembling, headache, dizziness, weakness, low blood glucose.
- Uncommon: constipation.
- Very rare (may affect up to 1 in 10,000 people): sore throat, runny nose.

Agartha and a glitazone:

- Common: weight increase, swollen hands, ankle or feet (oedema).
- Uncommon: headache, weakness, low blood glucose.

Agartha alone:

- Common: dizziness.
- Uncommon: headache, constipation, swollen hands, ankle or feet (oedema), joint pain, low blood glucose.
- Very rare: sore throat, runny nose, fever.

Some patients have had the following side effects while taking Agartha, metformin and a sulphonylurea:

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

Some patients have had the following side effects while taking Agartha and insulin (with or without metformin):

- 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

This medicinal product does not require any special temperature storage conditions. It should be stored in the original package in order to protect from moisture.

It must be kept out of the sight and reach of children.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Agartha 50 mg tablets. The procedure was finalised at 18 March 2020. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: Latvia, Poland and Romania) concerned the generic version of vildagliptin 50 mg tablets (Agartha tablets).

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Agartha 50 mg tablets (Gedeon Richter Plc).

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 (and reference) product is Galvus® 50 mg tablets by Novartis Europharm Ltd., authorised for marketing since 2007 in the European Union.

Agartha 50 mg tablets are indicated for treatment of type 2 diabetes mellitus in adults.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics.

II. QUALITY ASPECTS

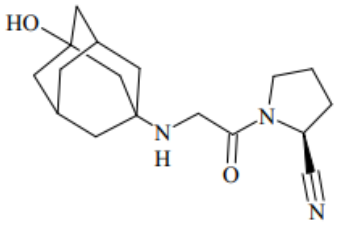
II.1 Introduction

This chemical-pharmaceutical assessment report concerns the application of Agartha 50 mg tablets via decentralized procedure according to Article 10(1) of Directive 2001/83/EC (i.e. generic application). The product has been developed by Gedeon Richter Plc.
The reference product is Galvus 50 mg tablets (containing 50 mg vildagliptin as active ingredient) which was the original products of Novartis Europharm Ltd.

II.2 Drug substance

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

I.N.N.: vildagliptin
Chemical name: (2S)-1-[2-[(3-hydroxy-1-adamantyl)amino]acetyl]pyrrolidine-2-carbonitrile
Structure:



The drug substance is white to yellowish-white or greyish-white crystalline powder. Vildagliptin is 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. It has one asymmetric carbon atom in the molecule, the active substance is the S-enantiomer. It shows polymorphism, the manufacturer consistently produces the correct isomer and the same polymorphic form.

The manufacturer presented complete details of the manufacturing process. Description of the manufacturing process of drug substance is adequate.

Evidence of the structure has been confirmed by NMR, MS and IR analysis as well as TGA, DSC and XRPD spectroscopy. The impurity profile of the substance contains detailed information about genotoxic impurities, residual solvents and catalysts.

As vildagliptin has no European Pharmacopoeia (Ph. Eur.) monograph, in-house specification has been set. General Ph. Eur. methods are used for characterisation, identification by IR, loss on drying and sulphated ash. The specification also includes the following in-house tests: related substances, assay, vildagliptin R-enantiomer content, residual solvents, particle size and

microbiological quality. The specification is in accordance with the Ph. Eur. general monograph on *Substances for pharmaceutical use* and the International Council of Harmonisation (ICH) Q6A guideline.

The specification reflects all relevant quality attributes of the drug substance and was found to be adequate to control its quality. The limits set are properly justified.

Testing methods not described in detail in the pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the drug substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the European Medicines Agency (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 with the following storage restriction: "Store in the original packaging".

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

II.3 Medicinal product

The aim was to develop film-coated tablets containing vildagliptin as drug substance in 50 mg doses, pharmaceutically equivalent and bioequivalent to the reference medicinal product Galvus 50 mg 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.

Agartha 50 mg tablets are white-yellowish to light grey, round, flat tablets with bevelled edges. One side is engraved with "AA3". Diameter: 8 mm.

The excipients used in the finished product are microcrystalline cellulose, lactose, sodium starch glycolate (type A) and magnesium stearate. All excipients used comply with their respective Ph. Eur. monograph. Compliance of the product with the general monograph of the Ph. Eur. 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 24 months is approved with the following storage restriction: "Store in the original package in order to protect from moisture. This medicinal product does not require any special temperature storage conditions."

The Summary of Product Characteristics, Package 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 are well known. As vildagliptin is a widely used, well-known active substance, 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 ingredient.

III.2 Pharmacology

Vildagliptin, a member of the islet enhancer class, is a potent and selective dipeptidyl-peptidase-4 (DPP-4) inhibitor.

The active substance is a well-known compound. No further information was provided regarding the pharmacology of vildagliptin.

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 (ERA)

Since Agartha 50 mg tablets are 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

Abridged applications avoid the need for repetitive tests on animals.

Pharmacodynamics, pharmacokinetics and toxicology of vildagliptin are well-known. As Agartha 50 mg tablets 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 application is submitted in accordance with Article 10(1) of Directive 2001/83/EC as amended.

The clinical pharmacology of vildagliptin is well known.

No clinical study has been submitted by the applicant, since the drug substance of the proposed medicinal product can be considered as a Biopharmaceutical Classification System (BCS) Class I drug, and *in vivo* bioequivalence studies could be exempted.

The application contains an adequate review of published clinical data.

IV.2 Pharmacokinetics

IV.2.1 Literature data

Following oral administration in the fasting state, vildagliptin is rapidly absorbed, with peak plasma concentrations observed at 1.7 hours. Food slightly delays the time to peak plasma concentration to 2.5 hours but does not alter the overall exposure (AUC). Administration of vildagliptin with food resulted in a decreased C_{max} (19%). However, the magnitude of change is not clinically significant, so that Agartha can be given with or without food. The absolute bioavailability is 85%.

The plasma protein binding of vildagliptin is low (9.3%) and vildagliptin distributes equally between plasma and red blood cells. The mean volume of distribution of vildagliptin at steady-state after intravenous administration (V_{ss}) is 71 litres, suggesting extravascular distribution.

Metabolism is the major elimination pathway for vildagliptin in humans, accounting for 69% of the dose. The major metabolite (LAY 151) is pharmacologically inactive and is the hydrolysis product of the cyano moiety, accounting for 57% of the dose, followed by the glucuronide (BQS867) and the amide hydrolysis products (4% of dose). *In vitro* data in human kidney microsomes suggest that the kidney may be one of the major organs contributing to the hydrolysis of vildagliptin to its major inactive metabolite, LAY151. DPP-4 contributes partially to the hydrolysis of vildagliptin based on an *in vivo* study using DPP-4 deficient rats. Vildagliptin is not metabolised by CYP 450 enzymes to any quantifiable extent. Accordingly, the metabolic clearance of vildagliptin is not anticipated to be affected by co-medications that are CYP 450 inhibitors and/or inducers. *In vitro* studies demonstrated that vildagliptin does not inhibit/induce CYP 450 enzymes. Therefore, vildagliptin is not likely to affect metabolic clearance of co-

medications metabolised by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1 or CYP 3A4/5.

Following oral administration of [^{14}C] vildagliptin, approximately 85% of the dose was excreted into the urine and 15% of the dose is recovered in the faeces. Renal excretion of the unchanged vildagliptin accounted for 23% of the dose after oral administration. After intravenous administration to healthy subjects, the total plasma, and renal clearances of vildagliptin are 41 and 13 l/h, respectively. The mean elimination half-life after intravenous administration is approximately 2 hours. The elimination half-life after oral administration is approximately 3 hours.

The C_{max} for vildagliptin and the area under the plasma concentrations (AUC) *versus* time curves increased in an approximately dose proportional manner over the therapeutic dose range.

IV.2.2 Bioequivalence

No clinical study has been performed by the applicant, since the drug substance of the proposed medicinal product can be considered as a BCS Class I drug, and *in vivo* bioequivalence studies could be exempted.

In accordance with the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) in case of highly soluble drug substances with known human absorption that are not considered to have narrow therapeutic index, the BCS-based biowaiver concept is a surrogate for the *in vivo* bioequivalence study. The concept can be applicable to immediate release, solid pharmaceutical products for oral administration and systemic action having the same pharmaceutical form.

As the proposed Test product (vildagliptin 50 mg tablets, i.e. Agartha) and Reference product (Galvus®) contain the same active ingredient, the same qualitative composition was used for the formulation, furthermore considering that vildagliptin is a BCS-I compound and does not to have a narrow therapeutic index, the biowaiver approach can be acceptable. The applicant has proven the high solubility and the high permeability (≥ 85% oral bioavailability according to the originator Galvus®) of the drug substance and introduced the excipients of the proposed product as same used for the Reference product. In addition, dissolution profiles of Test and Reference products can be accepted as similar without any statistical evaluation, since more than 85 % of the active substance dissolved in 15 minutes in all relevant pH media.

According to the above cited guideline, *Appendix III: BCS based biowaiver* requirements are fulfilled and the (BCS-I based) biowaiver can be acceptable from clinical point of view.

Considering all the submitted data and study literature, it may be concluded that vildagliptin has an extent of absorption of 85%, which is generally related to high permeability.

Vildagliptin doses up to 200 mg may be regarded as well tolerated, and the highest therapeutic dose is twice 50 mg/day, therefore the drug substance is not considered to be as narrow therapeutic index drug. The BCS-I classification of vildagliptin may be acceptable according to the bioequivalence guideline in force, as high solubility and high permeability of the active substance was presented, and it is not considered to be as a narrow therapeutic index drug.

Conclusion on bioequivalence

Vildagliptin 50 mg tablets (Agartha, manufactured by Gedeon-Richter-Romania and Gedeon Richter Plc.) can be considered bioequivalent with Galvus 50 mg tablets (manufactured by Novartis Europharm Ltd) according to the requirements of BCS-based biowaiver in Appendix III of the EMEA *Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1/Corr, 2010).

IV.3 Pharmacodynamics

Clinical pharmacology studies to evaluate the pharmacodynamics of Agartha 50 mg tablets were not performed.

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.

IV.5 Clinical safety

The applicant has provided an adequate literature review to describe the safety profile of vildagliptin.

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 Good Pharmacovigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

Summary of safety concerns	
Important identified risks	- Transaminase elevations and Drug-induced liver injury (DILl). - Angioedema. - Acute pancreatitis. - Skin lesions. - Hypoglycaemia.
Important potential risks	- Serious infections. - Cardiac events in Congestive Heart Failure (CHF) (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). - Pregnancy.

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage all safety concerns connected to Richter's product containing 50 mg vildagliptin.

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.
- Skin lesions.
- Hypoglycaemia.
- Muscle events/ myopathy/rhabdomyolysis, in particular with current statin use.
- Pancreatic cancer.

No additional activities are proposed.

Risk Minimisation Measures: routine measures (i.e. wording in Summary of Product Characteristics, Package Leaflet classification as a prescription only medicine) are considered sufficient to manage all safety concerns connected to Richter's product containing 50 mg vildagliptin. 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 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.

IV.7 Discussion on the clinical aspects

The application concerns a generic product.

Abridged applications avoid the need for repetitive tests on humans. For these applications, the bioequivalence proofs described in section IV.2 are pivotal.

To support the application the applicant has adequately demonstrated bioequivalence between Agartha 50 mg tablets and the reference product Galvus 50 mg tablets.

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 present application concerns Agartha 50 mg tablets, generic version of vildagliptin. The applicant and the future holder of authorisation is Gedeon Richter Plc.

The indication is the treatment of type 2 diabetes mellitus in adults.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The reference product was Galvus® 50 mg tablets by Novartis Europharm Ltd.,

To support the application the applicant has adequately justified the BCS-based biowaiver on the basis of bioequivalence guideline (*Appendix III, CPMP/EWP/QWP/1401/98/rev 1/Corr***).

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Agartha 50 mg tablets.

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and user consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

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