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Public Assessment Report

Name of the Product:

Assimil

25 mg film-coated tablet

(agomelatine)

Procedure number: HU/H/0514/001/DC

Marketing authorisation holder: Gedeon Richter Plc.

Date: 7 April 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 Assimil 25 mg film-coated tablets. The holder of the marketing authorisation is Gedeon Richter Plc.

The active substance is agomelatine. Each film-coated tablet contains agomelatine-citric acid co-crystal equivalent to 25 mg of agomelatine.

The other ingredients are silicified microcrystalline cellulose, mannitol, povidone K30, silica colloidal anhydrous, crospovidone (type A), sodium stearyl fumarate, magnesium stearate, stearic acid 50, hypromellose, macrogol 6000, titanium dioxide (E171), talc, iron oxide yellow (E172).

Assimil 25 mg film-coated tablets (further on: Assimil tablets) are yellow, oblong, biconvex, with a dimension of 9 x 4.5 mm. 10 or 14 tablets are packed in OPA/Al/PVC//Al unit-dose blister (the calendar blister contains 14 tablets). The blisters are packed into a cardboard box.

Assimil tablets contains the active ingredient agomelatine. It belongs to a group of medicines called antidepressants. Patients are been given Assimil tablets to treat their depression.

Assimil tablets are used in adults.

Depression is a continuing disturbance of mood that interferes with everyday life. The symptoms of depression vary from one person to another, but often include deep sadness, feelings of worthlessness, loss of interest in favourite activities, sleep disturbances, feeling of being slowed down, feelings of anxiety, changes in weight.

The expected benefits of Assimil tablets are to reduce and gradually remove the symptoms related to the depression.

How to take Assimil tablets

Those,

- who are allergic to agomelatine or any of the other ingredients of this medicine,
- whose liver does not work properly (hepatic impairment).
- who are taking fluvoxamine (another medicine used in the treatment of depression) or ciprofloxacin (an antibiotic)

should not take Assimil tablets.

Warnings and precautions

There could be some reasons why Assimil tablets may not be suitable for a patient:

- if taking medicines known to affect the liver. The doctor should be consulted for advice

on which medicine do this;
- if being obese or overweight, the doctor should be asked for advice;
- if being diabetic, the doctor should be asked for advice;
- if having increased levels of liver enzymes before treatment. The doctor will decide if Assimil tablets are right;
- if having bipolar disorder, having experienced or if developing manic symptoms (a period of abnormally high excitability and emotions). The doctor should be consulted before start taking this medicine or before continuing with this medicine;
- if suffering from dementia. The doctor will make an individual evaluation of whether it is right to take Assimil tablets.

During the treatment with Assimil tablets, what patients should do to avoid serious liver problems

The doctor should have checked that the patient's liver is working properly before starting the treatment. Some patients may get increased levels of liver enzymes in their blood during treatment with Assimil tablets. Therefore, follow-up tests should take place at the following time points:

	before initiation or dose increase	around 3 weeks	around 6 weeks	around 12 weeks	around 24 weeks
Blood tests	x	x	x	x	x

Based on the evaluation of these tests the doctor will decide whether the patient should receive or continue using Assimil tablets.

Patients should be vigilant about signs and symptoms that the liver may not be working properly. If observing any of these signs and symptoms of liver problems: unusual darkening of the urine, light coloured stools, yellow skin/eyes, pain in the upper right belly, unusual fatigue (especially associated with other symptoms listed above), seek urgent advice from a doctor who may advise the patient to stop taking Assimil tablets.

Effect of agomelatine is not documented in patients aged 75 years and older. Assimil tablets should therefore not be used in these patients.

Thoughts of suicide and worsening of your depression

If somebody is depressed, he/she can sometimes have thoughts of harming or killing himself/herself. These may be increased when first starting antidepressants, since these medicines all take time to work, usually about two weeks but sometimes longer.

Patients may be more likely to think like this, if they:

- have previously had thoughts about killing or harming themselves,
- are a young adult. Information from clinical trials has shown an increased risk of

suicidal behaviour in young adults (aged less than 25 years) with psychiatric conditions who were being treated with an antidepressant.

If patients have thoughts of harming or killing themselves at any time, they must contact their doctor or go to a hospital straight away. It may be helpful to confess a relative or close friend that the patient is depressed and ask them to read this leaflet. The patient might ask them to tell him/her if they think the patient's depression is getting worse, or if they are worried about changes in the patient's behaviour.

Children and adolescents

Assimil tablets are not intended for use in children and adolescents (under 18 years old).

Other medicines and Assimil tablets

Patients should tell their doctor if they are taking, have recently taken or might take any other medicines.

Patients should not take Assimil tablets together with certain medicines: fluvoxamine (another medicine used in the treatment of depression), ciprofloxacin (an antibiotic) can modify the expected dose of agomelatine in the blood.

Patients must make sure to tell their doctor if taking also any of the following medicines: propranolol (a beta-blocker used in the treatment of hypertension), enoxacin (antibiotic) and if the patient is smoking more than 15 cigarettes/day.

Assimil tablets with alcohol

It is not advisable to drink alcohol while being treated with Assimil tablets.

Pregnancy and breast-feeding

Those who are pregnant, think they may be pregnant or are planning to have a baby, ask their doctor for advice before taking this medicine. The same is valid for those who are breast-feeding or intending to breast-feed as breast-feeding should be discontinued if taking Assimil tablets.

Driving and using machines

Patients might experience dizziness or sleepiness which could affect their ability to drive or operate machinery. They should make sure that their reactions are normal before driving or operating machines.

How to take Assimil tablets

The recommended dose of Assimil tablets is one tablet (25 mg) at bedtime. In some cases, the doctor may prescribe a higher dose (50 mg), i.e. two tablets to be taken together at bedtime.

Assimil tablets start to act on symptoms of depression in most depressed people within two weeks of starting treatment. The doctor may continue to prescribe Assimil tablets when the patient is feeling better to prevent the depression from returning.

The depression should be treated for a sufficient period of at least 6 months to ensure that the patient is free of symptoms.

Patients should not stop taking this medicine without the advice of the doctor even if they feel better.

Assimil tablets are for oral use. The tablet should be swallowed with a drink of water.

Assimil tablets can be taken with or without food.

How to switch from an antidepressant medicine (SSRI/SNRI) to Assimil tablets?

If the doctor changes the previous antidepressant medicine from an SSRI or SNRI to Assimil tablets, he/she will advise the patient on how the previous medicine should be discontinued when starting Assimil tablets.

The patient may experience discontinuation symptoms related to stopping of the previous medicine for a few weeks, even if the dose of the previous antidepressant medicine is decreased gradually.

Discontinuation symptoms include the followings: dizziness, numbness, sleep disturbances, agitation or anxiety, headaches, feeling sick, being sick and shaking. These effects are usually mild to moderate and disappear spontaneously within a few days.

If Assimil tablets are initiated while tapering the dosage of the previous medicine, possible discontinuation symptoms should not be confounded with a lack of early effect of Assimil tablets.

Patients should discuss with their doctor on the best way of stopping their previous antidepressant medicine when starting Assimil tablets.

Surveillance of the liver function

The doctor will run laboratory tests to check that patient’s liver is working properly before starting treatment and then periodically during treatment, usually after 3 weeks, 6 weeks, 12 weeks and 24 weeks.

If the doctor increases the dose to 50 mg, laboratory tests should be performed at this initiation and then periodically during treatment, usually after 3 weeks, 6 weeks, 12 weeks and 24 weeks. Thereafter tests will be taken if the doctor finds it necessary. Patients whose liver does not work properly must not use Assimil tablets.

If the patient has trouble with the kidneys, the doctor will make an individual evaluation of whether it is safe for him/her to take Assimil tablets.

What to do if more Assimil tablets have been taken than it should have been?

If patients have taken more Assimil tablets than they should, or if for example a child has taken medicine by accident, the doctor must be contacted immediately.

The experience of overdoses with agomelatine is limited but reported symptoms include pain in the upper part of the stomach, somnolence, fatigue, agitation, anxiety, tension, dizziness, cyanosis or malaise.

What to do if taking Assimil tablets has been forgotten?

The patient should not take a double dose to make up for a forgotten dose. Just carry on with the next dose at the usual time.

The calendar printed on the blister containing the tablets should help remembering when the last Assimil tablet has been taken.

May patients stop taking Assimil tablets?

Patients should discuss with their doctor before stopping this medicine.

If patients think that the effect of Assimil tablets is too strong or too weak, talk to their doctor.

Possible side effects

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

Most side effects are mild or moderate. They usually occur within the first two weeks of the treatment and are usually temporary.

These side effects include:

- Very common side effect (may affect more than to 1 in 10 people): headache.
- Common side effects (may affect up to 1 in 10 people): dizziness, sleepiness (somnolence), difficulty in sleeping (insomnia), feeling sick (nausea), diarrhoea, constipation, abdominal pain, back pain, tiredness, anxiety, abnormal dreams, increased levels of liver enzymes in your blood, vomiting, weight increased.
- Uncommon side effects (may affect up to 1 in 100 people): migraine, pins and needles in the fingers and toes (paraesthesia), blurred vision, restless legs syndrome (a disorder that is characterized by an uncontrollable urge to move the legs), ringing in the ears, excessive sweating (hyperhidrosis), eczema, pruritus, urticaria (hives), agitation, irritability, restlessness, aggressive behaviour, nightmares, mania/hypomania, suicidal thoughts or behaviour, confusion, weight decreased.
- Rare side effects (may affect up to 1 in 1,000 people): serious skin eruption (erythematous rash), face oedema (swelling) and angioedema (swelling of the face, lips, tongue

and/or throat that may cause difficulty in breathing or swallowing), hepatitis, yellow coloration of the skin or the whites of the eyes (jaundice), hepatic failure, hallucinations, inability to remain still (due to physical and mental unrest), inability to completely empty the bladder.

How to store Assimil tablets

This medicine does not require any special temperature storage conditions. Store it in the original package in order to protect from moisture and keep it out of the sight and reach of children.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Assimil 25 mg film-coated tablet, The procedure was finalised at 3 August 2018. 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 state, CMS: the Czech Republic) concerned the generic version of agomelatine 25 mg tablets (Assimil tablets).

The application has been filed 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 Valdoxan 25 mg film-coated tablets by Les Laboratoires Servier, France, authorised for marketing via centralised procedure since February 2009.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Assimil 25 mg film-coated tablets from Gedeon Richter Plc., Hungary.

The product is indicated for the treatment of major depressive episodes in adults.

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

II. QUALITY ASPECTS

II.1 Introduction

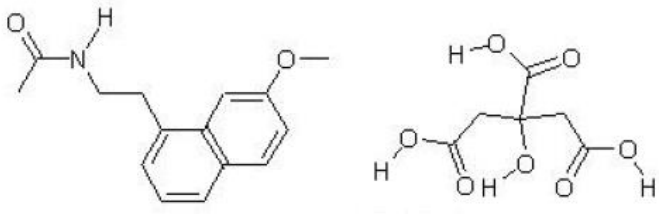
This chemical-pharmaceutical assessment report concerns the application of Assimil 25 mg film-coated tablets via a decentralized procedure according to Article 10(1) of Directive 2001/83/EC (i.e a generic application).

The reference product is Valdoxan 25 mg film-coated tablets (containing 25 mg agomelatine as active ingredient) which is the original product of Les Laboratoires Servier.

II.2 Drug substance

Data on the quality and manufacture of the active substance were provided in the submission using the Active Substance Master File (ASMF) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

Chemical name: co-crystal of *N*-[2-(7-methoxynaphthalen-1-yl)ethyl]acetamide and 2-hydroxy-1,2,3-propanetricarboxylic acid (1:1).
Structure:



The active substance is non- hygroscopic white or almost white powder, freely soluble in methanol, ethanol, acetone and tetrahydrofuran, soluble in 2-propanol and methylethylketone, unstable in water (decomposition to individual components). The manufacturer consistently produces the correct crystal form.

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

Evidence of the structure has been confirmed by FT-IR, UV, NMR, MS and XRD spectroscopy. The impurity profile of the drug substance contains detailed information about genotoxic impurities, residual solvents and catalysts.

Agomelatine citric acid co-crystal is not official in the European Pharmacopoeia (Ph. Eur.) Therefore, an in-house specification has been set for the active substance, which includes the following tests: appearance, identification by IR and XRDP, related substances, sulphated ash, water content, loss on drying, assay, residual solvents and microbiological purity. 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 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 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 no special storage condition.

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

II.3 Medicinal product

The aim of the development was to develop a generic drug product, agomelatine film-coated tablets (agomelatine expressed as a co-crystal with citric acid), which would be pharmaceutically equivalent and bioequivalent to Valdoxan film-coated tablets, the branded original products of Les Laboratoires Servier.

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: yellow, oblong, biconvex film-coated tablet with a dimension of 9 x 4.5 mm.

The excipients used in the finished product are silicified microcrystalline cellulose, mannitol, povidone K30, colloidal anhydrous silica, crospovidone (type A), sodium stearyl fumarate, magnesium stearate, stearic acid 50 and film-coating (Hypromellose, macrogol 6000, titanium dioxide (E171), talc and yellow iron oxide (E172)). All excipients used comply with their respective Ph. Eur. monographs. 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 International Council of Harmonization (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 unit-dose blister (calendar 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 2 years 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 agomelatine are well known. As agomelatine 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

Agomelatine, a structural analogue to melatonin (beta-methyl-6 chloromelatonin), acts as an agonist at melatonergic MT1 and MT2 receptors as well as an antagonist at the serotonergic 5 HT2C receptor, but does not affect monoamine uptake and adrenergic, histaminergic, cholinergic, dopaminergic and benzodiazepine receptors. Agomelatine increases noradrenaline and dopamine release specifically in the frontal cortex and has no influence on the extracellular levels of serotonin. It has also been shown to resynchronise circadian rhythms in animals.

By avoiding 5-HT2A stimulation, agomelatine shows a more favourable side-effect profile compared SSRIs, concerning sexual functioning, weight-gain and gastrointestinal disturbances without exhibiting discontinuation symptoms.

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

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 Assimil 25 mg film-coated 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 and humans.

Pharmacodynamics, pharmacokinetics and toxicology of agomelatine are well-known. As Assimil 25 mg film-coated 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 clinical pharmacology of agomelatine is well known.

Except for demonstrating bioequivalence, no specific clinical studies have been performed, as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EC as amended.

The application contains an adequate review of published clinical data.

IV.2 Pharmacokinetics

IV.2.1 Literature data

Absorption

After oral administration, agomelatine is rapidly and well (≥ 80%) absorbed, reaching peak plasma concentration at 1 - 2 h. After a single dose, considerable inter-individual variability was observed in plasma concentrations. Absolute bioavailability of a therapeutic oral dose is low (approximately 1%, in any case < 5%) due to its high first-pass metabolism. Large inter-individual and intra-individual differences are explained by highly variable CYP1A2 activity.

Food intake reduces the C_{max} by approximately 20 - 30%, but it does not modify overall absorption extent.

Dose linearity: in the therapeutic dose, systemic exposure increases proportionally with dose. With supra-therapeutic doses (from 200 to 1200 mg) a saturation of the first-pass effect occurs.

Distribution

Steady-state volume of distribution corresponds to 35 l. Plasma protein binding (albumin and a α-acid glycoprotein) is > 95% independent on agomelatine plasma concentration. Agomelatine has been found in the breast milk in a patient suffering from a depressive syndrome within a postpartum psychosis. Peak levels of agomelatine in the breast milk were reached 1 - 2 h after medication. On all 3 days, no traces of the drug were detected 4 h after medication.

Metabolism and Elimination

Following oral administration, agomelatine is rapidly metabolised (oxidised) mainly via hepatic cytochrome CYP 4501A2 (90%); CYP2C9 and CYP2C19 are also involved but with minor contribution (10%).

The drug is metabolised by 7-O-demethylation (leading to S-21517), hydroxylation (mainly leading to S-21540) and the formation of 3,4-dihydrodiol (S-22380). The major metabolites represent approximately 61–81% of the dose excreted in urine over the first 24 hours, unchanged compound finding in urine is negligible. A smaller amount of agomelatine is excreted faecally. The metabolites are not significantly pharmacologically active. Before elimination metabolites are conjugated with glucuronic acid and sulfonated. Elimination is rapid, the mean plasma half-life is 2.3 h and the clearance is high (about 1100 ml/min). This is unaffected by repeated dosing and there is no evidence of drug accumulation or autoinduction.

IV.2.2 Bioequivalence studies

One pilot and one pivotal bioequivalence studies have been performed in healthy adult human subjects under fasting conditions according to the bioequivalence guideline in force (*Guideline on Investigation of Bioequivalence* CPMP/EWP/QWP/1401/98/rev 1/Corr** 2010). The reference product was Valdoxan® 25 mg tablets (agomelatine, manufactured by Les Laboratoires Servier, France).

The active ingredient of the reference and test products are not the same – namely agomelatine form II versus agomelatine co-crystal. Submitting of bioequivalence studies with Valdoxan reference product is acceptable because according to the above guideline "..the different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy..". In addition, the *Reflection paper on the use of cocrystals of active substances in medicinal products* EMA/CHMP/CVMP/QWP/284008/2015 states the following: „Cocrystals, hydrates and solvates are held together by weak interactions that are in most cases broken upon dissolution. This is the same situation as with salts. Hence, with respect to oral administration, dissolution of such different forms of a drug substance in the stomach or the intestinal canal will lead to the release of the same substance, independent on the form that was taken in. The validity of this assumption is verified by the demonstration of bioequivalence. Cocrystals, hydrates and solvates will therefore be considered eligible for generic applications in the same way as salts are (Article 10(2)(b) of Directive 2001/83/EC and Article 13(2)(b) of Directive 2001/82/EC) unless they differ with respect to safety and/or efficacy."

The studies were conducted in compliance with the requirements of guideline on Good Clinical Practice ICH Topic E6 (R1) (CPMP/ICH/135/95) and ethical principles stated in the last revision of Declaration of Helsinki. The study sites had been inspected by an EU authority prior to the studies. These inspections were ended with acceptable results.

Pilot study

The aim of the study was to study 4 different formulations of Test preparations to determine their bioequivalence with the reference product. It was a randomized, open label, single dose, explorative bioavailability study.

Subjects were administered the Test- and Reference medications (as per the randomisation scheme) as a single oral dose of 1 film-coated tablet.

Pharmacokinetic parameters applied were:
• primary: $AUC_{(0-t)}$, C_{max},
• other: T_{max} , $AUC_{0-\infty}$.

Bioequivalence criteria: a Test and the Reference products can be considered bioequivalent, when the ln-transformed Test/Reference least-squares mean ratios and their 90% confidence intervals of the C_{max} and $AUC_{(0-t)}$ parameter fall entirely within the acceptance interval of 80.00 - 125.00% for agomelatine.

On the basis of the results the best formulation was selected for further studies.

Safety: no death or serious adverse events occurred during the study. Safety profiles of the Test and Reference products were comparable.

Pivotal study

Main objective of this study was to compare the rate and extent of absorption of agomelatine of the selected Test- and Reference products administered to healthy volunteers in a single dose, under fasting conditions. It was a single-dose, randomized, open-label, crossover study in healthy adult male and female subjects under fasting condition. The Test- and Reference products were administered as a single oral dose with 240 mL of water.

Pharmacokinetic parameters determined were:
• primary: $AUC_{(0-t)}$, C_{max},
• Other: T_{max}, $AUC_{(0-\infty)}$, $t_{1/2}$, λ_z, Residual area (%).

Statistical methods used in evaluations were:
descriptive statistics of pharmacokinetic parameters: arithmetic mean, standard deviation, minimum, maximum, median, CV%, geometric LS (least squares) means for test and reference pharmacokinetic data,
log-transformation of AUC and C_{max} data,
calculation of 90% confidence intervals for the difference between the least square means for primary parameters (at $\alpha = 0.05$ significance level),
applying non-parametric analysis of T_{max} on untransformed data,
descriptive statistics of safety data collected during the whole study period

Bioequivalence criteria: Test product can be considered bioequivalent to the Reference product, when the ln-transformed Test/Reference least-squares mean ratios and their 90% confidence intervals of the $AUC_{(0-t)}$ and C_{max} parameters fall entirely within the acceptance interval of 80.00 - 125.00% for agomelatine.

Summary of bioequivalence evaluation:

Pharmacokinetic parameter	Ratio T/R	Confidence interval	CV_{intra} %
$AUC_{(0-t)}$	100.59	95.98 – 105.42	28.81
C_{max}	99.08	91,90 – 106.82	47.70

*Safety results:*no death, serious or significant or unexpected adverse events occurred during the study. Overall, the drugs investigated were well tolerated by all subjects included in the study.

Conclusion on bioequivalence studies

On the basis of results of the pivotal bioequivalence study single dose of the applicant's agomelatine 25 mg film-coated tablets and Valdoxan® 25 mg film-coated tablets (manufactured by Les Laboratoires Servier, France) are bioequivalent in healthy adult human subjects under fasting conditions.

IV.3 Pharmacodynamics

Clinical pharmacology studies to evaluate the pharmacodynamics of Assimil 25 mg Film-coated 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 agomelatine.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence studies, no new safety data were submitted, and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data.

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

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 Vigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

Summary of safety concerns	
Important identified risks	1. Hepatotoxic reactions. 2. Interactions with potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin).
Important potential risks	3. Suicide.
Missing information	4. Paediatric age group (<18 years old). 5. Elderly (≥75 years). 6. Pregnancy. 7. Lactation. 8. Severe or moderate renal impairment.

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Richter's product containing agomelatine. No additional activities are proposed.

Risk Minimisation Measures: routine measures (i.e. wording in Summary of Product Characteristics, Package Leaflet and classification as a prescription-only medicine) are not considered sufficient to manage all of the safety concerns connected to connected to Richter's product containing agomelatine.

Similarly to the originator's product (Valdoxan), Assimil 25 mg film-coated tablet has educational materials for the risk of "Hepatotoxic reactions" for physicians (Physician's guide) and for the patients (Patient's booklet). The Physician's guide should include information relating to the risk of +Interactions with potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin)" as well.

The *Physician's guide* contains the following key messages:
- The need to inform patients about the potential risk of transaminases elevations, the risk of liver injury and interactions with potent CYP 1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin).

- The need to perform liver function tests in all patients before starting treatment and periodically thereafter around three, six (end of acute phase), twelve and twenty-four weeks (end of maintenance phase), and thereafter when clinically indicated.
- The need to perform liver function tests at the same frequency as at treatment initiation in all patients where the dosage is increased.
- Guidance in case of clinical symptoms of hepatic dysfunction.
- Guidance in case of liver function test abnormality.
- Caution should be exercised when therapy is administered to patients with pre-treatment elevated transaminases (> the upper limit of the normal ranges and < 3 times the upper limit of the normal range).
- Caution should be exercised when therapy is prescribed for patients with hepatic injury risk factors e.g. obesity/overweight/non-alcoholic fatty liver disease, diabetes, alcohol use disorder and /or substantial alcohol intake or concomitant medicinal products associated with risk of hepatic injury.
- Contra-indication in patients with hepatic impairment (i.e. cirrhosis or active liver disease).
- Contraindication in patients with transaminases exceeding 3 X upper limit of normal.
- Contra-indication in patients receiving concomitantly potent CYP1A2 inhibitors.
- The Marketing Authorisation Holder shall ensure that all physicians who are expected to prescribe or use the product, are provided with patient booklets to be distributed to their patients being prescribed this medicine.

The *Patient's Booklet* contains the following key messages:
- Information about the risk of hepatic reactions and clinical signs of liver problem.
- A guidance on the scheme of hepatic monitoring.
- A blood tests appointments reminder.

IV.6.3 Periodic Safety Update Reports

The marketing authorisation holder (MAH) shall submit the first periodic safety update report for this product with a period of 5 years following authorisation. Further, the MAH shall continuously check the European medicines web-portal if the active substance has been included in the list of Union reference dates (EURD list). If yes, after publication in the EURD list the periodic safety update reports shall be submitted in accordance with the requirements set out in the EURD list.

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 studies described in section IV.2 are pivotal.

On the basis of results of the pivotal bioequivalence study carried out a single dose of the Assimil 25 mg film-coated tablets and the reference product Valdoxan® 25 mg film-coated

tablets (manufactured by Les Laboratoires Servier, France) are bioequivalent in healthy adult human subjects under fasting conditions.

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 applications concern Assimil 25 mg film-coated tablets, generic versions of agomelatine. The applicant and the future holder of authorisation is Gedeon Richter Plc.

The product is indicated for the treatment of major depressive episodes in adults.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The reference product was Valdoxan 25 mg film-coated tablets (Les Laboratories Servier).

To support the application the applicant has adequately established bioequivalence between the product applied for and the reference product.

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 Assimil 25 mg film-coated 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
IB C.1.x. Changes in the Summary of Product Characteristics and Package Leaflet in order to harmonize the relevant section of documents in line with the appearance of the blister	HU/H/0514/001/IB/001 OGYÉI/54950/2018	yes	08. 11. 2018	08. 12. 2018	approval	no
IB C.1.2.a Changes in the relevant section of the Summary of Product Characteristics and Package Leaflet following assessment of the same changes for the reference product	HU/H/0514/001/IB/001 OGYÉI/17640/2018	yes	17. 04. 2019	17. 05. 2019	approval	no