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Public Assessment Report

Name of the Product:

Restigulin

10 mg, 15 mg and 30 mg film-coated tablets

(aripiprazole)

Procedure number: HU/H/0371/001-003/DC

Marketing authorisation holder: Gedeon Richter Plc.

Date: 8 July 2015

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Restigulin 10 mg, 15 mg and 30 mg film-coated tablets. The holder of the marketing authorisation is Gedeon Richter Plc.

The active substance is aripiprazole. Each tablet contains either 10 mg, 15 mg or 30 mg aripiprazole.

The other ingredients are lactose monohydrate, microcrystalline cellulose, maize starch, and hydroxylpropyl cellulose and magnesium stearate.

The 10 mg tablets are white or almost white, oval, biconvex ones marked with „N74" on one side, and score line on the other side. Their length is 8.5 mm, width is 5 mm. This tablet can be divided into equal doses.

The 15 mg tablets are white or almost white, round, biconvex ones marked with "N75" on one side and without marking on the other side. Their diameter is 7 mm.

The 30 mg tablets are white or almost white, round, biconvex ones marked with "N77" on one side and without marking on the other side. Their diameter is 9 mm.

The tablets are packed in PA/Aluminium/PVC/Aluminium blister. The blisters are packed into folded carton box with a patient leaflet.

Aripiprazole belongs to a group of medicines called antipsychotics. It is used to treat adults and adolescents aged 15 years and older who suffer from a disease characterised by symptoms such as hearing, seeing or sensing things which are not there, suspiciousness, mistaken beliefs, incoherent speech and behaviour and emotional flatness. People with this condition may also feel depressed, guilty, anxious or tense.

Aripirazole is used to treat adults and adolescents aged 13 years and older who suffer from a condition with symptoms such as feeling "high", having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas and sometimes severe irritability. In adults it also prevents this condition from returning in patients who have responded to the treatment with Restigulin tablets.

What patients need to know before taking Restigulin tablets?

Those who are allergic to aripiprazole or any of the other ingredients of this medicine should not take Restigulin tablets.

Warnings and precautions

Patients suffering from any of the following sicknesses should consult their doctor before taking Restigulin tablets:
- high blood sugar (characterised by symptoms such as excessive thirst, passing of large amounts of urine, increase in appetite, and feeling weak) or family history of diabetes,
- seizure,
- involuntary, irregular muscle movements, especially in the face,
- cardiovascular diseases, family history of cardiovascular disease, stroke or "mini" stroke, abnormal blood pressure,
- blood clots, or family history of blood clots, as antipsychotics have been associated with formation of blood clots,
- past experience of excessive gambling.

If the patient notices gaining weight, developing unusual movements, or he/she experiences somnolence that interferes with normal daily activities, any difficulty in swallowing or allergic symptoms, must consult the doctor.

If the patient is an elderly patient suffering from dementia (loss of memory and other mental abilities), he/she or the carer/relative should tell the doctor if the patient has ever had a stroke or "mini" stroke.

The doctor must be informed immediately if the patient has any thoughts or feelings about hurting himself/herself. Suicidal thoughts and behaviours have been reported during aripiprazole treatment.

The doctor must be informed immediately if the patient suffers from muscle stiffness or inflexibility with high fever, sweating, altered mental status, or very rapid or irregular heartbeat.

Children and adolescents

Restigulin tablets are not for use in children and adolescents under 13 years.

Other medicines and Restigulin tablets

The doctor should be informed if the patient is taking, has recently taken or might take any other medicines.

Blood pressure-lowering medicines: Restigulin tablets may increase the effect of medicines used to lower the blood pressure.

Taking Restigulin tablets with some medicines may need to change its dose. It is especially important to mention the following to the doctor:
- medicines to correct heart rhythm,
- antidepressants or herbal remedy used to treat depression and anxiety,
- antifungal agents,
- certain medicines to treat HIV infection,
- anticonvulsants used to treat epilepsy.

Medicines that increase the level of serotonin are triptans, tramadol, tryptophan, SSRIs (such as paroxetine and fluoxetine), tricyclics (such as clomipramine, amitriptyline), pethidine, St John's Wort and venlafaxine. These medicines increase the risk of side effects; if the patient gets any unusual symptom taking any of these medicines together with Restigulin tablets, the doctor should be informed.

Restigulin tablets with food, drink and alcohol

Restigulin tablets can be taken regardless of meals, however, alcohol should be avoided.

Pregnancy, breast-feeding and fertility

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

The following symptoms may occur in new-born babies, of mothers that have used Restigulin tablets in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding. If the baby develops any of these symptoms, the doctor may need to be contacted.

Women must be sure to tell their doctor immediately if they are breast-feeding. Those who are taking Restigulin tablets should not breast-feed.

Driving and using machines

Patients should not drive or use any tools or machines, until they know how Restigulin tablets affect them.

Restigulin tablets contain lactose

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

How to take Restigulin tablets?

The recommended dose for adults is 15 mg once a day. However, the doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

Use in children and adolescents above 13 years

Aripiprazole may be started at a low dose (2 mg) for 2 days. For this starting dose aripiprazole-containing oral solution 1 mg/ml (liquid) form should be used.

It means that the right dosage in adolescents at the beginning of the therapy (2 mg/day for 2 days) with Restigulin 10 mg, 15 mg and 30 mg tablets cannot be ensured. Appropriate formu-

lation (e.g. the mentioned 1 mg/ml solution) of Restigulin is not available. An alternative product with the same active ingredient should be used.

After the first 2 days, the recommended dose is higher (5 mg), which is already available using half of the tablet of Restigulin 10 mg. This dosage is recommended for another 2 days.

After these steps, the dose may be gradually increased to the recommended dose for adolescents of Restigulin tablets 10 mg once a day. However, the doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

The 10 mg tablet can be divided into two equal doses.

Patients should try to take the Restigulin tablets at the same time each day. It does not matter whether it is taken it with or without food but they should always be taken with water and swallow it whole.

Patients are discouraged to *alter or discontinue* the daily dose of Restigulin tablets even if they feel better without first consulting their doctor.

What to do if more Restigulin tablets have been taken then prescribed?

Patients realising that they you have taken more Restigulin tablets than the doctor has recommended (or if someone else has taken some of their tablets), should contact their doctor right away. If the doctor cannot be reached, the nearest hospital should be visited presenting also the pack of the tablets.

What to do if taking Restigulin tablets was forgotten?

Realising a missing dose, the patient should take it as soon as possible but two doses in one day should not be taken.

Possible side effects

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

Common side effects (that may affect up to 1 in 10 people): uncontrollable twitching or jerking movements, headache, tiredness, nausea, vomiting, an uncomfortable feeling in the stomach, constipation, increased production of saliva, light-headedness, trouble sleeping, restlessness, feeling anxious, sleepiness, shaking and blurred vision.

Uncommon side effects (that may affect up to 1 in 100 people): some people may feel dizzy, especially when getting up from a lying or sitting position, or may experience a fast heart rate or double vision., increased blood levels of the hormone prolactin. Some people may feel depressed.

The following side effects have been reported since the marketing of aripiprazole tablets but the frequency for them to occur is not known (the frequency cannot be estimated from the available data): changes in the levels of some blood cells; unusual heartbeat, sudden unexplained death, heart attack; allergic reaction (e.g. swelling in the mouth, tongue, face and throat, itching, rash); high blood sugar, onset or worsening of diabetes, ketoacidosis (ketones in the blood and urine) or coma, low sodium level in the blood; weight gain, weight loss, anorexia; nervousness, agitation, feeling anxious, excessive gambling; thoughts of suicide, suicide attempt and suicide; aggression; speech disorder, seizure, serotonin syndrome (a reaction which may cause feelings of great happiness, drowsiness, clumsiness, restlessness, feeling of being drunk, fever, sweating or rigid muscles), combination of fever, muscle stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and heart rate; fainting, high blood pressure, blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through blood vessels to the lungs causing chest pain and difficulty in breathing (if any of these symptoms is noticed, seek medical advice immediately); spasm of the muscles around the voice box, accidental inhalation of food with risk of pneumonia, difficulty in swallowing; inflammation of the pancreas; liver failure, inflammation of the liver, yellowing of the skin and white part of eyes, reports of abnormal liver test values, abdominal and stomach discomfort, diarrhoea; skin rash and sensitivity to light, unusual hair loss or thinning, excessive sweating; stiffness or cramps, muscle pain, weakness; involuntary loss of urine, difficulty in passing urine; prolonged and/or painful erection; difficulty controlling core body temperature or overheating, chest pain, and swelling of hands, ankles or feet.

In elderly patients with dementia, more fatal cases have been reported while taking aripiprazole. In addition, cases of stroke or "mini" stroke have been reported.

Additional side effects in children and adolescents

Adolescents aged 13 years and older experienced side effects that were similar in frequency and type to those in adults except that sleepiness, uncontrollable twitching or jerking movements, restlessness, and tiredness were very common (greater than 1 in 10 patients) and upper abdominal pain, dry mouth, increased heart rate, weight gain, increased appetite, muscle twitching, uncontrolled movements of the limbs, and feeling dizzy, especially when getting up from a lying or sitting position, were common (greater than 1 in 100 patients).

How to store {(Invented) Name}

This medicine does not require any special temperature storage conditions. Keep the blister in the outer carton in order to protect from light.

Keep this medicine out of the sight and reach of children.

Scientific discussion

during the initial procedure

This module reflects the scientific discussion for the approval of Restigulin 10 mg, 15 mg and 30 mg film-coated tablets. The procedure was finalised at 28 April 2015. 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: Bulgaria, the Czech Republic, Poland, Romania and the Slovak Republic) concerned the generic version of aripiprazole 10 mg, 15 mg and 15 mg tablets.

The products are indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older, for moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in adults, and in the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.

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

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Restigulin 10 mg, 15 mg, 30 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 and reference products.

The originator/reference products are Abilify 10 mg, 15 mg and 30 mg tablets marketed by Otsuka Pharmaceutical Europe Ltd. approved for more than 10 years within the European Economic Area.

II. QUALITY ASPECTS

II.1 Introduction

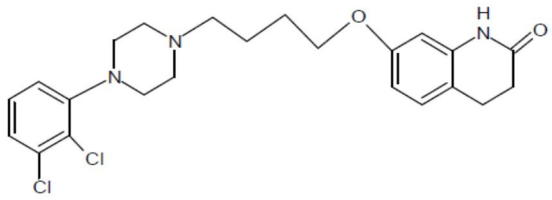
The chemical-pharmaceutical assessment report concerns the application of Restigulin 10 mg, 15 mg and 30 mg tablets via a decentralized procedure according to Article 10(1) of Directive 2001/83/EC (i.e. a generic application). The products have been developed by Gedeon Richter Plc.

The reference products are Abilify 10 mg, 15 mg, 30 mg tablets (containing 10, 15 and 30 mg aripiprazole, as active ingredient, respectively) which were the original products of Otsuka Pharmaceutical Europe Ltd.

II.2 Drug substance

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

Recommended international non-proprietary name (rINN):
aripiprazole
Chemical name: 7-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydroquinolin-2(1*H*)-one.
Structure:



The active substance is white or almost white crystals or crystalline powder; not hygroscopic; practically insoluble in water, soluble in methylene chloride, very slightly soluble in ethanol (96 %). The molecule has no chiral centre, and does not exhibit stereoisomerism. It shows poly-morphism, the manufacturer consistently produces the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the active pharmaceutical ingredient (API) is adequate.

Evidence of the structure has been confirmed by spectroscopy (FT-IR, UV, ^{1}H-NMR, ^{13}C-NMR), mass spectrometry (MS) and elemental analysis. The discussion of the impurity profile of the API contains detailed information about genotoxic impurities, residual solvents and catalysts.

The substance is specified according to the requirements of the current European Pharmacopoeia (Ph. Eur.) monograph. Additional specification has only been set for residual solvents, certain related substances and particle size distribution.

The specification is in accordance with the Ph. Eur. monograph of aripiprazole, the Ph. Eur. general chapter No. 2034 on *Substances for pharmaceutical use* and with the International Conference on Harmonisation (ICH) Q6A, ICH Q3A (R2) guidelines.

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 satisfactorily 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 the restriction “Store below 25°C”.

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

II.3 Medicinal product

The aim was to develop tablets containing aripiprazole as drug substance in 10, 15 and 30 mg doses that are pharmaceutically equivalent and bioequivalent to the reference medicinal product Abilify 10 mg, 15 mg, 30 mg tablets, the branded original products of Otsuka Pharmaceutical Europe 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, composition and packaging was obtained.

Restigulin 10 mg tablets are white or almost white, oval, biconvex ones with engraving “N74”

on one side, and score line on the other side. Their length is 8.5 mm, width is 5 mm. The 10 mg tablets can be divided into two equal doses.

Restigulin 15 mg tablets are white or almost white, round, biconvex ones with engraving "N75" on one side, without engraving on the other side. Their diameter is 7 mm.

Restigulin 30 mg tablets are white or almost white, round, biconvex ones with engraving "N77" on one side, without engraving on the other side. Their diameter is 9 mm.

The excipients used in the finished product are lactose monohydrate, microcrystalline cellulose, maize starch, hydroxypropylcellulose, magnesium stearate, and purified water (which does not appear in the finished product). 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 PA/Al/PVC//Al blister and box. 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 with the storage condition **"**This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from light" is approved.

The Summary of Product Characteristics, the Patient Information Leaflet (PIL, 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 quality points of view the products are approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of aripirazole are well known. As aripirazole is a widely used, well-known active substance, no further non-clinical 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, aripiprazole.

III.2 Pharmacology

The drug product Restigulin contains as active substance aripiprazole. It is an antipsychotic drug. The efficacy of aripiprazole in schizophrenia and Bipolar I Disorder is mediated through a combination of partial agonism at dopamine D2 and serotonin 5HT1a receptors and antagonism of serotonin 5HT2a receptors. 'Partial agonist' properties means that aripiprazole acts like dopamine and 5-hydroxytryptamine by activating these receptors, but less strongly than the neurotransmitters. Aripiprazole helps to normalise the activity of the brain, reducing psychotic or manic symptoms and preventing them from returning. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.
The active substance is a well-known compound. No further information was provided regarding the pharmacology of aripiprazole.

III.3 Pharmacokinetics

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

III.4 Toxicology

Published information on toxicological studies with aripiprazole was the basis for the evaluation.

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 Restigulin 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 aripiprazole are well-known. As Restigulin film-coated tablets are generic products, 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 aripiprazole is well known.

Except for establishing 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

Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3-5 hours after dosing. Aripiprazole undergoes minimal pre-systemic metabolism. The absolute oral bioavailability of the tablet formulation is 87%. There is no effect of a high fat meal on the pharmacokinetics of aripiprazole.

Aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4.9 l/kg, indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and dehydro-aripiprazole are greater than 99% bound to serum proteins, binding primarily to albumin.

Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on in vitro studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicinal product moiety in systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

The mean elimination half-lives for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6.

The total body clearance of aripiprazole is 0.7 ml/min/kg, which is primarily hepatic.

Following a single oral dose of [14C]-labelled aripiprazole, approximately 27% of the administered radioactivity was recovered in the urine and approximately 60% in the faeces. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% was recovered unchanged in the faeces.

IV.2.2 Bioequivalence study

The development studies focused on obtaining products having similar characteristics to the reference products, Abilify tablets (marketed by Otsuka Pharmaceutical Europe Ltd.,), i.e. dissolution profile and bioavailability.

Biowaiver

The applicant claimed for biowaiver for the 15 mg and 30 mg dose strengths on the basis of general biowaiver requirements (CPMP/EWP/QWP/1401/98 Rev 1 Corr**) in order to apply the results of the bioequivalence study done with the 10 mg dose strength to the other strengths. The requirements met were as follows:

a) All the three strengths (10, 15 and 30 mg) of proposed pharmaceutical products are manufactured by the same manufacturer and using the same manufacturing process.
b) The qualitative composition of Aripiprazole 15 mg and 30 mg tablets is same as that of Aripiprazole 10 mg tablets.
c) The composition of all the strengths are quantitatively proportional, i.e. the ratio between the amounts of each excipient to the amount of active substance is the same for all the three strengths.
d) The in-vitro dissolution profiles are similar under identical conditions for the additional strengths i.e. 15 mg and 30 mg, the strength of batch used in the bioequivalence study (i.e. 10 mg) and reference.
e) Aripiprazole has linear pharmacokinetics in the therapeutic dose range (5 - 30 mg).

The biowaiver claim for 15 mg and 30 mg dose-strengths is justified as general requirements for biowaiver are completely fulfilled.

Bioequivalence study

It was a single-dose, open, randomised, two-way, cross-over bioequivalence study between Aripiprazole 10 mg tablets (Gedeon Richter Plc., Test) and Abilify 10 mg tablets (marketed by Otsuka Pharmaceutical Europe Ltd., manufactured by Bristol-Myers Squibb S.r.I., Reference), in healthy, male and female volunteers under fasting conditions. Its main objective was to compare the rate and extent of absorption and prove bioequivalence of the test and reference products.

Validated LC-MS-MS was used with selective quantification of aripiprazole and dehydro-aripiprazole.

All statistical tests were evaluated at the 95% significance level (α=0.05).
All continuous variables were summarized by the usual descriptive statistics: mean, median, minimum, maximum, standard deviation (SD), range. Normality test

(Shapiro-Wilk) was performed when necessary. In case of categorical variables, frequencies were given.

The continuous target parameters were tested by analysis of variance (ANOVA) after logarithmic transformation.

The primary target parameters were:

- $AUC_{0\text{-tlast}}$ for aripiprazole (area under the plasma concentration time-curve, calculated by means of linear trapezoidal rule from time zero to the last data point above quantitation limit);
- C_{max} for aripiprazole (observed maximal concentration after administration);
- $AUC_{0\text{-}\infty}$ for aripiprazole (area under the plasma concentration time-curve extrapolated from time zero to infinity).

The bioequivalence could be concluded if the 90% confidence intervals for the intra-individual ratios (test/reference) for all three primary target parameters were within the following range: [0.80; 1.25] for ln-transformed values.

The applicant stated that the bioequivalence studies were undertaken according to GCP guidelines. No issues regarding GLP or GCP aspects have been identified during the review of this dossier.

The resulting point estimates and 90% confidence intervals for (log-transformed) aripiprazole pharmacokinetic parameters are as follows:

Pharmacokinetic parameter	Point estimate T/R ratio (%)	90% CI (%)
$AUC_{0\text{-tlast}}$	102.4	98.7 – 106.2
C_{max}	98.5	92.2 – 105.2
$AUC_{0\text{-}\infty}$	100.2	99.8 – 100.8

The confidence intervals for all continuous primary parameters are enclosed within the predetermined bioequivalence range [80%;125%] considering bioequivalence between the two preparations Aripiprazole 10 mg tablets (Gedeon Richter Plc.) and Abilify 10 mg tablets (Market Authorization holder: Otsuka Pharmaceutical Europe Ltd, manufacturer: Bristol-Myers Squibb S.r.I).

The results of the study with the 10 mg formulation can be extrapolated to other strengths 15 and 30 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/corr*, section 4.1.6.

IV.3 Pharmacodynamics

Clinical pharmacology studies to evaluate the pharmacodynamics of Restigulin 10 mg, 15 mg and 30 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 review of clinical trials published in the literature, describing the efficacy profile of aripiprazole.

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. No serious AEs were reported in this study. Both formulations were considerably well tolerated, no clinically significant difference in safety profiles was found, and the results from the post-study laboratory tests confirmed the absence of significant changes in the subjects' state of health.

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	Extrapyramidal symptoms, including tardive dyskinesia Neuroleptic Malignant Syndrome Seizures Suicide-related events Somnolence and fatigue Pathological gambling Weight gain Hyperglycaemia/diabetes Serotonin syndrome Cardiovascular-related disorders (including conduction abnormalities, orthostatic hypotension, increased mortality and cerebro-vascular accident in elderly patients with dementia) Dysphagia Hepatic adverse events related with hepatic injury
Important potential risks	Concomitant administration with potent inhibitor or inducer of CYP3A4 or CYP2D6 inhibitors and with other CNS medicinal product or alcohol
Missing information	Pregnancy and lactation

Summary of safety concerns	
	Use in paediatric patients

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to products of aripiprazole 10 mg, 15 mg and 30 mg film-coated tablets of Gedeon Richter. No additional activities are proposed.

Risk Minimisation Measures: the originator's product has additional risk minimisation measures (educational materials for healthcare professionals and for patients and their caregivers) in the indication of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older relating to the risks of Extrapyramidal symptoms, weight gain, somnolence, fatigue and the use in paediatric patients. Since the originator has distributed these educational materials recently in Hungary, furthermore, starting the treatment of this population can be possible only with the originator's oral solution, routine risk minimisation measures (i.e. wording in SmPC, PIL and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns connected to Gedeon Richter Plc.'s product of aripiprazole 10 mg, 15 mg and 30 mg tablets. No additional activities are requested.

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. To support it the applicant has adequately demonstrated bioequivalence between Restigulin 10 mg, 15 mg, 30 mg tablets and the reference product Abilify 10 mg, 15 mg, 30 mg tablets.

Abridged applications avoid the need for repetitive tests on animals and humans. For these application the bioequivalence studies described in section IV.2 are pivotal.

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 Restigulin 10 mg, 15 mg and 30 mg film-coated tablets, generic versions of aripiprazole. The applicant and the future holder of marketing authorisation is Gedeon Richter Plc.

The indications are the treatment of schizophrenia in adults and in adolescents aged 15 years and older, moderate to severe manic episodes in Bipolar I Disorder and the prevention of a new manic episode in adults, and in the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The reference products were Abilify 10 mg, 15 mg and 30 mg film-coated tablets (Otsuka Pharmaceutical Europe Ltd.).

To support the application the applicant has adequately justified the bioequivalence between the submitted and the reference products.

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 Restigulin 10 mg, 15 mg and 30 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 Hungarian.

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