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Public Assessment Report

Name of the Product:

Explemed Rapid

5 mg, 10 mg, 15 mg and 30 mg orodispersible tablets

(aripiprazole)

Procedure number: HU/H/0374/001-004/DC

Marketing authorisation holder: Egis Pharmaceuticals Plc.

Date: 28 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 Explemed Rapid 5 mg, 10 mg, 15 mg and 30 mg orodispersible tablets. The holder of the marketing authorisation is Egis Pharmaceuticals Plc.

The active substance of the tablets is aripiprazole. Each orodispersible tablet contains 5mg, 10 mg, 15 mg or 30 mg of aripiprazole, respectively.

The other ingredients are microcrystalline cellulose, mannitol, fructose, low-substituted hydroxypropylcellulose, colloidal anhydrous silica and magnesium stearate.

The 5 mg orodispersible tablets are white or almost white, homogenous or slightly dotted, round, flat, bevelled edged, odourless or almost odourless ones with stylized E on both sides. The diameter of the tablets is about 5.5 mm.

The 10 mg orodispersible tablets are white or almost white, homogenous or slightly dotted, round, flat, bevelled edged, odourless or almost odourless ones with stylized E and code 565 code on one side and no code on the other side. The diameter of the tablets is about 8 mm.

The 15 mg orodispersible tablets are white or almost white, homogenous or slightly dotted, round, flat, bevelled edged, odourless or almost odourless ones with stylized E and 566 code on one side and no code on the other side. The diameter of the tablets is about 9 mm.

The 30 mg orodispersible tablets are white or almost white, homogenous or slightly dotted, round, flat, bevelled edged, odourless or almost odourless ones with stylized E and 567 code on one side and no code on the other side. The diameter of the tablets is about 12 mm.

The tablets are packed in OPA/Aluminium/PVC//PET/Aluminium blister in folded cardboard box.

The active substance 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.

Explemed Rapid orodispersible tablets are 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 aripiprazole.

What patients need to know before taking Explemed Rapid orodispersible tablets?

Should not take Explemed Rapid orodispersible tablets those who are allergic to aripiprazole or any of the other ingredients of this medicine.

Warnings and precautions

Ptaients who suffer in any of the following illnesses should talk to their doctor before taking Explemed Rapid orodispersible 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, develops unusual movements, experiences somnolence that interferes with normal daily activities, any difficulty in swallowing or allergic symptoms, should consult the doctor.

Elderly patients suffering from dementia (loss of memory and other mental abilities) should (or their carer/relative should) tell the doctor if the patient has ever had a stroke or "mini" stroke.

Patients who have any thoughts or feelings about hurting themselves, must inform the doctor. Suicidal thoughts and behaviours have been reported during aripiprazole treatment.

Those who suffer from muscle stiffness or inflexibility with high fever, sweating, altered mental status, or very rapid or irregular heartbeat, should inform their doctor immediately.

Children and adolescents

Explemed Rapid orodispersible tablets are not for use in children and adolescents under 13 years.

Other medicines and Explemed Rapid orodispersible tablets

Patients who are taking, have recently taken or might take any other medicines must inform their doctor.

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

Taking Explemed Rapid orodispersible tablets with some medicines may need to change the dose of Explemed Rapid tablets. 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 Explemed Rapid orodispersible tablets should see their doctor.

Explemed Rapid orodispersible tablets with food, drink and alcohol

They can be taken regardless of meals, however, alcohol should be avoided when taking Explemed Rapid orodispersible tablets.

Pregnancy and breast-feeding

Women who are pregnant should not take Explemed Rapid orodispersible tablets unless having been discussed this with the doctor. The doctor should be informed immediately if the patient is pregnant, thinks she may be pregnant, or is planning to become pregnant.

The following symptoms may occur in new-born babies of mothers that have used aripiprazole 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.

Patients must be sure to tell their doctor immediately if they are breast-feeding. In general taking aripiprazole during breast-feeding is discouraged.

Driving and using machines

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

Explemed Rapiod orodispersible tablets contain fructose

Explemed Rapid 5 mg, 10 mg, 15 mg and 30 mg orodispersible tablets contain also 5, 10, 15 and 30 mg fructose, respectively. Those who have been told by their doctor that they have an intolerance to some sugars should contact their doctor before using this medicinalé product.

The fructose may also be hatmful to the teeth.

How to take Explemed Rapid orodispersible 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: the treatment may be started at a low dose, and may be gradually increased to the recommended dose for adolescents of 10 mg once a day. However, the doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

> As it is not possible to obtain lower than 5 mg doses with the use of Explemed Rapid orodispersible tablets, the doctor may prescribe an aripiprazole-containing oral solution for this purpose.

The patient should try to take Explemed Rapid orodispersible tablets at the same time each day. It does not matter whether taking it with or without food. However, the tablets should always be taken with water and swallowed whole.

The patients are discouraged to alter or discontinue the daily dose of Explemed Rapid orodispersible tablets without first consulting their doctor even if they feel better.

What happens if the patient takes more Exlemed orodispersible tablets than he/she should?

If the patient realises having taken more Explemed Rapid orodispersible tablets than the doctor has recommended (or if someone else has taken some of their Explemed Rapid orodispersible tablets), the doctor should be contacted right away. If the doctor cannot be reached, the nearest hospital should be visited bringing the pack along.

What to do if taking Explemed Rapid orodispersible tablets was forgotten?

The missed dose should be taken as soon as realising it, but two doses two doses in one day should never be taken.

Possible side effects

Like all medicines, Explemed Rapid orodispersible tablets can cause side effects, although not everybody experiences them.

Common side effects (that may affect up to 1 in 10 people) are**:** 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) are**:** 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. Some people may feel depressed.

Moreover, the following side effects have been reported since the marketing of aripiprazole but their frequency is not known (it 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 you notice any of these symptoms, 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 Explemed Rapid orodispersible tablets?

This medicinal product does not require any special temperature storage conditions. Store in the original blister in order to protect from moisture.

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

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Explemed Rapid 5 mg, 10 mg, 15 mg and 30 mg orodispersible tablets. The procedure was finalised at 22 May 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 5 mg, 10 mg, 15 mg and 30 mg tablets (Explemed Rapid orodispersible tablets, named Explemed Rapid in Bulgaria, in the Czech Republic, in Poland and in the Slovak Republic over in Romania Explemed ODT).

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 products and reference products. The originator (and reference) products are Abilify 5 mg, 10 mg, 15 mg and 30 mg orodispersible tablets marketed by Otsuka Pharmaceutical Europe Ltd. approved for more than 10 years within the European Economic Area.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisations for Explemed 5 mg, 10 mg, 15 mg and 30 mg orodispersible tablets from Egis Pharmaceuticals Plc.

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).

II. QUALITY ASPECTS

II.1 Introduction

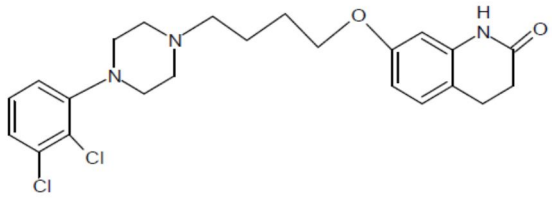
This chemical-pharmaceutical assessment report concerns the application of Explemed Rapid 5 mg, 10 mg, 15 mg and 30 mg orodispersible tablets via a decentralized procedure according to Article 10(1) of Directive 2001/83/EC (i.e. a generic application). The products have been developed by Egis Pharmaceuticals Plc.

The reference products are Abilify 5 mg, 10 mg, 15 mg, 30 mg orodispersible tablets (containing 5, 10, 15 and 30 mg aripiprazole, respectively as active ingredient) 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) procedures 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 polymorphism, the manufacturer consistently produces the same polymorphic form.

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

Evidence of the structure has been confirmed by spectroscopy (FT-IR, ^{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, *Substances for pharmaceutical use* and with International Conference on Harmonisation (ICH) Q6A and 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 manufacturers 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 in a well-closed container”.

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

II.3 Medicinal product

The aim was to develop orodispersible tablets containing aripiprazole as drug substance in 5, 10, 15 and 30 mg doses that are pharmaceutically equivalent and bioequivalent to the reference medicinal product Abilify 5 mg, 10 mg, 15 mg, 30 mg orodispersible 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 products are shown to be similar to the reference products.

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.

Explemed Rapid 5 mg orodispersible tablets are white or almost white, homogeneous or slightly

dotted, round, flat, bevelled edged, odourless or almost odourless with stylized E on both sides of the tablets and diameter of ~ 5.5 mm.

Explemed Rapid 10 mg orodispersible tablets are white or almost white, homogeneous or slightly dotted, round, flat, bevelled edged, odourless or almost odourless with stylized E and code 565 on one side and no code on the other side of the tablets and diameter of ~ 8.0 mm.

Explemed Rapid 15 mg orodispersible tablets are white or almost white, homogeneous or slightly dotted, round, flat, bevelled edged, odourless or almost odourless with stylized E and code 566 on one side and no code on the other side of the tablets and diameter of ~ 9.0 mm.

Explemed Rapid 30 mg orodispersible tablets are white or almost white, homogeneous or slightly dotted, round, flat, bevelled edged, odourless or almost odourless with stylized E and code 567 on one side and no code on the other side of the tablet and diameter of ~ 12.0 mm.

The excipients used in the finished product are microcrystalline cellulose, mannitol, fructose, low substituted hydroxypropylcellulose, colloidal anhydrous silica and magnesium stearate. All excipients used comply with their respective Ph. Eur. monograph/USP 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//PET/Al peelable 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 3 years with the storage condition **"**This medicinal product does not require any special temperature storage conditions. Store in the original blister in order to protect from moisture" is approved.

The Summary of Product Characteristics, Patient Information Leaflet (PIL, package leaflet) and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The products have been shown to meet the current regulatory requirements with regards to their

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 products.

From quality points of view the products are approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of aripiprazole are well known. As aripiprazole 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 Explemed Rapid orodispersible tablets contain the 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

Since Explemed Rapid 5 mg, 10 mg, 15 mg and 30 mg orodispersible 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 Explemed Rapid orodispersible 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 proving 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.

Moreover, 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 studies

The development studies focused on obtaining products having similar characteristics to the reference products, i.e. dissolution profile and bioavailability.

For the purpose of the marketing authorisation two bioequivalence studies were performed with Aripiprazole 15 mg orodispersible tablets (Egis Pharmaceuticals Plc., Hungary – test product) and the relevant strength of the innovator product, Abilify® 15 mg orodipersible tablets.

Similarities of in-vitro dissolution profiles were also justified. Dissolution studies were performed for the 4 strengths.

Biowaiver

The applicant claimed for biowaiver for the 5 mg, 10 mg and 30 mg dose strengths on the basis of general biowaiver requirements (CPMP/EWP/QWP/1401/98 Rev. 1 Corr**), as follows:
a) All the four strengths (5, 10, 15 and 30 mg) of proposed pharmaceutical products are manufactured by the same manufacturer and using the same manufacturing process.
b) Qualitative composition of the different strengths is the same.
c) The ratio between amounts of each active ingredient and excipients is the same in all strengths.
d) Appropriate in vitro dissolution data confirm the adequacy of waiving additional *in vivo* bioequivalence testing.
e) Aripiprazole has linear pharmacokinetics in the therapeutic dose range.

Biowaiver claim for the 5 mg, 10 mg and 30 mg dose-strengths is justified as all requirements of the *Note for Guidance on Investigation of bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1 Corr**), concerning biowaiver were met.

Bioequivalence

The pilot bioequivalence study

The objective of this pilot study was to estimate the intrasubject variability and to compare the bioavailability of aripiprazole from two formulations of Aripiprazole 15 mg orodispersible tablets (EGIS Pharmaceuticals Plc.) and Abilify® 15 mg orodispersible Tablets (Otsuka Pharmaceutical Europe Ltd.) in healthy non-smoking Caucasian male and female volunteers under fasting conditions.

This was a single-dose, randomized, open-label, three-period, three sequence, three-treatment, single-centre, crossover, comparative bioavailability study.

Concentrations of aripiprazole in human plasma samples were determined with HPLC-MS/MS assay.

Incurred sample reanalysis was performed as part of the in-process validation of the bioanalytical method.

Healthy, non-smoking, Caucasian adult male and female volunteers having pre-determined limits of body mass index, confirmed CYP2D6 extensive metabolizer have been enrolled in the study.

The primary pharmacokinetic parameters were: AUC_{72} and C_{max} for aripiprazole.

Descriptive statistics of all pharmacokinetic parameters (min, max, median, mean, standard deviation and coefficient of variability) were provided for the test and reference products.

Bioequivalence was to be concluded if the 90% geometric confidence intervals of the ratio (test/reference) of least-squares means for ln-transformed AUC_{72} and C_{max} were within the acceptable range of 80.00% to 125.00%.

Results: both test formulations showed comparable bioavailability to the reference product regarding the rate and extent of absorption in healthy male and female volunteers under fasting conditions.

The test products and reference product were well tolerated by all subjects.

The pivotal bioequivalence study

An open label, single-dose, randomized, two-period, two treatment crossover study was performed in healthy non-smoking adult subjects under fasting conditions. Its main objective was to assess the relative bioavailability of 15 mg Aripiprazole orodispersible tablets by Egis Pharmaceuticals Plc. (Explemed Rapid, test product) compared to that of Abilify® 15 mg orodispersible tablets (Otsuka, reference product).

Concentrations of aripiprazole in human plasma samples were determined using a liquid extraction procedure coupled to a HPLC-MS/MS assay.

The bioanalytical method has been successfully validated. The validation procedure and the analysis of study samples in the bioanalytical study were in line with the guideline EMEA/CHMP/EWP/192217/2009.

Incurred sample reanalysis was performed and met the requirements.

All assay runs were performed within the verified plasma stability period and the acceptance criteria of the bioanalytical runs met the international standard.

Statistical methods: the mean, standard deviation (SD), coefficient of variation (CV (%)) and range were calculated for plasma concentrations of aripiprazole for each sampling time and treatment. Arithmetic means, standard deviations and coefficients of variation and range were calculated for AUC_{0-72}, AUC_{0-t}, C_{max} and T_{max}. Additionally, geometric

means were calculated for AUC_{0-72}, AUC_{0-t} and C_{max}. The calculation of pharmacokinetic parameters was performed according to standard non-compartmental method recommended by PMP/EWP/QWP/1401/98 Rev.1/Corr**. The pharmacokinetic results were judged reliable and valid.

Bioequivalence criteria: bioequivalence was based on the ratio of means and 90% confidence intervals for AUC_{0-72} and C_{max} of aripiprazole. For the test formulation, the ratios of means and their 90% confidence intervals should have been within 80.00 to 125.00% for AUC_{0-72} and C_{max}.

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

Results:

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%
AUC_{0-72}	104.07	100.08 – 108.22	7.91
C_{max}	98.30	91.24 – 105.90	13.1

Conclusion on bioequivalence studies:

According to the statistical analysis the Test to Reference ratio of geometric means and corresponding 90% confidence interval for the C_{max} and AUC_{0-72} met the predefined acceptance criteria.

Based on the submitted bioequivalence study Explemed 15 mg tablets (EGIS Pharmaceuticals Plc.) is considered bioequivalent with Abilify 15 mg tablets (Otsuka Pharmaceutical Europe Ltd).

The results of the study with 15 mg formulation can be extrapolated to other strengths 5 mg, 10 mg and 30 mg according to conditions set in *Guideline on the Investigation of Bioequivalence* CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

IV.3 Pharmacodynamics

No clinical pharmacology studies to evaluate the pharmacodynamics of Explemed Rapid 5 mg, 10 mg, 15 mg and 30 mg orodispersible tablets were 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 and safety 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.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance Plan

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 (EPS), including tardive dyskinesia Neuroleptic malignant syndrome (NMS) Seizures Somnolence and fatigue Pathological gambling Suicide-related events Weight gain Hyperglycaemia and diabetes mellitus Cardiovascular-related disorders (including conduction abnormalities, orthostatic hypotension, and increased mortality and cerebrovascular adverse reactions (CVA) in elderly patients with dementia-related psychosis) Dysphagia Serotonin syndrome Hepatic adverse events 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 Use in paediatric patients

Routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to products of aripiprazole 5 mg, 10 mg, 15 mg and 30 mg tablets of Egis. No additional activities are proposed.

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, initiation of 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 products of aripiprazole 5 mg, 10 mg, 15 mg and 30 mg tablets of Egis in Hungary. 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.

Currently, no routine PSUR reporting is required for generic products containing aripiprazole.

IV.7 Discussion on the clinical aspects

The application concerns generic products. Abridged applications avoid the need for repetitive tests on animals and humans. For these applications the bioequivalence study described in section IV.2 is pivotal.

To support the application the applicant has adequately demonstrated bioequivalence between Explemed 5 mg, 10 mg, 15 mg, 30 mg tablets and the reference product Abilify 5 mg, 10 mg, 15 mg, 30 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 applications concern Explemed Rapid 5 mg, 10 mg, 15 mg and 30 mg orodispersible tablets, generic versions of aripiprazole. The applicant and the future holder of authorisation is Egis 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 5 mg, 10 mg, 15 mg and 30 mg orodispersible tablets marketed by Otsuka Pharmaceutical Europe Ltd.

The applicant has adequately demonstrated bioequivalence between the Explemed Rapid orodispersible tablets 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 Explemed Rapid 5 mg, 10 mg, 15 mg and 30 mg orodispersible 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*.