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Public Assessment Report

Name of the Product:

Aripiprazole Focus

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

(aripiprazole)

Procedure number: HU/H/0381/001-004/DC

Marketing authorisation holder: Focus Care Pharmaceuticals B.V.

Date: 7 April 2015

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted marketing authorisation of the Aripiprazole Focus 5 mg, 10 mg, 15 mg and 30 mg tablets. The holder of the marketing authorisation is Focus Care Pharmaceuticals B.V.

The active substance is aripiprazole. Each tablet contains 5 mg, 10 mg, 15 mg or 30 mg aripiprazole.

The other ingredients are lactose monohydrate, microcrystalline cellulose (E460), maize starch, hydroxypropylcellulose (E463), red iron oxide (E172) – only in the 10 mg and 30 mg tablets, yellow iron oxide (E172) – only in the 15 mg tablets, indigo carmine (E132) – only in the 5 mg tablets and magnesium stearate (E470b).

The appearance of the tablets is as follows:
- 5 mg tablets: blue, round with bevelled edges and with possible darker and lighter spots, diameter: 5 mm, thickness: 1.4–2.4 mm;
- 10 mg tablets: light pink, rectangular with possible darker and lighter spots and engraved with A10 on one side, length: 8 mm, width: 4.5 mm, thickness: 2.1–3.1 mm;
- 15 mg tablets: light yellow to brownish yellow, round, slightly biconvex with bevelled edges and with possible darker and lighter spots and engraved with A15 on one side, diameter: 7.5 mm, thickness: 2.5–3.7 mm;
- 30 mg tablets: light pink, round, biconvex with bevelled edges and with possible darker and lighter spots and engraved with A30 on one side, diameter: 9 mm, thickness: 3.9–5.3 mm).

Aripirazole Focus tablets are available in boxes in blisters.

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.

Aripiprazole Focus 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 Aripiprazole Focus.

What patients need to know before taking Aripiprazole Focus

Those who are allergic to aripiprazole or any of the other ingredients of this medicine *should not take Aripiprazole Focus*.

Warnings and precautions

Those who suffer from any of the following diseases should consult their doctor before taking Aripiprazole Focus:

- 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.

Those who notice gaining weight, develop unusual movements, experience somnolence that interferes with normal daily activities, any difficulty in swallowing or allergic symptoms, tell it their 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.

Those who are having any thoughts or feelings about hurting themselves tell it their doctor immediately. 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 heart beat consult their doctor immediately.

Children and adolescents

Aripiprazole Focus is not for use in children and adolescents under 13 years.

Other medicines and Aripiprazole Focus

Those who are taking, have recently taken or might take any other medicines tell it their doctor, for

- Aripiprazole Focus may increase the effect of medicines used to lower the blood pressure;
- taking Aripiprazole Focus together with some medicines may need to change the dose of Aripiprazole Focus. 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: 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. Those

who experience any unusual symptom taking any of these medicines together with Aripiprazole Focus, should see their doctor.

Aripiprazole Focus with food, drink and alcohol

Aripiprazole Focus can be taken regardless of meals but alcohol should be avoided when taking this medicine.

Pregnancy and breast-feeding

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

Breast-feeding should be avoided when taking Aripiprazole Focus.

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 should be contacted.

Driving and using machines

Patients taking Aripiprazole Focus should not drive or use any tools or machines, until they know how this medicine affects them.

Aripiprazole Focus contains lactose

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

How to take Aripiprazole Focus

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

Treatment may be started at a low dose with aripiprazole oral solution (liquid) form. The dose 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.

Appropriate formulation (e.g. 1 mg/ ml solution) of the brand Aripiprazole Focus is not available. An alternative product with the same active ingredient should be used.

Aripiprazole Focus tablets should be taken, if possible, at the same time each day. It does not matter whether it is taken with or without food but it should always be taken with water and swallowed whole.

Patients, even if feeling better, should not alter or discontinue the daily dose of Aripiprazole Focus without first consulting your doctor.

What to do if more Aripiprazole Focus has been taken than it should have been

Patients who realise they have taken more Aripiprazole Focus tablets than the doctor has prescribed (or if someone else has taken some Aripiprazole Focus tablets not intended to him/her), the doctor should be contacted right away. If the doctor cannot be reached, the nearest hospital should be visited taking also the pack of the medicine.

What to do if taking Aripiprazole Focus was forgotten

If a dose was missed, it should be taken as soon as realising it but two doses in the same day should not be taken.

Possible side effects

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

Common side effects (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 (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. Some people may feel depressed.

The following side effects have been reported since starting the marketing of aripiprazole but their frequency 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; 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 (more frequent 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 (affecting up to 1 in 100 patients).

How to store Aripiprazole Focus

This medicine does not require any special storage conditions but keep it out of the sight and reach of children.

Scientific discussion

during the initial procedure

This module reflects the scientific discussion for the approval of Aripiprazole Focus 5 mg, 10 mg, 15 mg and 30 mg tablets. The procedure was finalised at 16 January 2015. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

This application concerns generic versions of aripiprazole. With Hungary as the Reference Member State (RMS) as well as Belgium, Cyprus, France, Ireland, Italy, Netherland and Spain as Concerned Member States (CMS) the application has been submitted according to Article 10(1) of Directive 2001/83/EC (as amended, e.g. a generic application) Therefore, it contains no new non-clinical and clinical data, other than the bioequivalence study as well as supporting literature where necessary, in accordance with the provisions of the article indicated above.

The applicant has adequately demonstrated bioequivalence between the product and reference products. The latter have been Abilify 5 mg, 10 mg, 15 mg and 30 mg tablets marketed by Otsuka Pharmaceutical Europe Ltd., approved for more than 10 years.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Aripiprazole Focus 5 mg, 10 mg, 15 mg and 30 mg tablets. The holder of the marketing authorisation is Focus Care Pharmaceuticals B.V. (the Netherlands).

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

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

The chemical-pharmaceutical assessment report concerns the application for marketing authorisations via Decentralised Procedure products Aripiprazole Focus 5 mg, 10 mg, 15 mg and 30 mg tablets, according to Article 10(1) of Directive 2001/83/EC (i.e. a generic application).

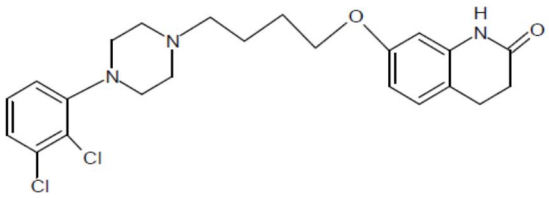
The bioequivalence study has been performed using the products Abilify® 10 mg tablets containing aripiprazole (Otsuka Pharmaceutical Europe Ltd) as reference medicine.

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.

International non-proprietary name (INN): 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. There are certain known polymorphic forms of aripiprazole.

Detailed description of the manufacturing process of the drug substance was provided by the manufacturer. It is adequate.

Evidence of the structure of aripiprazole was presented and confirmed by various spectroscopic methods. It has been demonstrated that the manufacturing process consistently produces the same stable crystalline form of aripiprazole. The impurity profile of the active substance including detailed information about genotoxic impurities, residual solvents and other carryover impurities has been appropriately discussed.

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 *Substances for pharmaceutical use* and with the 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 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.

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

It has been demonstrated by the presented stability and forced degradation studies that the substance is very stable, the available stability data support the proposed re-test period packed in laminated PET/Al/PE bag (placed desiccant silica gel on the top) and in cardboard drum.

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

II.3 Medicinal product

The aim was to develop immediate release oral tablets containing aripiprazole as active substance, which are pharmaceutically equivalent and bioequivalent to the reference products Abilify® 5 mg, 10 mg, 15 mg and 30 mg strength tablets, with the same strengths and same qualitative composition.

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:

- 5 mg: blue, round tablets with bevelled edges and with possible darker and lighter spots (diameter: 5 mm, thickness: 1.4–2.4 mm);
- 10 mg: light pink, rectangular tablets with possible darker and lighter spots and engraved with A10 on one side (length: 8 mm, width: 4.5 mm, thickness: 2.1–3.1 mm);
- 15 mg: light yellow to brownish yellow, round, slightly biconvex tablets with bevelled edges and with possible darker and lighter spots and engraved with A15 on one side (diameter: 7.5 mm, thickness: 2.5–3.7 mm);
- 30 mg: light pink, round, biconvex tablets with bevelled edges and with possible darker and lighter spots and engraved with A30 on one side (diameter: 9 mm, thickness: 3.9–5.3 mm).

The tablets are packed in OPA/Al/PVC-Al foil blisters.

The excipients used are lactose monohydrate, microcrystalline cellulose, maize starch, hydroxypropyl cellulose (type LF), yellow or red iron oxides or indigo carmine aluminium lake (E132), magnesium stearate, and purified water.

All excipients comply with their respective Ph. Eur. monograph, except from the colouring agents. Iron oxide yellow and red comply with USP/NF and E172. The colours are in accordance with Commission Regulation (EU) No 231/2012. Indigo carmine aluminium lake is controlled according to an in-house specification.

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 required 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 blister consisting of OPA/Al/PVC foil and aluminium foil. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 24 months without any special storage condition is approved.

The Summary of Product Characteristics, Patient Information 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 product.

From chemical-pharmaceutical point of view the products are approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of aripiprazole are well known. As it is a generic application based on bioequivalence studies and aripiprazole 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, aripiprazole.

III.2 Pharmacology

The Aripiprazole Focus tablets contain the active substance aripiprazole. It is an antipsychotic medicine. 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 mean 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. Such studies are not needed for this type of application.

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 Aripiprazole Focus 5 mg, 10 mg, 15 mg, 30 mg tablets are intended for generic substi-

tution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Abridged applications avoid the need for repetitive tests on animals.

Pharmacodynamics, pharmacokinetics and toxicology of aripiprazole are well-known. As Aripiprazole Focus 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 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 a product having similar characteristics to the reference product, i.e. dissolution profile and bioavailability.

Essential similarity was demonstrated by means of a pivotal bioequivalence study between the test product and reference product. The study has demonstrated that a single dose of the applicant's Aripiprazole 10 mg tablets is bioequivalent to a single dose of Abilify® 10 mg 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, 15 mg and 30 mg dose strengths on the basis of general biowaiver requirements (CPMP/EWP/QWP/1401/98 Rev 1 Corr**):
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) the qualitative compositions of Aripiprazole 5 mg, 15 mg and 30 mg tablets are the 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 four strengths;
d) the in-vitro dissolution profile is similar under identical conditions for the additional strengths i.e. 5 mg, 15 mg and 30 mg, and the strength of the batch used in the bioequivalence study (i.e. 10 mg);
e) aripiprazole exhibits linear pharmacokinetics in the range of 5 mg - 30 mg.

Biowaiver claim for the 5 mg, 15 mg and 30 mg dose-strengths is justified as general requirements for biowaiver are completely fulfilled.

The pivotal bioequivalence study was performed at the strength of 10 mg in line with the requirement of bioequivalence guideline in force (CPMP/EWP/QWP/1401/98 Rev 1 Corr**, page 12), and to the draft FDA guideline of Aripiprazole (Draft Guidance of Aripiprazole, FDA/CDER, last modified: 2007).

The main objective of the *bioequivalence study* was to compare the rate and extent of absorption of Aripiprazole 10 mg tablet (Test) versus Abilify® 10 mg tablet (Reference) administered under fasting conditions.

The bioequivalence study was designed as a single-dose, randomized, single centre, two-way crossover study conducted under fasting conditions in healthy male and female subjects with a sufficient washout period between the doses.

Aripiprazole in plasma samples was determined using a validated method.

Incurred sample reanalysis (ISR) was performed according to the guideline on bioanalytical method validation (EMA/CHMP/EWP/192217/2009, 21 July 2011). Results of the ISR met acceptance criteria.

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.

Demographic parameters were summarized descriptively.

Bioequivalence was to be concluded if the 90% geometric confidence intervals of the ratio (T/R) of least-squares means for ln-transformed AUC_{0-72} and C_{max} were within the acceptable range of 80.00% to 125.00%. The results are presented in Table 1.

The bioequivalence study was undertaken according to GCP guidelines. No issues regarding GLP or GCP aspects have been identified during the review of this dossier.

Table 1: **Summary of study results**

Parameter	Ratio (T/R)[1]	90% Geometric C.I.[2]		Intra-subject CV	Inter-subject CV
		Lower	Upper		
AUC_{0-72}	103.26%	98.02%	108.78%	11.23%	21.28%
C_{max}	104.17%	95.83%	113.24%	18.08%	21.99%

[1]Calculated using least-squares means according to the formula: $e^{(DIFFERENCE)}$ X 100.
[2]90% Geometric Confidence Interval using ln-transformed data.

Conclusion on the bioequivalence study

Results derived from the analysis of log-transformed primary target parameters, C_{max} and AUC_{0-72} parameters for aripiprazole, the T/R ratios of group means and their 90% confidence intervals were also included within the acceptance range of 80% - 125%. Thus, results support the bioequivalence between the test and reference products.

Based on the clinical laboratory assessments, it can be concluded that both study medications were relatively well tolerated by subjects involved in the study.

Based on the submitted bioequivalence study Aripiprazole Focus 10 mg tablets (Focus Care Pharmaceuticals B.V) is considered bioequivalent with Abilify 10 mg tablets (Otsuka Pharmaceutical Europe Ltd).

The results with 10 mg formulation can be extrapolated to other strengths 5 mg, 15 mg 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

No clinical pharmacological studies to evaluate the pharmacodynamics of Aripiprazole Focus 5 mg, 10 mg, 15 mg, 30 mg 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 serious or severe adverse events were reported in the bioequivalence study. Thus, the formulations were well tolerated, with no major side effects. No relevant differences in safety profiles were observed between the preparations, particularly with respect to the number of adverse events.

IV.6 Pharmacovigilance

IV.6.1 Pharmacovigilance System

The future marketing authorisation holder has submitted a signed Summary of the Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

IV.6.2 Risk Management Plan

The Risk Management Plan for aripiprazole, submitted by the applicant was accepted.

The applicant has identified the following safety concerns in the RMP:

Summary of safety concerns	
Important identified risks	• Extrapyramidal symptoms, including tardive dyskinesia • Neuroleptic Malignant Syndrome • Seizures • Suicide-related events • Somnolence and fatigue • Pathological gambling

Summary of safety concerns	
	• Weight gain • Hyperglycaemia/diabetes • Cardiovascular-related disorders (including conduction abnormalities, orthostatic hypotension, increased mortality and cerebro-vascular accident in elderly patients with dementia) • Dysphagia • Serotonin syndrome • 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	• Safety in pregnancy and lactation • Use in paediatric patients

On-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

The marketing authorisation holder has not planned to perform post-authorisation safety studies.

Summary of Post authorisation efficacy development plan

The marketing authorisation holder has not planned to perform post-authorisation efficacy studies.

Summary table of Risk Minimisation Measures

Safety concern	*Routine risk minimisation measures*	*Additional risk minimisation measures*
Extrapyramidal symptoms, including tardive dyskinesia	Content in the SmPC: *4.4 Special warnings and precautions for use*: warning of possible development of tardive dyskinesia and other extrapyramidal symptoms from clinical trials. The dose should be reduced or the treatment discontinued. When the dose is reduced close monitoring is necessary. *4.6 Fertility, pregnancy and lactation:* neonates exposed to antipsychotics (including aripiprazole) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms. *4.8 Undesirable effects:* listed in this section.	None proposed

	4.9 Overdose: potentially medically serious symptoms of overdose include extrapyramidal symptoms. 5.1 Pharmacodynamic properties: identification of studies. Prescription-only medicine.	
Neuroleptic malignant syndrome	Content in the SmPC: *4.4 Special warnings and precautions for use*: warning of possible development of neuroleptic malignant syndrome from clinical trials with the described signs and symptoms. *4.8 Undesirable effects:* listed in this section. Prescription-only medicine.	None proposed
Seizures	Content in the SmPC: *4.4 Special warnings and precautions for use* warning of possible development of seizures from clinical trials. Aripiprazole should be used with caution especially in patients who have a history of seizure disorder or have conditions associated with seizures. *4.8 Undesirable effects*: listed in this section. Prescription-only medicine.	None proposed
Suicide-related events	Content in the SmPC: **4**.*4 Special warnings and precautions for use* the occurrence of suicidal behaviour is inherent in psychotic illnesses and mood disorders however a warning about possible suicidal behaviour early after initiation or switch of antipsychotic therapy was stated and that high-risk patients should be closely supervised. *4.8 Undesirable effects*: listed in this section. Prescription-only medicine.	None proposed
Somnolence/fatigue	Content in the SmPC: *4.2 Posology and method of administration*: it is stated that the treatment duration for the indication Manic episodes in Bipolar I Disorder in adolescents aged 13 years and older should be the minimum necessary for symptom control and must not exceed 12 weeks and that daily dose exceeding 10 mg has not demonstrated enhanced efficacy, while daily doses of 30 mg were associated with a substantially higher incidence of significant undesirable effects including EPS related events, somnolence, fatigue and weight gain. *4.7 Effects on ability to drive and use machines* stating that some paediatric patients with Bipolar I Disorder have an increased incidence of somnolence and fatigue. *4.8 Undesirable effects*: stating that in the paediatric population somnolence and fatigue were observed more frequently in patients with	None proposed

	bipolar disorder compared to patients with schizophrenia. Prescription-only medicine.	
Pathological gambling	Content in the SmPC: *4.4 Special warnings and precautions for use* it is stated that post-marketing reports of pathological gambling have been reported among patients prescribed aripiprazole, regardless of whether these patients had a prior history of gambling and that therefore patients with a prior history of pathological gambling may be at increased risk and should be monitored carefully. *4.8 Undesirable effects*: listed in this section. Prescription-only medicine.	None proposed
Weight gain	Content in the SmPC: *4.4 Special warnings and precautions for use* weight gain is commonly seen in schizophrenic and bipolar mania patients due to comorbidities, use of antipsychotics known to cause weight gain, poorly managed life-style, and might lead to severe complications. When weight gain has been reported from post-marketing among patients prescribed aripiprazole, it is usually in those with significant risk factors such as history of diabetes, thyroid disorder or pituitary adenoma. In clinical trials of adolescent patients with bipolar mania, aripiprazole has been shown to be associated with weight gain after 4 weeks of treatment. Therefore, weight gain should be monitored in adolescent patients with bipolar mania and if it is clinically significant, dose reduction should be considered. *4.8 Undesirable effects*: listed in this section. Prescription-only medicine.	None proposed.
Hyperglycaemia/diabetes	Content in the SmPC: *4.4 Special warnings and precautions for use:* warning of possible development of hyperglycaemia or diabetes in patients treated with atypical antipsychotic agents including aripiprazole. It may be extreme with ketoacidosis or hyperosmolar coma or even death. *4.8 Undesirable effects*: listed in this section. Prescription-only medicine.	None proposed.
Cardiovascular-related disorders (including conduction abnormali-	Content in the SmPC: *4.4 Special warnings and precautions for use* warning that aripiprazole should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, conditions which would predispose patients to hypotension or hypertension. Describing clinical trials	None proposed

ties, orthostatic hypotension, increased mortality and cerebrovascular accident in elderly patients with dementia)	and warning that aripiprazole should be used with caution in patients with a family history of QT prolongation. Information from trials is provided and the conclusion that aripiprazole is not indicated for the treatment of dementia-related psychosis is being reached. *4.8 Undesirable effects*: listed in this section. Prescription-only medicine.	
Dysphagia	Content in the SmPC: *4.4 Special warnings and precautions for use* as oesophageal dysmotility and aspiration have been associated with antipsychotic treatment, including aripiprazole, aripiprazole and other antipsychotic active substances should be used cautiously in patients at risk for aspiration pneumonia. *4.8 Undesirable effects*: listed in this section. Prescription-only medicine.	None proposed
Serotonin syndrome	Content in the SmPC: *4.5 Interaction with other medicinal products and other forms of interaction*: it is written that cases of serotonin syndrome have been reported in patients taking aripiprazole, and possible signs and symptoms for this condition can occur especially in cases of concomitant use with other serotonergic drugs, such as SSRI/SNRI, or with drugs that are known to increase aripiprazole concentrations. *4.8 Undesirable effects*: listed in this section. Prescription-only medicine.	None proposed
Hepatic adverse events related with hepatic injury	Content in the SmPC: *4.8 Undesirable effects*: listed in this section. Prescription-only medicine.	None proposed
Concomitant administration with potent inhibitor or inducer of CYP3A4 or CYP2D6 inhibitors and with other CNS medicinal product or alcohol	Content in the SmPC: *4.5 Interaction with other medicinal products and other forms of interaction*: in this section information on various potential drug interactions with drugs that are inhibitors or inducers of CYP3A4 or CYP2D6 inhibitors is provided as aripiprazole is metabolised by multiple pathways involving the CYP2D6 and CYP3A4 enzymes. Caution is advised when aripiprazole is taken in combination with alcohol or other CNS medicinal products with overlapping adverse reactions such as sedation. Prescription-only medicine.	None proposed

Safety in pregnancy and lactation	Content in the SmPC: *4.6 Fertility, pregnancy and lactation*: warning that no adequate well-controlled trials in pregnant women and that aripiprazole should not be used in pregnancy unless the expected benefit clearly justifies the potential risk to foetus. Neonates exposed to antipsychotics during third trimester are at risk of adverse events, especially neurologic. Aripiprazole is excreted in milk, therefore the patients are advised not to breastfeed when they are taking aripiprazole. *5.3 Preclinical safety data*: animal studies could not exclude potential developmental toxicity. Prescription-only medicine.	None proposed
Safety in paediatrics	Content in the SmPC: *4.1 Therapeutic indications*: aripiprazole is not indicated for use in paediatric population under 15 years of age (for treatment of schizophrenia) or 13 years of age (for bipolar disorder) *4.2 Posology and method of administration*: aripiprazole is not recommended for use in patients with schizophrenia below 15 years of age due to insufficient data on safety and efficacy. And for the treatment of manic episodes in Bipolar I Disorder in adolescents aged 13 years and older the treatment duration should be the minimum necessary for symptom control and must not exceed 12 weeks and daily dose of 10 mg should not be exceeded or should therefore only be used in exceptional cases and with close clinical monitoring. In the treatment of irritability associated with autistic disorder the safety and efficacy of aripiprazole in children and adolescents aged below 18 years have not yet been established. *4.4 Special warnings and precautions for use:* warning about possible development of other extrapyramidal symptoms from paediatric trials. Warning that aripiprazole has been shown to be associated with weight gain after 4 weeks of treatment as seen in clinical trials of adolescent patients with bipolar mania with recommendations that weight gain should be monitored in adolescent patients with bipolar mania and that dose reduction should be considered if weight gain is clinically significant. *4.8 Undesirable effects*: the adverse events from paediatric trials are listed separately in this section. *5.1 Pharmacodynamic properties*: listing of studies. Prescription-only medicine.	An educational programme is in place by the originator to communicate and reinforce the core safety messages conveyed in the SmPC and PIL to carefully consider the indicated age range, dose, and duration of treatment before considering aripiprazole for patients with paediatric bipolar disorder.

The RMS is of the opinion that routine pharmacovigilance activity and routine risk minimisation is sufficient for all safety concerns for the marketing authorisation holder of the originator product had introduced educational program in the concerned member states**.** The necessity of preparing educational material should be decided at national level concerning those member states where the innovator or other marketing authorisation holders of the oral solution form of aripiprazole have not distributed educational material in the indication of manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.

IV.6.3 Periodic Safety Update Report cycle

With regard to Periodic Safety Update Report (PSUR) submission, the marketing authorization holder should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorization holders shall continuously check the European medicines web-portal for the Data Lock Point (DLP) and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to 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 animals and humans.

To support the application the applicant has adequately demonstrated bioequivalence between Aripiprazole Focus 5 mg, 10 mg, 15 mg, 30 mg tablets and the reference product Abilify 5 mg, 10 mg, 15 mg, 30 mg tablets tablets.

For this type of application the bioequivalence studies described in section IV.2 are pivotal.

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.

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 concerns Aripirazole Focus 50 mg, 10 mg, 15 mg and 30 mg tablets. The holder of the marketing authorisation is Focus Care Pharmaceutical B.V.

The products are indicated for 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.

To support the application the applicant has adequately demonstrated bioequivalence between Aripiprazole Focus 5 mg, 10 mg, 15 mg, 30 mg tablets and the reference product Abilify 5 mg, 10 mg, 15 mg, 30 mg tablets tablets.

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 Aripiprazole Focus 50 mg, 10 mg, 15 mg and 30 mg tablets.

V.2 Classification

The classification for supply of these products is prescription-only medicine in the RMS.

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