IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Aripiprazole Krka 30mg Tablets
Aripiprazole
PA1347/089/004

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number HU/H/0381/001-004 with the UK as RMS. The responsibility of RMS was transferred to Ireland on 25th March 2021 under procedure number IE/H/1182/001-004/DC

Please note the following detail for the product in IE:
Marketing Authorisation Number: PA1347/089/001-004
Marketing Authorisation Holder: KRKA, d.d., Novo mesto

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The Hungarian public assessment report published at the time of the initial marketing authorisation is provided herein

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 author- isations 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).

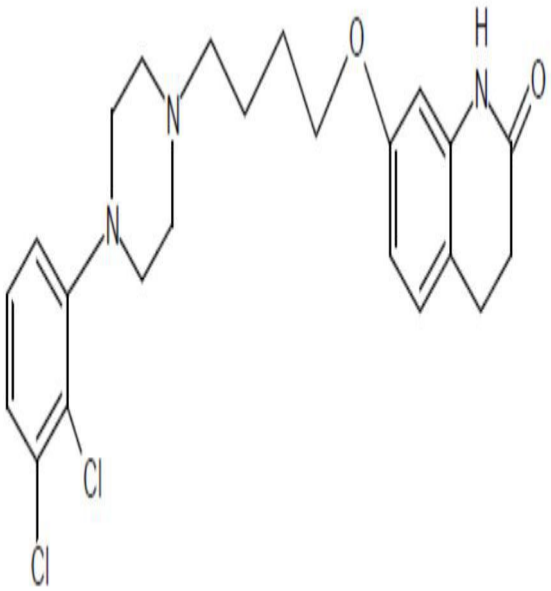
The bioequivalence study has been performed using the products Abilify® 10 mg tablets con- taining aripiprazole (Otsuka Pharmaceutical Europe Ltd) as reference medicine.

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] but- oxy]-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 in- cluding 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 Pharmaco- poeia (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 sub- stance 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 sub- stance, 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 discus- sion 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 for- mulation 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, hydrox- ypropyl 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 accord- ance with Commission Regulation (EU) No 231/2012. Indigo carmine aluminium lake is con- trolled according to an in-house specification.

Compliance of the product with the general monograph of the Ph. Eur. on the *Productswiththe riskofTSE* 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 se- lected. The test methods have been described and have been adequately validated, as appropri- ate. 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 alu- minium foil. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guide- lines. 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 phar- maceutically 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 ade- quately 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 regard- ing 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 evalua- tion.

No new toxicity studies were submitted by the Applicant for the product, which is acceptable for this type of application.

III.5 Ecotoxicology/environmentalrisk assessment

Since Aripiprazole Focus 5 mg, 10 mg, 15 mg, 30 mg tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussionon 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 ab- solute 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 dis- tribution of 4.9 l/kg, indicating extensive extravascular distribution. At therapeutic con- centrations, 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 biotransfor- mation 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. Aripipra- zole 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 approxi- mately 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 be- tween 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 be- tween 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 bioequiv- alence 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 bioana- lytical 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 AUC0-72 and Cmax 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 re- garding 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		
AUC0-72	103.26%	98.02%	108.78%	11.23%	21.28%
Cmax	104.17%	95.83%	113.24%	18.08%	21.99%

1Calculated using least-squares means according to the formula: e(DIFFERENCE) X 100.
290% Geometric Confidence Interval using ln-transformed data.

Conclusion on the bioequivalenc estudy

Results derived from the analysis of log-transformed primary target parameters, Cmax and AUC0-72 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.5Clinical 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 for- mulations 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 Phar- macovigilance 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 ac- ceptable.

IV.6.2Risk 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 • Weight gain • Hyperglycaemia/diabetes • Cardiovascular related disorders (including conduction abnormalities, orthostatic hypotension, increased mortality and cerebrovascular 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 CYP3A4orCYP2D6 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 re- duced or the treatment discontinued. When the dose is reduced close monitoring is necessary. *4.6 Fertility,pregnancy and lactation:* neo- nates exposed to antipsychotics (including aripiprazole) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms. *4.8Undesirable effects:* listed in this section.	None proposed
	4.9 Overdose: potentially medically serious symptoms of overdose include extrapyramidal symptoms. 5.1 Pharmacodynamic properties: identifi- cation 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*	None proposed

	use the occurrence of suicidal behaviour is inherent in psychotic illnesses and mood disorders how- ever a warning about possible suicidal behav- iour early after initiation or switch of antipsy- chotic therapy was stated and that high-risk pa- tients should be closely supervised. *4.8 Undesirable effects*: listed in this section. Prescription-only medicine.	
Somnolence/fatigue	Content in the SmPC: *4.2 Posology and method ofa dministration*: it is stated that the treatment duration for the indication Manic episodes in Bipolar I Disor- der in adolescents aged 13 years and older should be the minimum necessary for symp- tom 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 substan- tially higher incidence of significant undesira- ble effects including EPS related events, som- nolence, 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 bipolar disorder compared to patients with schizophrenia. Prescription-only medicine.	None proposed
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, regard- less of whether these patients had a prior his- tory of gambling and that therefore patients with a prior history of pathological gambling may be at increased risk and should be moni- tored 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	None proposed.

	to severe complications. When weight gain has been reported from post marketing among patients prescribed aripiprazole, it is usually in those with significant risk fac- tors such as history of diabetes, thyroid disor- der 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 ado- lescent 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.	
Hyperglycaemia/diabetes	Content in the SmPC: *4.4 Special warnings and precautions for use:* warning of possible development of hypergly- caemia or diabetes in patients treated with atypical antipsychotic agents including ari- piprazole. 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 abnormalities, orthostatic hypotension, increased mortality and cerebro vascular accident in elderly patients with dementia)	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 hypoten- sion or hypertension. Describing clinical trials 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.	None proposed
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	None proposed

	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.	
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 justi- fies 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*: aripip- razole is not recommended for use in patients with schizophrenia below 15 years of age due to insuffi- cient data on safety and efficacy. And for the treatment of manic episodes in Bipolar I Disorder in adolescents aged 13 years and older the	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.

	treatment duration should be the minimum necessary for symp- tom 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 as- sociated with weight gain after 4 weeks of treat- ment 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.	

The RMS is of the opinion that routine pharmacovigilance activity and routine risk min- imisation 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 authori- sation 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 au- thorization 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 au- thorization 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 other- wise 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 CONCLUSIONS

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.

VI. REVISION DATE

23/04/2024

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From HU/H/0381/001-004 to IE/H/1182/001-004	N/A	25.03.2021	N/A