CBG MEB

Public Assessment Report

Scientific discussion

Aripiprazol Sandoz 10 mg, 15 mg and 30 mg orodispersible tablets

(aripiprazole)

NL/H/3231/001-003/DC

Date: 28 September 2016

This module reflects the scientific discussion for the approval of Aripiprazol Sandoz 10 mg, 15 mg and 30 mg orodispersible tablets. The procedure was finalised on 22 July 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Aripiprazol Sandoz 10 mg, 15 mg and 30 mg orodispersible tablets, from Sandoz B.V.

Aripiprazole is indicated for the treatment:
- Of schizophrenia in adults and in adolescents aged 15 years and older.
- Of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole 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 SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Abilify 10 mg, 15 mg and 30 mg orodispersible tablets which has been registered in the European Union by Otsuka Pharmaceutical Europe Ltd. since 4 June 2004 by the centralised procedure EMEA/H/C/000471.

The concerned member states (CMS) involved in this procedure were for:
- Aripiprazol Sandoz 10 mg and 15 mg orodispersible tablets: Austria, Belgium, Czech Republic, Germany, Spain, France, Italy, Luxembourg, Poland, Slovenia and the Slovak Republic.
- Aripiprazol Sandoz 30 mg orodispersible tablets: Austria, Belgium, Germany, Spain, France, Luxembourg, Poland and Slovenia.

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

II. QUALITY ASPECTS

II.1 Introduction

Aripiprazol Sandoz is an orodispersible tablet available in three strengths.

- Aripiprazol Sandoz 10 mg are round, flat, pink tablets, engraved with ‘10’ on one side and plain on the other side. Each orodispersible tablet contains 10 mg of aripiprazole.
- Aripiprazol Sandoz 15 mg are round, flat, yellow tablets, engraved with ‘15’ on one side and plain on the other side. Each orodispersible tablet contains 15 mg of aripiprazole.
- Aripiprazol Sandoz 30 mg are round, flat, pink tablets, engraved with ‘30’ on one side and plain on the other side. Each orodispersible tablet contains 30 mg of aripiprazole.

The orodispersible tablets are packed in peelable paper/PET/aluminium//PVC/aluminium/oPA blisters and peelable paper/PET/aluminium//PVC/aluminium/oPA unit dose blisters.

The excipients for all orodispersible tablets are: lactose monohydrate, microcrystalline cellulose (E460), croscarmellose sodium, silica colloidal anhydrous, aspartame (E951), magnesium stearate (E470b), vanilla flavour (containing Maltodextrin, Acacia gum, Propylene glycol, Benzyl alcohol, Vanilla flavouring).
To create different colours, the 10 mg and 30 mg strengths contain as extra ingredient iron oxide red (E172) and the 15 mg strength iron oxide yellow (E172).

The 10 mg and 30 mg tablets are fully dose proportional. The 15 mg strength is also dose proportional to the 10 mg and 30 mg strengths, but slightly differs with respect to the quantity of the iron oxide colouring agent.

II.2 Drug Substance

The active substance is a well established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is practically insoluble in water, soluble in methylene chloride, very slightly soluble in ethanol (96%). Aripiprazole does not exhibit optical isomerism The substance shows polymorphism and is manufactured as polymorphic form Type I. The polymorphic identity is routinely controlled by the drug substance specification.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The synthesis consists of four stages, two chemical reaction steps both followed by a purification step of the crude intermediate from both synthesis branches. No class 1 organic solvents or heavy metal catalysts are used in the process. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance
The drug substance specification by the MAH is in line with the Ph.Eur. monograph on aripiprazole with additional tests in line with the specification of the ASMF holder. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 4 batches.

Stability of drug substance
Stability data on the active substance have been provided for three pilot scale batches in accordance with applicable European guidelines. The active substance was stored for 60 months at 25°C/60% RH, for 6 months at 40°C/75% RH and for an additional three production scaled batches data is available of 36 months storage at 25°C/60% RH, and 6 months storage at 40°C/75% RH. No trends or changes were seen in any of the tested parameters at both storage conditions. Based on the data submitted, a retest period could be granted of 5 years when stored under the condition: 'Keep protected from light under nitrogen. Store at a temperature below 30°C'.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The excipients are well known. The main development studies were the characterisation of the reference product, dissolution method development, optimisation of the formulation, the development of the manufacturing process and the performance of comparative dissolution studies complementary to the bioequivalence study with the 10 mg product strength and in support of the biowaiver for the additional strengths. The comparative dissolution studies between the test and reference batch in pH 1.2, 4.5 and 6.8 dissolution media confirm their similarity. The test batch used in the bioequivalence study was manufactured according to the finalised manufacturing process and composition. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps of the manufacturing process are the dry mixing and wet granulation of the intragranular components, mixing of the granules with the extragranular components, lubrication and compression. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for four pilot scaled batches per strength in accordance with the relevant European guidelines. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
Except for the colourants and the vanilla flavour, the excipients comply with the Ph.Eur. The colourants comply with the relevant EU regulation. Vanilla flavour is tested according to an in-house specification. The specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identity, dimensions, disintegration, assay, related substances, dissolution, uniformity of dosage units, uniformity of mass, water content and microbial quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from four pilot scaled batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided on four pilot scaled batches per strength stored at 25°C/60% RH (24 months, one batch only 12 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed blisters. The stability data show no clear changes or trends in any of the tested parameters at both storage conditions. Results of a photostability study showed that the drug product is not sensitive to light exposure. The prosed shelf-life of 36 months without any special storage requirements is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is the only material of animal origin that is used in the manufacture of the drug product. A BSE statement for lactose monohydrate stating that it has been produced from milk sourced from healthy cows in the same conditions as milk collected for human consumption and is produced without the use of other ruminant material than calf rennet, according to the description as published in Public Statement EMEA/CPMP/571/02.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Aripiprazol Sandoz orodispersible tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Aripiprazol Sandoz 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.2 Discussion on the non-clinical aspects

This product is a generic formulation of Abilify which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Aripiprazole is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Aripiprazole 10 mg orodispersible tablets (Medana Pharma Spólka Akcyjna, Poland) is compared with the pharmacokinetic profile of the reference product Abilify 10 mg, orodispersible tablets (Otsuka Pharmaceutical Europe Ltd., UK).

The choice of the reference product in the bioequivalence study is accepted, as Abilify has been registered through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
The MAH applied for a biowaiver for the additional drug product strengths (15 mg and 30 mg). All strengths are manufactured with the same manufacturing process. Except for a slight difference with respect to the colour and quantity of the iron oxide colouring agent for the 15 mg strength, the different tablet strengths are quantitatively proportional.
The comparative dissolution studies between the bioequivalence study test and reference batch in pH 1.2, 4.5 and 6.8 dissolution media confirm their similarity and these results are complementary to the results of the *in vivo* bioequivalence study. Where dissolution was less than 85% in 15 minutes, f2-values have been adequately calculated.
The biowaiver is supported by the presented *in vitro* dissolution data. Similarity could not be demonstrated in pH 4.5 medium between one tablet of 10 mg versus 1 tablet of 30 mg, clearly due to the dose dependent solubility in this medium. However, when 3 tablets of 10 mg were compared with 1 tablet of 30 mg, the calculated f2-value was >50, confirming similarity. This is an acceptable approach. Dissolution was shown to be very poor in pH 6.8 medium for all three strengths.

Bioequivalence study
Design
An open label, balanced, randomised, two-treatment, two-sequence, two-period, single-dose, crossover pivotal comparative bioequivalence study was carried out under fasted conditions in 28 healthy male subjects, aged 45-59 years. Each subject received a single dose (10 mg) of one of the 2 aripiprazole formulations. Subjects were fasted for at least 10 hours prior to scheduled time for dosing. Just before dosing, 20 ml of water was administered to the subjects and asked to swirl around the mouth to moisten the buccal cavity and then swallow it. As per the randomisation schedule, one 10 mg tablet of test or reference product was placed over tongue. The subjects were asked to close their mouth in a natural way, without chewing, biting or breaking the study drug. Once the tablet was completely dissolved after being placed on the tongue, the subjects swallowed the saliva. There were 2 dosing periods, separated by a washout period of 35 days.

Blood samples were collected at prior to dosing and at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. The proposed tablets can be taken with or without food. Thus, a study in fasting conditions is appropriate. Administration of the tablets under thirsting conditions is adequate as Abilify orodispersible may be taken with or without water. Considering that aripiprazole is a drug with low solubility, in principle, the highest strength should be used to show bioequivalence. A lower strength was used due to serious safety consideration of healthy volunteers, as the highest

strength cannot be administered to healthy volunteers for safety/ tolerability reason. Based on the justification provided by the MAH, the choice of 10 mg strength for the bioequivalence study is considered justified.
The wash-out period of 35 days is long enough to prevent carry-over effects as this is ≥ 5X aripiprazole's half-life. e mean elimination half-lives for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6. Estimation of the extent of absorption over a period of 72 hours is appropriate.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Two subjects were withdrawn from the study due to emesis. Twenty-six subjects completed the study and were included in the pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 10 mg aripiprazole under fasted conditions.

Treatment N=26	**AUC_{0-72}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	2065 ± 414	48.8 ± 10	3.8 (1-12)
Reference	1940 ± 343	47.0 ± 10	4.3 (1-10)
***Ratio (90% CI)**	1.06 (1.01-1.11)	1.04 (0.96-1.12)	--
AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration			

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-72} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Aripiprazol Sandoz 10 mg orodispersible tablets is considered bioequivalent with Abilify 10 mg orodispersible tablets.

Safety
A total of three adverse events (2 vomiting and 1 anxiety) in 3 subjects were experienced with the reference over the course of the study which were mild in nature. No serious adverse event were observed.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Aripiprazol Sandoz orodispersible tablets.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Extrapyramidal syndrome (EPS), including tardive dyskinesia • Neuroleptic Malignant Syndrome (NMS)

Important potential risks	• Seizures • Hyperglycaemia/diabetes mellitus • Suicide-related events • Orthostatic hypotension • Dyslipidaemia • Weight gain • Somnolence/fatigue • Cardiovascular-related disorders • Conduction abnormalities • Growth • Low prolactin in paediatric patients • Dysphagia (predominantly applies to schizophrenic population) • Lactose intolerance (if applicable) • ADHD comorbidity • Drug interactions • Increased mortality and CVA in elderly patients with dementia • Pathological gambling • Serotonin syndrome • Hepatic adverse events
Missing information	• Use in pregnancy and lactation • Use in paediatrics

As an additional risk minimisation measure the MAH should provide educational material. All healthcare professionals who are expected to prescribe aripiprazole product are provided with an information pack:

- Summary of Product Characteristics (SmPC) and Package Leaflet (PL)
- Educational material for the healthcare professionals
- Educational material for the patients and their caregivers.

The content and distribution of the educational material will be agreed with the National Authority of each member state.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Abilify orodispersible tablets. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The PL 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 test consisted of a pilot test, followed by two rounds. In both test rounds all participants were able to find the correct information and to answer the questions correctly.
The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Aripiprazol Sandoz 10 mg, 15 mg and 30 mg orodispersible tablets have a proven chemical-pharmaceutical quality and are generic forms of Abilify 10 mg, 15 mg and 30 mg orodispersible tablets. Abilify is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Aripiprazol Sandoz 10 mg, 15 mg and 30 mg orodispersible tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 July 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
MAH, due to their Internal Quality Standards, wants to submit an additional bioequivalence study for the product with a type II variation under code C.I.13.	NL/H/3231/ 001-003/II/001	II	15-10-2015	26-1-2016	Approval	
Implementation of change(s) for which no new additional data is required to be submitted by the MAH. Reference text is updated.	NL/H/3231/ 001-003/IB/002	IB	25-4-2016	25-5-2016	Approval	No
Change in the product name in Slovenia.	NL/H/2131/ 001-003/IB/003	IB	21-6-2016	21-7-2016	Approval	No
Implementation of wording agreed by the competent authority	NL/H/3231/ 001-003/IA/004	IA	5-7-2016	4-8-2016	Approval	No