CBG MEB

# Public Assessment Report

# Scientific discussion

# Aripiprazol Universal Farma 5 mg, 10 mg, 15 mg and 30 mg tablets

# (aripiprazole)

## NL/H/3253/001-004/DC

## Date: 1 August 2016

**This module reflects the scientific discussion for the approval of Aripiprazol Universal Farma 5 mg, 10 mg, 15 mg and 30 mg tablets. The procedure was finalised on 23 June 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 |
| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| CHMP | Committee for Medicinal Products for Human Use |
| CMD(h) | Coordination group for Mutual recognition and Decentralised procedure for human medicinal products |
| CMS | Concerned Member State |
| EDMF | European Drug Master File |
| EDQM | European Directorate for the Quality of Medicines |
| EEA | European Economic Area |
| 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 Universal Farma 5 mg, 10 mg, 15 mg and 30 mg tablets, from Universal Farma, S.L.
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 5 mg, 10 mg, 15 mg and 30 mg 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:

- 5 mg and 30 mg tablets: Germany, Ireland and Italy.
- 10 mg and 15 mg tablets: Germany Ireland, Italy and Portugal.

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

# II. QUALITY ASPECTS

## II.1 Introduction

Apiriprazol Universal Farma is a tablet.

- 5 mg tablets: Round plane pale pink tablet and each tablet contains 5 mg aripiprazole.
- 10 mg tablets: Round biconvex pale pink tablet and each tablet contains 10 mg aripiprazole.
- 15 mg tablets: Round biconvex pale pink tablet scored in one side. The score line is not intended for breaking the tablet. Each tablet contains 15 mg aripiprazole.
- 30 mg tablets: Round biconvex pale pink tablet and each tablet contains 30 mg aripiprazole.

The tablets are packed in Aluminium-Aluminium blisters.

The excipients are: lactose monohydrate, maize starch, microcrystalline cellulose, hydroxypropyl cellulose, magnesium stearate and red iron oxide (E172)

The four tablet strengths are dose proportional.

## II.2 Drug Substance

The active substance is aripiprazole, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is practically insoluble in water, very slightly soluble in ethanol and soluble in methylene chloride. The substance shows polymorphism and Type-I is produced. The substance does not contain any chiral carbon atoms and does not exhibit any optical isomerism.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of

reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is is in line with the Ph.Eur. and CEP, with additional requirements for particle size distribution. The specification is acceptable in view of the route of synthesis. Batch analytical data demonstrating compliance with this specification have been provided for three full scaled batches.

Stability of drug substance
The active substance is stable for 2 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

## 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. Furthermore the choice of manufacturing process, critical parameters and scalability issues has been justified.

A bioequivalence study was performed, using the 10 mg strength. Dissolution profiles of the test product and reference product were recorded, in 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. Individual results of the dissolution studies are provided. Dissolution was >85% in 15 min in 0.1 N HCl and in pH 4.5 acetate buffer and these profiles are similar. The profiles of test and reference products in pH 6.8 phosphate buffer are also similar as mathematical evaluation has been performed.

The MAH has provided dissolution comparison of the 5 mg, 15 mg and 30 mg test products with the 10 mg product used in the biostudy in order to obtain a biowaiver of strengths. The dissolution profiles of the 5 mg, 15 mg and 30 mg strength are considered similar to the 10 mg biobatch. The dissolution conditions (temperature and volume) and apparatus are based on requirements of Note for Guidance on the Investigation of Bioequivalence and therefore justified.

Manufacturing process
The manufacturing process consists of blending, granulation, mixing, lubrication and compression. Process validation data on the product have been presented for three batches of each strength in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques and is considered a standard process.

Control of excipients
The excipients comply with Ph.Eur. requirements, except for the colourant Iron Oxide Red. The in-house specification for this colourant (E172) is acceptable as it is tested according to EU 231/2012. These 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 appearance, uniformity of mass, water, uniformity of dosage units, dissolution, identity , identity of iron colourant, assay, related substances and microbiological purity. 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 3 small commercial scaled batches from both proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided on three smallest commercial scaled batches of the 5 mg, 10 mg and 30 mg strength from one manufacturer stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). Matrixing design is applied for the 15 mg strength. Stability studies have been started with the validation batches manufactured at the second manufacturer (three batches each of 5 mg, 10 mg and 30 mg and one batch of 15 mg). Tablets were stored in the proposed packages. The proposed shelf-life of 24 months is therefore justified. The products are not sensitive to light and no specific storage restrictions apply.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is the only excipient of animal origin. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

### II.4 Discussion on chemical, pharmaceutical and biological aspects

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

The following post-approval commitments were made:
- The MAH committed to continue the stability studies of the batches from the second manufacturer in order to obtain real time results covering the entire shelf-life of the product. The MAH committed to perform comparative dissolution profiles in accordance with the dissolution method described in the dossier for a total of three commercial scale batches of each strength of the second manufacturer.

## III. NON-CLINICAL ASPECTS

### III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Aripiprazol Universal Farma is 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 one bioequivalence study, which is discussed below.

## IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Aripiprazol Universal Farma 10 mg tablet (Universal Farma, S.L., Spain) is compared with the pharmacokinetic profile of the reference product Abilify 10 mg tablet (Otsuka Pharmaceutical Europe Ltd., UK).

The choice of the reference product in the bioequivalence studies 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 5 mg, 15 mg and 30 mg strengths. Comparative dissolution testing was performed between the biobatch 10 mg and 5, 15 and 30 mg at pH 1.2, 4.5 and 6.8. Dissolution at pH 1.2 and 4.5 is very fast for all strengths as more than 85% dissolved in 15 minutes. The calculation of the f2 similarity factor between 10 mg biobatch and 5 mg, 15 mg and 30 mg resulted in values of 87, 86 and 72 respectively, thus the batches were found to be similar in phosphate buffer pH 6.8.The biowaiver for the additional strengths 5 mg, 15 mg and 30 mg can therefore be granted.

Bioequivalence study

*Design*

A randomized, open label, balanced, two-treatment, two-sequence, two-period, single-dose, crossover pivotal comparative bioequivalence study was carried out under fasted conditions in 30 healthy male (n=15) and female (n=15) subjects, aged 45-64 years. Each subject received a single dose (10 mg) of one of the 2 aripiprazole formulations. The tablet was orally administered with 240 ml water after a 10 hour fasting period. There were 2 dosing periods, separated by a washout period of 35 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 60 and 72 hours after dosing.

The overall study design is acceptable. 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 reasons. Based on the justification provided by the MAH, the choice of 10 mg strength for the bioequivalence study is considered justified.
As the half life of aripiprazole is about 90 hours, estimation of the extent of absorption over a period of 72 hours is acceptable. Also the washout period is acceptable. The product can be taken regardless of food intake, therefore a study under fasting conditions is justified.

*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*

24 subjects completed all the periods of the study and were included in the pharmacokinetic analysis and statistical analysis. One subject was withdrawn for adverse events reasons, and 5 subjects were withdrawn in the first period according to protocol, as they vomited after intake of the drugs.

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

| Treatment N=24 | $AUC_{0-72}$ ng.h/ml | $C_{max}$ ng/ml | $t_{max}$ h |
|---|---|---|---|
| **Test** | 1436 ± 23 | 44.9 ± 37 | 2.3 |
| **Reference** | 1357 ± 24 | 40.8 ± 437 | 3.3 |
| ***Ratio (90% CI)** | 1.06 (1.01 – 1.11) | 1.09 (0.97 – 1.22) | -- |
| **CV (%)** | 8.7 | 23 | -- |

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|---|---|
| $AUC_{0-72}$ | area under the plasma concentration-time curve from time zero to 72 hours |
| $C_{max}$ | maximum plasma concentration |
| $t_{max}$ | time for maximum concentration |
| CV | coefficient of variation |

**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 Universal Farma 10 mg tablets are considered bioequivalent with Abilify 10 mg tablets.

*Safety*

A total of 29 mild and 8 moderate adverse events (AEs) were experienced by the subjects after taking the test product. A total of 32 mild and 5 moderate AEs were experienced by the subjects after taking the reference product. A total of 5 mild AEs associated with clinical laboratory tests were experienced by the subjects post-study. No serious adverse events were reported during the conduct of this study. Both the test product and reference product were well tolerated by all subjects.

The MEB has been assured that the bioequivalence study has 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 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 Universal Farma. However, the RMP was not in line with that of the reference product. After finalisation of the decentralised procedure, the MAH submitted a variation to introduce an updated, revised RMP in accordance with the innovator's.

Summary table of safety concerns as approved in RMP:

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|---|---|
| Important identified risk | • Extrapyramidal syndrome (EPS), including tardive dyskinesia<br>• Neuroleptic Malignant Syndrome (NMS) |
| Important potential risk | • Seizures<br>• Hyperglycaemia/diabetes mellitus<br>• Suicide-related events<br>• Orthostatic hypotension<br>• Dyslipidaemia<br>• Weight gain<br>• Somnolence/fatigue<br>• Cardiovascular-related disorders |

| | |
|---|---|
| | • Conduction abnormalities<br>• Growth<br>• Low prolactin in paediatric patients<br>• Dysphagia (predominantly applies to schizophrenic population)<br>• Lactose intolerance (if applicable)<br>• ADHD comorbidity<br>• Drug interactions<br>• Increased mortality and CVA in elderly patients with dementia<br>• Pathological gambling<br>• Serotonin syndrome<br>• Hepatic AEs |
| Missing information | • Use in pregnancy and lactation<br>• Use in paediatrics |

As an additional risk minimisation measure the MAH should provide educational material. This should contain the following key elements:

Key elements of the Healthcare Professional FAQ Brochure (Q&A format) intended for Healthcare Providers treating adolescent patients with bipolar mania:

- Brief introduction to aripiprazole indication and the purpose of the tool
- Instructions reinforcing that the indicated age range is 13-17 years and that aripiprazole is not recommended for use in patients below 13 years of age due to safety concerns
- Instructions that the recommended dose is 10 mg/day and that enhanced efficacy at higher doses has not been demonstrated
- Information regarding the safety and tolerability profile of aripiprazole, in particular potential consequences regarding adverse effects at doses higher than 10 mg/day, in particular with respect to:
    - Weight gain, including a recommendation to monitor patients
    - Extrapyramidal symptoms
    - Somnolence
    - Fatigue
- Reminder to educate patients/caregivers and distribute the Patient/Caregiver Information Brochure

Key elements of the Patients/Caregiver Information Brochure:

- Brief introduction to aripiprazole indication and the purpose of the tool
- Information that the indicated age range is 13-17 years and that aripiprazole is not recommended for use in patients below 13 years of age
- Information that aripiprazole can cause adverse effects at doses higher than 10 mg/day, in particular with respect to:
    - Weight gain, including a recommendation to monitor patients
    - Extrapyramidal symptoms
    - Somnolence
    - Fatigue
- Request to inform the physician of all medical conditions before treatment
- The importance of not attempting to self-treat any symptoms without consulting their Healthcare professional

### IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Abilify. 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 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 test consisted of: a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Sufficient questions were asked (19). All participants were able to trace the information for the questions and answered all questions correctly.
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. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Aripiprazol Universal Farma 5 mg, 10 mg, 15 mg and 30 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Abilify 5 mg, 10 mg, 15 mg and 30 mg 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 Universal Farma with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 June 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 |
|---|---|---|---|---|---|---|
| Variation in order to bring the RMP in line with that of the reference product. | NL/H/3253/ 1-4/1A/001 | IA | 13-11-2015 | 13-12-2015 | Approved | No |