Public Assessment Report

Scientific discussion

Aripiprazol Bristol 5 mg, 10 mg, 15 mg, 20 mg and 30 mg tablets

(aripiprazole)

NL/H/3687/001-005/DC

Date: 12 April 2019

This module reflects the scientific discussion for the approval of Aripiprazol Bristol 5 mg, 10 mg, 15 mg, 20 mg and 30 mg tablets. The procedure was finalised on 17 August 2017. 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
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 Bristol 5 mg, 10 mg, 15 mg, 20 mg and 30 mg tablets from Bristol Laboratories Ltd.

The product is 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 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 EU/1/04/276/001-005.

The concerned member states (CMS) involved in this procedure were Germany, Ireland and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) (5 mg, 10 mg, 15 mg, 30 mg strengths) and Article 10(3) (20 mg strength) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Aripiprazol Bristol is a tablet.
- 5 mg tablets: Light blue to blue, modified rectangular bevel edged biconvex tablets debossed with ‘I’ on one side and ‘95’ on other side.
- 10 mg tablets: Light pink to pink, modified rectangular, bevel edged biconvex tablets debossed with ‘I’ on one side and ‘96’ on other side.
- 15 mg tablets: Light yellow to yellow, round, bevel edged biconvex tablets debossed with ‘I’ on one side and ‘97’on other side.
- 20 mg tablets: White to off-white, round, bevel edged biconvex tablets debossed with ‘I’ on one side and ‘98’ on other side.
- 30 mg tablets: Light pink to pink, round, bevel edged biconvex tablets debossed ‘I’ on one side and ‘99’ on other side.

Each tablet contains as active substance 5 mg, 10 mg, 15 mg, 20 mg or 30 mg of aripiprazole.

The tablets are packed in PVC/Aluminium/OPA-Aluminium blister packs.

The excipients are:
5 mg - lactose monohydrate, maize starch, microcrystalline cellulose, indigo carmine aluminium lake (E132), hydroxypropyl cellulose and magnesium stearate.
10 mg - lactose monohydrate, maize starch, microcrystalline cellulose, hydroxypropyl cellulose, iron oxide red (E172) and magnesium stearate.
15 mg - lactose monohydrate, maize starch, microcrystalline cellulose, hydroxypropyl cellulose, iron oxide yellow (E172) and magnesium stearate.
20 mg - lactose monohydrate, maize starch, microcrystalline cellulose, hydroxypropyl cellulose and magnesium stearate.

30 mg - lactose monohydrate, maize starch, microcrystalline cellulose, hydroxypropyl cellulose, iron oxide red (E172) and magnesium stearate.

The five 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.). Aripiprazole is white or almost white crystals or crystalline powder. It is practically insoluble in water, soluble in methylene chloride and very slightly soluble in ethanol. It is hygroscopic in nature and it exhibits polymorphism. The polymorph manufactured is aripiprazole anhydrous type I crystals.

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 manufacturing process is adequately described and appropriately validated. In-process controls are well described. Raw materials are well controlled. Two starting materials are being proposed. One of the starting materials, has been redefined back to earlier steps in the route of synthesis, as requested.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. In addition, in-house tests for particle size, microbiological purity, hygroscopicity and in-house related substances are included and the limits are acceptable. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Stability data have been provided of three validation batches at long-term (25°C/60%RH) and accelerated (40°C/75% RH) conditions. The results show that all tests were within the approved specification and no negative trends were observed. Based on the data submitted, a retest period of five years could be granted.

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. An extensive development program has been performed. Experiments were carried out to optimise the concentration of inactive ingredients like binder, disintegrant, diluent and lubricant and compressed tablets were evaluated for tablet compression parameters and dissolution profiles.

Two bioequivalence studies have been performed, using the 5 mg test product and 10 mg test product. A biowaiver of strength is applied for the 15 mg, 20 mg and 30 mg strengths. Dissolution profiles (supportive in case of the 5 mg and 10 mg strengths but required for the 15 mg, 20 mg and 30 mg strength) are provided and similarity has been confirmed except for the 10 mg bioequivalence batch versus the reference product in pH 4.5. However, as both products have been shown to be bioequivalent, this prevails. The discriminatory nature of the dissolution method for commercial batches has been shown.

Manufacturing process
The product is manufactured using conventional manufacturing techniques. Common granules are manufactured for the 10 mg, 15 mg, 20 mg and 30 mg. These are then divided to form a common blend for the 10 mg and 30 mg strengths (use of iron oxide red), a blend for 15 mg strength (using iron oxide yellow) and a blend for 20 mg strength (no colourant added). Blends are then used for compression of the tablets. Separately, granules are prepared for the 5 mg strength (using FD & C Blue #2 Indigo Carmine AL 30-60%), of which a blend is prepared and which is used for compression of 5 mg strength tablets.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three commercial scaled batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph.Eur. and/or United States Pharmacopoeia National Formulary (USP/NF), and in-house specifications (indigo carmine). 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, identity of aripiprazole, average weight, dissolution, assay, degradation products, water, uniformity of dosage units 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 three commercial scaled batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided on three commercial scaled batches of each strength stored at 25°C/60% RH (36 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 packaging. All results remain with limits. On the basis of the data submitted, a shelf life was granted of 36 months in the blisters with no specific storage restriction. The drug product is not sensitive to light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
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 Bristol has 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 Bristol 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 two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

Bioequivalence studies
The MAH conducted two bioequivalence studies in which the pharmacokinetic profile of the test product Aripiprazol Bristol tablets (Bristol Laboratories Ltd, United Kingdom) is compared with the pharmacokinetic profile of the reference product Abilify tablets (Otsuka Pharmaceutical Europe Ltd, United Kingdom).

The choice of the reference product
The choice of the reference product in the bioequivalence studies has been justified.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
The bioequivalence studies were carried out with the 5 mg and 10 mg tablets. The 20 mg strength is a new strength but is within the dose range of 10 to 30 mg/day, for which the benefit-risk has been demonstrated for Abilify. Therefore, a waiver of strength could be applicable for the 20 mg strength. Based on an acceptable bioequivalence study for aripiprazole 10 mg, a biowaiver is granted for aripiprazole 15 mg, 20 mg and 30 mg tablets as per following considerations:

- Aripiprazole 10 mg, 15 mg, 20 mg and 30 mg tablets are manufactured by the same manufacturer and using the same manufacturing process.
- The pharmacokinetics of aripiprazole are linear and dose proportional in a dose range of 5-30mg/day.
- The qualitative composition of aripiprazole 15 mg, 20 mg and 30 mg tablets is the same as that of aripiprazole 10 mg tablets.
- Aripiprazole 15 mg, 20 mg and 30 mg tablets are dose proportional with aripiprazole 10 mg tablets. Thus, the ratio of amount of active substance and the excipients is the same for all the strengths.
- The dissolution profile of aripiprazole 15 mg, 20 mg and 30 mg tablets is similar to aripiprazole 10 mg tablets i.e. test batch used in bioequivalence study in 0.1N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. The dissolution tests in pH 6.8 were performed with a high rotation speed (60 rpm). A lower rotation speed in pH 6.8 makes it difficult to compare profiles of the BE batch and the other strengths due to incomplete dissolution (< 5%).

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.

Bioequivalence study 5 mg tablets

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 20-44 years. Each subject received a single dose (5 mg) of one of the two aripiprazole formulations. The tablet was orally administered with 240 ml water after a supervised overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 36 days.

Blood samples were collected pre-dose and at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 9.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 after administration of the products.

The design of the study is acceptable. Taking into account the expected time to peak concentration and the elimination half-life of aripiprazole, the sampling schedule and the sampling time period of 72 hours are adequate. 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 5 mg strength for the bioequivalence studies is considered justified.

Results

One subject was withdrawn from the study due to vomiting during period-I and one subject withdrew consent on his accord during period-I. Two subjects were withdrawn from the study due to breath alcohol test found to be positive during period-II and two subjects did not report to the facility for period-II check-in, hence considered as dropout from the study. Therefore 30 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 5 mg aripiprazole under fasted conditions.

Treatment N=30	**AUC_{0-t}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	1267.6 ± 364.16	39.31 ± 9.13	2.25 ± 1.20
Reference	1209.7 ± 371.40	37.05 ± 10.09	2.50 ± 1.20
***Ratio (90% CI)**	1.05 (1.02 - 1.09)	1.07 (1.01 - 1.13)	--
CV (%)	7.59	12.61	--

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

**ln-transformed values*

Safety results

Overall, the safety profile of both the test and reference products was similar. There were five adverse events reported for four subjects. These adverse events were mild in severity and considered possible related with the reference product. During post study safety assessment, a total thirteen adverse events were reported for seven subjects. The study medications were well tolerated by all subjects who participated in the study.

Bioequivalence study 10 mg tablets

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy male subjects, aged 20-43 years. Each subject received a single dose (10 mg) of one of the two aripiprazole formulations. The tablet was orally administered with 240 ml water after a supervised overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 36 days.

Blood samples were collected pre-dose and at 0.50, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 9.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 after administration of the products.

The design of the study is acceptable. Taking into account the expected time to peak concentration and the elimination half-life of aripiprazole, the sampling schedule and the sampling time period of 72 hours are adequate. 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 studies is considered justified.

Results
Four subjects did not report to the facility for period-II check-in, hence considered as dropout from the study. Therefore 32 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 10 mg aripiprazole under fasted conditions.

Treatment N=32	**AUC_{0-t}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	2223.85 ± 635.26	67.39 ± 24.77	2.50 ± 1.72
Reference	2297.57 ± 754.92	69.60 ± 25.73	2.50 ± 1.89
***Ratio (90% CI)**	1.00 (0.88 – 1.15)	0.99 (0.84 - 1.17)	--
CV (%)	32.84	40.18	--

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

**ln-transformed values*

Safety results
Overall, the safety profile of both the test and reference products was similar. There were two adverse events reported during entire duration of the study. These adverse events were mild in severity and considered possible related with the reference product. During post study safety assessment, a total ten adverse events were reported for six subjects. The study medications were well tolerated by all subjects, who participated in the study.

Conclusion on bioequivalence studies
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Aripiprazol Bristol is considered bioequivalent with Abilify.

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 Bristol.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Neuroleptic malignant syndrome • Extrapyramidal symptoms (EPS), including tardive dyskinesia • Leukopenia
Important potential risks	• Seizures • Hyperglycaemia/diabetes • Suicide-related events • Orthostatic hypotension • Dyslipidemia
Missing information	• Use in paediatrics • Use in pregnancy and lactation • Use in elderly patients above 65 years of age

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

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 bioequivalence studies 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Abilify. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Aripiprazol Bristol 5 mg, 10 mg, 15 mg, 20 mg and 30 mg tablets has a proven chemical-pharmaceutical quality. The 5 mg, 10 mg, 15 mg and 30 mg strengths are a generic form of Abilify 5 mg, 10 mg, 15 mg and 30 mg; the 20 mg strength is a hybrid form. 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 Bristol with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 August 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse