CBG MEB

Public Assessment Report

Scientific discussion

Aripiprazol Sciecure 10 mg and 15 mg orodispersible tablets

(aripiprazole)

NL/H/3855/001-002/DC

Date: 11 December 2018

This module reflects the scientific discussion for the approval of Aripiprazol Sciecure 10 mg and 15 mg orodispersible tablets. The procedure was finalised on 3 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

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 Sciecure 10 mg and 15 mg orodispersible tablets from Sciecure Pharma Ltd.

The product 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 a centralised procedure (EMEA/H/C/000471).

The concerned member state (CMS) involved in this procedure was the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Aripiprazol Sciecure is an orodispersible tablet.
- 10 mg tablets: Pale pink, round tablets. Each tablet contains 10 mg aripiprazole.
- 15 mg tablets: Pale brown, round tablets. Each tablet contains 15 mg aripiprazole.

The orodispersible tablets are packed in Alu-Alu blisters.

The excipients are calcium silicate, microcrystalline cellulose, crospovidone, croscarmellose sodium, silica colloidal anhydrous, xylitol, aspartame (E951), acesulfame potassium, tartaric acid, magnesium stearate, vanillin, red iron oxide (E172) (10 mg strength) and yellow iron oxide (E172) (15 mg strength)

The two 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 a white or almost white crystals or crystalline powder. The active substance is practically insoluble in water. Aripiprazole can exist in several crystalline forms; the manufacturer (Polpharma) consistently produces the anhydrous crystalline aripiprazole form B (or Type I).

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 considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for five batches.

Stability of drug substance
The active substance is stable for three 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. The excipients are well known. To prevent hydration and any subsequent unwanted polymorphic transformation, aripiprazole anhydrous is used and the manufacturing process is performed by direct compression. The main development studies were the characterisation of the reference product, dissolution method development, optimisation of the formulation, manufacturing process development and the performance of comparative dissolution studies complementary to the bioequivalence study with the 10 mg product strength.
A biowaiver to 15 mg strength is considered approvable. Comparative dissolution between the 10 mg strength and 15 mg strength has been shown at pH 1.2, 4.5 and 6.8.

Manufacturing process
The manufacturing processes consists of mixing, mixing/lubrication, tabletting, blistering and final packaging. The process is described in sufficient detail and is considered to be a standard process. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for one pilot scale batch in accordance with the relevant European guidelines.

Control of excipients
All excipients are controlled conform Ph.Eur. or United States Pharmacopoeia (USP). 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, average weight, resistance to crushing, uniformity of dosage units, identification, identification of colourants, water content, dissolution, assay, related substances, each specified impurity, any unspecified impurity, total related substances and microbiological 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 one laboratory scale and two pilot scale batches of the 10 mg strength product and on one laboratory scale batch and one pilot scale batch of the 15 mg strength product from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability testing was performed on three batches (two pilot scale and one laboratory scale) of aripiprazole 10 mg strength tablets and two batches (one laboratory scale and one pilot scale) 15 mg strength tablets stored under long term (25°C/60% RH, up to 36 months), intermediate (30°C/65% RH, up to 36 months) and accelerated (40°C/75% RH up to 6 months) conditions. The conditions used in the stability studies are according to the ICH stability guideline.
Based on the currently available stability results of 36 months of the dissolution test with time point 15 min, which show compliance to the approved (tightened) limit, a shelf-life period of 36 months is acceptable. As data of intermediate conditions have not been provided showing compliance to the dissolution test with 15 min time point, the storage condition ‘store below 25°C’ is necessary for now.

It has been committed (post-approval point) that the storage conditions will be re-evaluated (by application for a variation) when additional stability data has been generated using the dissolution method with a time point of 15 min and according to the approved (tightened) limit.

Although the Ph.Eur. monograph for aripiprazole prescribes storage protected from light and the results of the photostability study show slight degradation of the photo irradiated samples, no special storage conditions regarding protection from light are claimed. This is acceptable, as the proposed packaging (Al/Al-blisters) is expected to provide sufficient protection from light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

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

The following post-approval commitments (PAC) were made:

- The MAH has committed to finding a suitable analytical procedure for performing thermogravimetry analysis of the excipient magnesium stearate and to implement this method and a suitable limit in the specification of the excipient.. It is expected that the resulting specification and description of analytical method are provided to the NCA's in order to fulfil the PAC.
- The MAH has committed to perform additional stability studies on commercial batches. As a significant change at the accelerated storage condition for the primary batches, it is expected that in line with the "guideline on stability testing: stability testing of existing active substances and related finished products", testing on the commitment batches will be conducted at either the intermediate or the accelerated storage condition. If results at accelerated conditions up to 6 months comply with the new limits, the MAH is requested to apply for a variation application to change the storage condition to 'no specific storage conditions'. If results at intermediate conditions up to 12 months comply with the new limits, the MAH is requested to apply for a variation application to change the storage condition to 'store below 30°C'.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Aripiprazol Sciecure 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

Aripiprazol Sciecure 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

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Aripiprazol Sciecure 10 mg orodispersible tablets (Sciecure Pharma Ltd, Greece) is compared with the pharmacokinetic profile of the reference product Abilify 10 mg orodispersible tablets (Otsuka Pharmaceutical Europe Ltd, United Kingdom).

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

Biowaiver
A biowaiver for 15 mg strength is justified based on the following:
- Both strengths are manufactured by the same manufacturing process.
- The qualitative composition of the different strengths is the same.
- The quantitative composition of the different strength is the same.
- Both strengths show similar dissolution profiles at three different pH levels.

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 30 healthy male and female subjects, aged 40-60 years. Each subject received a single dose (10 mg) of one of the two aripiprazole formulations. The subjects fasted under supervision overnight for at least 10 hours before the drug administration. Water intake was not limited except 1 hour prior to and 2 hours after drug administration. The subjects drank only 20 ml of water directly before administration to wet the mouth. The orodispersible tablet was placed in the mouth on the tongue and after dispersion in saliva it was swallowed. The tablet was not sucked, chewed or broken. Immediately after administration (swallowing the dispersed tablet), the subject's oral cavity and hands were checked to confirm complete medication and fluid intake. The administration procedure was witnessed by a nurse. There were two dosing periods, separated by a washout period of 28 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4, 5, 6, 7, 8, 10, 12, 16, 24, 48, and 72 hours after administration of the products.

The design of the study is acceptable. Administration of the tablets under thirsting conditions is adequate as Abilify orodispersible tablets may be taken with or without water. The wash-out period of 28 days is long enough to prevent carry-over effects. The sampling schedule is considered adequate to estimate pharmacokinetic parameters. A lower strength was used due to serious safety consideration of healthy volunteers.

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
Thirty subjects were enrolled into the study. One subject was withdrawn from the study due to adverse events in Period 1. Another subject dropped out of the study during washout for personal reasons. Therefore, 28 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=28	**AUC_{0-t}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	1557.2 ± 314	43.2 ± 8	2.75 (1.0 - 10.0)
Reference	1513.0 ± 357	41.7 ± 9	2.75 (1.5 - 6.0)
***Ratio (90% CI)**	1.04 (0.99 - 1.09)	1.04 (0.99 - 1.10)	--
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			

**ln-transformed values*

Conclusion on bioequivalence study

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 study Aripiprazol Sciecure is considered bioequivalent with Abilify.

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 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 Sciecure.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Extrapyramidal symptoms (EPS), including tardive dyskinesia • Neuroleptic Malignant Syndrome (NMS)
Important potential risks	• Seizures • Hyperglycemia/diabetes mellitus • Suicide-related events • Orthostatic hypertension • Dyslipidaemia
Missing information	• Use in pregnancy and lactation • Use in paediatrics

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 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 (PL) 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 two participants, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. 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 Sciecure 10 mg and 15 orodispersible tablets has a proven chemical-pharmaceutical quality and is a generic form of Abilify 10 mg and 15 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 Sciecure with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 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