Public Assessment Report

Scientific discussion

Preheftari
5 mg, 10 mg, 15 mg and 30 mg tablets

(Aripiprazole)

DK/H/2422/001-004/DC

6 November 2015

This module reflects the scientific discussion for the approval of Preheftari. The procedure was finalised on 13 May 2015. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Preheftari 5 mg, 10 mg, 15 mg and 30 mg tablets, from Sigillata Ltd.

The product is indicated for:

- The treatment of schizophrenia in adults and in adolescents 15 years and older.
- The treatment 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.
- 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 SmPC.

Aripiprazole is an atypical antipsychotic with serotonin 5-HT1A-receptor partial agonist and 5-HT2A-receptor antagonist properties. It is also a partial agonist at dopamine D2 receptors.

This decentralised procedure concerns a generic application claiming essential similarity with the reference product Abilify tablets which has been registered in Europe by Otsuka Pharmaceutical Europe Ltd. since 2004.

The marketing authorisation is granted based on article 10.1 of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

The finished product is conventional uncoated tablets, in the strengths of 5 mg, 10 mg, 15 mg and 30 mg aripiprazole. The tablet strengths are dose proportional.

The 5 mg tablets are round, biconvex and white, 5 mm, debossed "5" on one side and "ZL" on one side.
The 10 mg tablets are capsule shaped, biconvex and white, 8 mm x 5 mm, debossed "10" on one side and "ZL" on one side.
The 15 mg tablets are round, biconvex and white 7 mm, debossed "15" on one side and "ZL" on one side.
The 30 mg tablets are round, biconvex and white 9 mm, debossed "30" on one side and "ZL" on one side.

The tablets are packed in blister packs (OPA/Aluminium/PVC/Aluminium blisters.) with push-through foil and in bottles (high density polyethylene) with child resistant and tamper evident screw cap (PP) closure.
The following pack sizes are available:
Push-through blister packs: 14, 28, 30, 56, and 98 tablets.
Bottles: 100 tablets.
However, not all pack sizes may be marketed.

The tablets contain: Microcrystalline cellulose; Lactose monohydrate; Maize starch; Hydroxypropyl cellulose and Magnesium stearate.

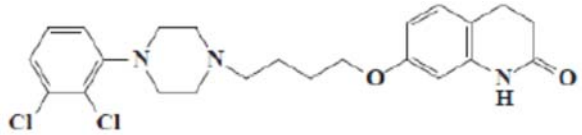
The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

II.2 Drug Substance

The active substance, aripiprazole, is described in the European Pharmacopoeia. It 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 (96 per cent). It shows polymorphism.

INN: Aripiprazole
Chemical names:
7-[4-(4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-2-(lH)- quinolinone
7 -[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril

Molecular structure:



Molecular formula: $C_{23}H_{27}Cl_2N_3O_{21}$
Molecular mass: 448.4

The documentation on the active substance is presented as a European Active Substance Master File.

The synthesis has been properly described from justified starting materials. An impurity discussion is provided including possible impurities in the starting materials. Several impurities are genotoxic and controlled in the final API. The active substance specification is set in accordance with the Ph. Eur. monograph on aripiprazole. Based on the stability data presented an appropriate re-test period has been set.

The finished product manufacturer's drug substance specification has been compiled taking into consideration the Ph.Eur. monograph requirements for aripiprazole and the specifications of the ASM. Requirements relevant for product performance are included as well (particle size and polymorphic form).

II.3 Medicinal Product

The development of the drug product has been adequately described. The chosen excipients are the same as those present in the originator formulation. The excipients are well known and commonly employed in tablet manufacture.

The manufacturing process has been satisfactorily validated at pilot scale, two batches of each strength. A process validation scheme is provided in the dossier for further process evaluation on production scale batches.
The finished product specification is standard for the pharmaceutical form and includes relevant physicochemical, identification, assay and related substances tests. Satisfactory validations of the analytical methods have been presented. Batch analysis results are provided showing that the finished products meet the specifications proposed.

Stability data are provided for two pilot scale batches of all strengths in both the proposed market packagings under long term (30°C/75% RH) and accelerated conditions (40°C/75% RH). The proposed shelf lives of 36 months are supported by the data. The tablets packed in Al/Al blister should be stored in the original package in order to protect from moisture while a storage condition of "Do not store

above 30°C" is employed for the tablets in polyethylene containers.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of aripiprazole are well known. As aripiprazole is a widely used, well-known active substance, the MAH has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview report refers 49 publications up to year 2011. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Preheftari 5 mg, 10 mg, 15 mg and 30 mg tablets 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

Aripiprazole is a well-known active substance combination with established efficacy and tolerability. As aripiprazole is a widely used, well-known active substance, the MAH has not provided additional studies (apart from a supportive bioequivalence study referenced below) and further studies are not required. Overview based on literature review is, thus, appropriate.

The clinical report refers 43 publications up to year 2012. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

IV.2 Pharmacokinetics

To support the application, the MAH submitted as report one single dose bioequivalence study performed under fasting conditions in order to show bioequivalence between the generic Preheftari 10 mg tablets and the reference product Abilify (Otsuka Pharmaceutical Europe Ltd.) 10 mg tablets (from the UK market).

The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of 35 days between the two administrations. One tablet of 10 mg was administered with 240 ml of water in each period.

The study included 34 healthy subjects, of which 20 completed both periods and were considered for the pharmacokinetic and statistical analysis.

The primary variables for the assessment of bioequivalence were AUC_{0-72} and C_{max}. The calculation of AUC_{0-72} instead of AUC_{0-inf} is acceptable for a substance with long half-life like aripiprazole.

The 90% confidence interval of the test/reference ratio (difference in least square means) from ANOVA of the log-transformed AUC_{0-72} and C_{max} of aripiprazole should be within 80.00% to 125.00% in order to conclude bioequivalence.

Results

Table 1. Summary of Pharmacokinetic Parameters for Aripiprazole

PK Parameter (unit)	Statistics	Test Drug - T	Reference Drug- R
AUC(0-72) (h*ng/mL)	N	20	20
	Arithmetic Mean	1705.52	1734.20
	SD (+/-)	347.320	317.907
	CV (%)	20.36	18.33
	Minimum	950.99	1243.94
	Median	1690.37	1624.35
	Maximum	2317.17	2238.25
	Geometric Mean	1669.83	1706.98
Cmax (ng/mL)	N	20	20
	Arithmetic Mean	47.25	48.81
	SD (+/-)	11.346	8.600
	CV (%)	24.01	17.62
	Minimum	20.32	34.88
	Median	44.88	47.80
	Maximum	70.32	66.94
	Geometric Mean	45.86	48.09
Tmax (h)	N	20	20
	Arithmetic Mean	4.60	3.88
	SD (+/-)	2.873	1.385
	CV (%)	62.45	35.74
	Minimum	1.50	1.50
	Median	3.75	4.00
	Maximum	12.00	6.50
	Geometric Mean	3.87	3.61

Table 2. Ratio and 90% Confidence Intervals of Test Product versus Reference Product and Intra-variation Coefficient

Pharmacokinetic Parameter	Ratio	90% Confidence Intervals		Intra-variation Coefficient
		Lower 90% CI	Upper 90% CI	
AUC_{0-72}	97.80	92.38	103.54	10.37
C_{max}	95.37	87.26	104.23	16.23

The 90% Confidence Interval of the relative means for the log transformed pharmacokinetic parameters C_{max} and AUC_{0-72} of the test (T) and reference (R) products fell within 80.00% to 125.00%.

Biowaiver for 5 mg, 15 mg and 30 mg strengths

The bioequivalence study was carried out with the 10 mg strength. Based on the following a biowaiver was requested for 5 mg, 15 mg and 30 mg strengths:

- All strengths are immediate release tablets
- The qualitative composition of the different strengths is the same
- The composition of the strengths are quantitatively proportional
- Pharmacokinetics is linear from 5 mg to 30 mg
- The molecule is highly soluble at lower pH's and absorption is fast and almost complete
- Appropriate in-vitro dissolution data confirm the adequacy of waiving additional in vivo
- bioequivalence testing (refer to section 3.2.5)

The extrapolation of data from the results of the BE studies using the 10 mg strength to the other strengths (5 mg, 15 mg and 30 mg) is accepted.

Pharmacokinetic conclusion
Based on the submitted bioequivalence studies Preheftari 10 mg tablets is considered bioequivalent with Abilify 10 mg tablets.

The results of the BE study with the 10 mg aripiprazole 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 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 Preheftari.

The agreed summary list of safety concerns with no additional pharmacovigilance measures is as follows:

Table 3. Summary table of safety concerns as approved in RMP

Summary of safety concerns	
Important identified risks	• Extrapyramidal symptoms (EPS) , including tardive dyskinesia • Neuroleptic malignant syndrome (NMS)
Important potential risks	• Drug interactions • Suicide-related events • Growth • Increased mortality and CVA in elderly patients • Hepatic adverse events • Cardiovascular-related disorders • Conduction abnormalities • Seizure • Hyperglycaemia and diabetes mellitus • Weight gain • Dysphagia (primarily applies to schizophrenia population) • Pathological gambling • Orthostatic hypotension • Serotonin Syndrome • Somnolence/fatigue • Low prolactin in paediatric patients • Dyslipidemia • Use in patients with lactose intolerance • ADHD co-morbidity
Missing information	• Safety in pregnancy and lactation • Safety in paediatrics

Additional risk minimisation measures are required for the risks: Extrapyramidal Symptoms/Weight Gain/Adverse Events Related to Somnolence and Fatigue. These measures take the form of educational materials for healthcare professionals and patients/caregivers.

The summary table of safety concerns for the reference product Abilify has been modified and ratified by PRAC at their April 2015 meeting to the following shorter list, which is now also considered applicable in full to the current generic application:

Table 4. Summary table of safety concerns as approved in RMP for Abilify

Summary of safety concerns	
Important identified risks	• Extrapyramidal symptoms (EPS), including tardive dyskinesia • Neuroleptic Malignant Syndrome (NMS)
Important potential risk	• Seizures • Hyperglycaemia/diabetes • Suicide-related events • Orthostatic hypotension • Dyslipidemia
Missing information	• Safety in pregnancy and lactation • Safety in paediatrics

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 language used for the purpose of user testing the PIL was English.
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.

The test consisted of: a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Preheftari 5 mg, 10 mg, 15 mg and 30 mg tablets has a proven chemical-pharmaceutical quality and is a generic form of Abilify. 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations. A risk management plan describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Preheftari has been presented. Educational materials for both health care providers and patients/caregivers are required to be distributed at the time of launch.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity has been demonstrated for Preheftari with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised on 13 May 2015. Preheftari was authorised in Denmark on 15 September 2015.

According to the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs), no PSURs are required for this product.

The date for the first renewal will be: 13 May 2020.

The following post-approval commitments have been made during the procedure:

Risk Management Plan (RMP)
The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Additional risk minimisation measures
Educational materials for both health care providers and patients/caregivers are required to be distributed to the healthcare providers at the time of launch with the aim of clearly highlighting the need to give careful consideration to the indicated age range, dose, and duration of treatment before prescribing aripiprazole to a paediatric patient with bipolar I type disorder.
The MAH has confirmed that the educational materials will be submitted nationally for acceptance (where applicable) before the launch of the products.