Public Assessment Report

Scientific discussion

Aripiprazole "Orion"
5 mg, 10 mg, 15 mg and 30 mg tablets

(Aripiprazole)

DK/H/2398/001-004/DC

7 October 2015

This module reflects the scientific discussion for the approval of Aripiprazole "Orion". The procedure was finalised on 7 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 Aripiprazole "Orion" 5 mg, 10 mg, 15 mg and 30 mg tablets, from Orion Corporation.

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.

The MAH acknowledges not infringing indications under patent.

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 10 mg tablet strength is dose proportional with 15 mg and 30 mg strengths.

The 5 mg tablets are blue coloured, modified rectangular shaped, uncoated tablets debossed with '62' on one side and 'H' on other side.
The 10 mg tablets are white coloured, modified rectangular shaped, uncoated tablets debossed with '63' on one side and 'H' on other side.
The 15 mg tablets are white coloured, round shaped, uncoated tablets debossed with '64' on one side and 'H' on other side.
The 30 mg tablets are white coloured, round shaped, uncoated tablets debossed with '66' on one side and 'H' on other side.

The tablets are packed in PA/Aluminium/PVC/Aluminium blister packs in pack sizes of 14, 28, 56 and 98 tablets and in HDPE bottles with PP lid in pack sizes of 100 and 200 tablets. The container contains a silica gel desiccant. However, not all pack sizes may be marketed.

The tablets contain: Lactose monohydrate; Cellulose microcrystalline; Maize starch; Hydroxypropyl cellulose; Silica, colloidal anhydrous and Magnesium stearate. In addition, the 10 mg, 15 mg and 30 mg tablets contain Indigo carmine aluminium lake (E132).

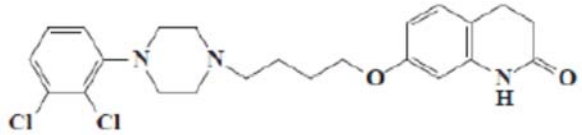
The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

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. The active substance specification is set in accordance with the Ph. Eur. monograph on aripiprazole. It includes relevant tests and the limits for impurities and degradation products have been justified. 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 excipients are well known and commonly employed in tablet manufacture.

The manufacturing process has been satisfactorily validated at pilot scale, three 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 three commercial scale batches of all strengths in both the proposed market packagings under long term (25°C/75% RH) and accelerated conditions (40°C/75% RH). The proposed shelf life of 36 months with no special storage conditions are supported by the data.

A photostability study has been performed for the 5 mg, 10 mg and 30 mg tablets. The product is therefore regarded photostable.

In-use stability data up to 36 months has been provided. The results comply with the shelf life specifications.

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 Aripiprazole “Orion” 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 supportive bioequivalence studies referenced below) and further studies are not required. Overview based on literature review is, thus, appropriate.

The clinical report refers 48 publications up to year 2011. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

IV.2 Pharmacokinetics

To support the application, the MAH submitted as reports two single dose bioequivalence studies performed under fasting conditions in order to show bioequivalence between the generic Aripiprazole “Orion” 5 mg tablets and the reference product Abilify (Otsuka Pharmaceutical Europe Ltd.) 5 mg tablets (from the UK market) and between Aripiprazole “Orion” 10 mg tablets and Abilify (Otsuka Pharmaceutical Europe Ltd.) 10 mg tablets (from the UK market).

Study 5 mg tablets
The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose of 10 mg (administered as 2 x 5 mg tablets) bioavailability study conducted under fasting conditions with a wash out period of 34 days between the two administrations. 10 mg aripirazole was administered in each period.

42 healthy male subjects participated in the study. 37 subjects completed the study and were included in the statistical analysis.

The primary variables for conclusion of bioequivalence were AUC_{0-72} and C_{max}.

The 90% confidence intervals were constructed for the geometric mean ratios from Ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-72} of aripiprazole for the test and reference formulations. Bioequivalence was to be concluded if the confidence intervals fell within the bioequivalence limits of 80.00%-125.00%.

Results

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range), N=36

Treatment	**AUC_{0-t}** **ng/ml/h**	**C_{max}** **ng/ml**	**t_{max}** **h**	**$T_{1/2}$** **h**
Test	1957.4033± 389.32313	51.3551± 13.88693	4.50 1.00-8.00	109.418± 85.2055
Reference	1859.8042± 375.61751	47.2448± 11.53273	4.50 1.00-8.00	113.023± 84.1472
***Ratio (90% CI)**	105.51 101.64 – 109.52	108.32 102.13 – 114.89	-	-
CV (%)	9.4	14.9	-	-

**ln-transformed values*

The bioequivalence accept criteria i.e. 90% confidence intervals for primary variable AUC_{0-72} and C_{max} are within acceptance range of 80.00-125.00%.

Study 10 mg tablets
The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose of 10 mg (1x10 mg tablet) bioavailability study conducted under fasting with a wash out period of 36 days between the two administrations. 10 mg aripiprazole was administered in each period.

42 healthy male subjects participated in the study. 35 subjects completed the study and were included in the statistical analysis

The primary variables for conclusion of bioequivalence were AUC_{0-72} and C_{max}.

The 90% Confidence Intervals were constructed for the geometric mean ratios from Ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-72} of aripiprazole for the test and reference formulations. Bioequivalence was to be concluded if the confidence intervals fell within the bioequivalence limits of 80.00%-125.00%.

Results

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) N=34, 10 mg tablets, fasting conditions

Treatment	AUC_{0-72} xg/ml/h	C_{max} xg/ml	t_{max} h	$T_{1/2}$ h
Test	1767.7000± 319.07236	45.7826± 9.64137	3.00 1.00-8.00	93.412± 46.8202
Reference	1685.4915± 336.93398	43.6880± 9.07069	4.50 1.50-8.00	89.663± 44.9566
*Ratio (90% CI)	105.18 100.31 – 110.29	104.69 97.09 – 112.89	-	-
CV (%)	11.6%	18.5%	-	-

**ln-transformed values*

The bioequivalence accept criteria i.e. 90% confidence intervals for primary variables AUC_{0-72} and C_{max} are within acceptance range of 80.00-125.00%.

Biowaiver for 15 mg and 30 mg strengths
The bioequivalence study has been conducted on the 10 mg strength and not on the highest strength (30 mg) due to safety of the volunteers. The biowaiver is accepted for 15 mg and 30 mg strengths based on *in vitro* dissolution similarity between the respective strengths and the generic biobatch (10 mg strength) in three dissolution media (pH 1.2, pH 4.5 and pH 6.8). The qualitative composition of the strengths is the same and their composition is quantitatively proportional. The 10 mg, 15 mg and 30 mg strengths of the test product are manufactured using the same manufacturing process. The drug substance exhibits linear kinetics in the respective dose range.

Pharmacokinetic conclusion
Based on the submitted bioequivalence studies Aripiprazole" Orion" 5 mg and 10 mg, is considered bioequivalent with Abilify 5 mg and 10 mg tablets, respectively.

The results of the BE study with the 10 mg aripiprazole formulation can be extrapolated to other strengths 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 Aripiprazole "Orion".

The following summary of safety concerns with additional risk minimisation measures has been agreed:

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 risk	• Seizures • Hyperglycaemia/diabetes • Suicide-related events • Orthostatic hypotension • Dyslipidemia
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.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Abilify, EMEA/H/C/471. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Aripiprazole “Orion” 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 Aripiprazole “Orion” 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 Aripiprazole “Orion” with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised on 7 May 2015. Aripiprazole “Orion” was authorised in Denmark on 3 June 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: 7 May 2020.

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

Risk Management Plan (RMP)
Orion Corporation commits to 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.