CBG MEB

Public Assessment Report

Scientific discussion

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

(aripiprazole)

NL/H/3209/001-004/DC

Date: 18 August 2016

This module reflects the scientific discussion for the approval of Aricogan 5 mg, 10 mg, 15 mg and 30 mg tablets. The procedure was finalised on 5 August 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 Aricogan 5 mg, 10 mg, 15 mg and 30 mg tablets from G.L. Pharma GmbH

The product is indicated for:

- Treatment of schizophrenia in adults and in adolescents aged 15 years and older
- Treatment of moderate to severe manic episodes in Bipolar I Disorder and prevention of new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment
- 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:

- Aricogan 5 mg tablets: Austria and Poland.
- Aricogan 10 mg tablets: Austria, Czech Republic, Estonia, Hungary, Lithuania, Latvia, Poland, Romania and Slovak republic.
- Aricogan 15 mg tablets: Austria, Bulgaria, Czech Republic, Estonia, Hungary, Lithuania, Latvia, Poland, Romania and Slovak republic.
- Aricogan 30 mg tablets: Austria, Czech Republic, Hungary and Poland.

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

II. QUALITY ASPECTS

II.1 Introduction

- Aricogan 5 mg tablets is a modified rectangular, blue, uncoated mottled tablet and debossed with “250” on one side . Each tablet contains 5 mg of aripiprazole.
- Aricogan 10 mg tablets is a modified rectangular, pink, uncoated mottled tablet and debossed with “252” on one side. Each tablet contains 10 mg of aripiprazole.
- Aricogan 15 mg tablets is a round, yellow, bevelled edge, uncoated mottled tablet, and debossed with “253” on one side. Each tablet contains 15 mg of aripiprazole.
- Aricogan 30 mg tablets is a round, pink, bevelled edge, uncoated mottled tablet and debossed with “L255” on one side. Each tablet contains 30 mg of aripiprazole.

The tablets are packed in OPA/Aluminium/PVC-aluminium blisters.

The excipients are: lactose monohydrate, maize starch, microcrystalline cellulose, hydroxypropylcellulose, crospovidone type A, colloidal anhydrous silica and magnesium stearate.
In addition, the 5 mg tablets contain indigo carmine aluminium lake colorant, the 10 mg and 30 mg tablets contain iron oxide red as a colorant and the 15 mg contain iron oxide yellow as a colorant.

Except for some slight qualitative and quantitative differences in the colouring agents present in the tablets, the different tablet strengths are quantitatively 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, soluble in methylene

chloride, very slightly soluble in ethanol (96%). Aripiprazole does not exhibit optical isomerism. The substance shows polymorphism and is manufactured as polymorphic form type 1. The polymorphic identity is routinely controlled.

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 proposed synthesis consist of five chemical step and two purification steps. No class 1 organic solvents or heavy metal catalysts are used in the process. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance
The drug substance specification is in line with the Ph.Eur. monograph on aripiprazole with additional requirements for residual solvents, crystalline form, microbial limits and particle size determination. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for four batches.

Stability of drug substance
Stability data on the active substance have been provided for three pilot scale batches in accordance with applicable European guidelines. The active substance was stored for 18 months (current manufacturing process) and 60 months (previous process) at 25°C/60% RH and for 6 months at 40°C/75% RH. No trends or changes were seen in any of the tested parameters at both storage conditions. Based on the data submitted, a retest period could be granted of 36 months when stored under the condition: 'Keep the container tightly closed at controlled room temperature'.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described, the choice of excipients is justified and their functions explained. The main development studies were the characterisation of the reference product, dissolution method development, optimization of the formulation, the development of the manufacturing process and the performance of comparative dissolution studies complementary to the two bioequivalence studies with the 5 mg and 10 mg product strengths and in support of the biowaiver for the additional strengths. Comparative dissolution testing was performed between the test and reference formulations, and between the 10 mg biobatch and the 15 mg and 30 mg strengths at pH 1.2, 4.5 and 6.8. All results were satisfactory except for the 10 mg versus the reference product in buffer 4.5 pH, however there was no objection to this discrepancy as bioequivalence was demonstrated *in vivo*. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps of the manufacturing process are sifting, blending, lubrication and compression. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three pilot scaled batches per strength. The product is manufactured using conventional manufacturing techniques and is considered a standard process. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
Except for the colorants, the excipients comply with the Ph. Eur. The colorants comply with the relevant in-house specifications. 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, average mass, water content, dissolution, assay, uniformity of dosage units, degradation products, dimensions and microbiological purity (as non-routine). Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Except for water content, specified impurity and total impurities, the release and shelf-life requirements are identical. Satisfactory validation data for the analytical methods have been provided. Batch analytical data on three pilot scaled batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three full scale batches per strength in accordance with the applicable ICH stability guidelines. The data cover 48 months stored at 25°C/60% RH and 6 months stored at 40°C/75% RH. The batches were stored in the proposed packaging. The stability data show no clear changes or trends in any of the tested parameters at both storage conditions. Results of the photostability study showed that the drug product was not sensitive to light exposure. The proposed shelf-life of 48 months and storage condition 'store in the original package in order to protect from moisture' are justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is the only material of animal origin that is used in the manufacture of the drug product. A TSE/BSE statement for lactose monohydrate stating that it has been produces from milk sourced from healthy cows in the same conditions as milk collected for human consumption, was submitted.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Aricogan 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 Aricogan 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 is discussed below.

IV.2 Pharmacokinetics

The MAH conducted two bioequivalence studies in which the pharmacokinetic profiles of the test product Aricogan 10 mg tablets (G.L. Pharma GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Abilify 10 mg tablets (Otsuka Pharmaceutical Europe Ltd, UK) and Aricogan 5 mg tablets (G.L. Pharma GmbH, Germany) with Abilify 5 mg tablets (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 15 mg and 30 mg strengths. Comparative dissolution testing was performed between the 10 mg strength and 15 and 30 mg strengths at pH 1.2, 4.5 and 6.8. A biowaiver is justified based on the following:

1. the pharmaceutical products are manufactured by the same manufacturing process;
2. the qualitative composition of the different strengths is the same
3. the ratio between amounts of active substance and excipients is the same
4. the *in vitro* dissolution profile is similar under identical conditions for all strengths.

Bioequivalence studies

Bioequivalence study I: aripiprazole 10 mg tablet

Design

An open label, single dose, randomised, two-period, two-treatment, two-sequence, balanced, crossover bioequivalence study was carried out under fasted conditions in 44 healthy, adult, Asian, male subjects, aged 45-60 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 fasting period of approximately 10 hours. There were 2 dosing periods, separated by a washout period of 37 days.

Blood samples were collected pre-dose and at 0.5, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5 6, 7, 8, 9, 10, 12, 16, 20, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. The proposed tablets can be taken with or without food. Thus, a study in fasting conditions is appropriate as this is considered to be the most sensitive condition to detect a potential difference between formulations. 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.

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 reason. Based on the justification provided by the MAH, the choice of 10 mg strength for the bioequivalence study is considered 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

One subject was withdrawn from the study due to an adverse event (emesis) and one subject had a pre-dose plasma concentration above 5% of C_{max} and was not statistically evaluated. A total of 42 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=42	AUC_{0-72} ng/ml/h	C_{max} ng/ml	t_{max} h
Test	1787 ± 607	51.6 ± 18.7	4.0 (2.0 - 10.0)
Reference	1751 ± 562	51.6 ± 18.6	4.5 (2.0 - 12.0)
***Ratio (90% CI)**	1.00 (0.93- 1.08)	0.98 (0.91 - 1.06)	--

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*

Bioequivalence study II: aripiprazole 5 mg tablet

Design

An open label, single dose, randomised, two-period, two-treatment, two-sequence, balanced, crossover bioequivalence study was carried out under fasted conditions in 44 healthy, adult, Asian male subjects, aged 45-60 years. Each subject received a single dose (5 mg) of one of the 2 aripiprazole formulations. The tablet was orally administered with 240 ml water after a fasting period of at least 10 hours. There were 2 dosing periods, separated by a washout period of 40 days.

Blood samples were collected pre-dose and at 0.5, 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5 6, 7, 8, 9, 10, 12, 16, 20, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. The proposed tablets can be taken with or without food. Thus, a study in fasting conditions is appropriate as this is considered to be the most sensitive condition to detect a potential difference between formulations. 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.

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 reason. Based on the justification provided by the MAH, the choice of 5 mg strength for the bioequivalence study is considered 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

Four subjects were withdrawn from the study due to adverse events (emesis, fever and chills). . One subject withdrew his consent on his own accord. In addition, 4 subjects were excluded from the statistical analysis, because their pre-dose concentration was more than 5% of C_{max}. A total of 35 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=35	AUC_{0-72} ng/ml/h	C_{max} ng/ml	t_{max} h
Test	799.9 ± 234.3	19.3 ± 5.0	4.5 (1.0 - 10.0)
Reference	821.6 ± 176.3	20.3 ± 4.2	4.5

			(2.0 - 9.0)
***Ratio (90% CI)**	0.96 (0.91 - 1.01)	0.94 (0.87 - 1.02)	--

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 studies:
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 Aricogan is considered bioequivalent with Abilify.

Safety
In the 10 mg bioequivalence study the test formulation and the reference drug were equally well tolerated and one non-serious adverse event was registered in one subject in the course of the trial (emesis occurred at or before 2 times t_{max}). The adverse event completely resolved.
In the 5 mg bioequivalence study the test formulation and the reference drug were equally well tolerated and 11 non-serious adverse event was registered in 7 subjects in the course of the trial. The adverse events were mild and completely resolved.
There were no deaths and serious adverse events reported during either study.

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 Aricogan.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Extrapyramidal syndrome (EPS), including tardive dyskinesia • Neuroleptic Malignant Syndrome (NMS)
Important potential risks	• Seizures • Hyperglycaemia/diabetes mellitus • Suicide-related events • Orthostatic hypotension • Dyslipidaemia • Weight gain • Somnolence/fatigue • Cardiovascular-related disorders • Conduction abnormalities • Low prolactin in paediatric patients • Dysphagia (predominantly applies to schizophrenic population) • Lactose intolerance (if applicable) • ADHD comorbidity • Drug interactions • Increased mortality and CVA in elderly patients with dementia • Pathological gambling

	• Serotonin syndrome • Hepatic adverse events
Missing information	• Use in pregnancy and lactation • 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Aricogan 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.

In the Board meeting of 30 July 2015, the quality section of the dossier was discussed with regard to a starting material of the active substance. The Board considered that this starting material is adequately controlled.
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 Aricogan 5 mg, 10 mg, 15 mg and 30 mg tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 5 August 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
Changes in the SmPC and Package Leaflet intended to implement the outcome of a procedure concerning PSUR [EMEA/H/C/471/234/201507].	NL/H/3209/ 1-4/IB/001	IB	08-07-2016	07-08-2016	Approved	No