23 April 2015
EMA/CHMP/747323/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Aripiprazole Pharmathen

International non-proprietary name: aripiprazole

Procedure No. EMEA/H/C/003803/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Aripiprazole Pharmathen
Applicant:	Pharmathen S.A. 6 Dervenakion str. Pallini 153 51 Athens GREECE
Active substance:	aripiprazole
International Nonproprietary Name:	aripiprazole
Pharmaco-therapeutic group (ATC Code):	Antipsychotics, other antipsychotics (N05AX12)
Therapeutic indication(s):	• 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 a 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
Pharmaceutical form(s):	Tablet
Strength(s):	5 mg, 10 mg, 15 mg and 30 mg
Route(s) of administration:	Oral use
Packaging:	blister (PA/Alu/PVC/Alu)
Package size(s):	14 tablets, 28 tablets and 98 tablets

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List of abbreviations

AEs	Adverse events
Alu	Aluminium
AUC_{0-72h}	Area under the concentration curve from time zero to 72 hours
BE	Bioequivalence
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
c_{max}	Maximum measured plasma concentration over the time span specified
CV	Coefficient of variation
CYP	Cytochrome P450 isoenzymes
ERA	Environmental Risk Assessment
f_2	Similarity factor in comparative dissolution tests
GC	Gas chromatography
GCP	Good clinical practice
GMP	Good manufacturing practice
HPLC	High-performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Infrared radiation
mg	Milligram
NMR	Nuclear magnetic resonance
PA	Polyamide
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PVC	Polyvinyl chloride
QP	Qualified person
RH	Relative humidity
SmPC	Summary of product characteristics
t_{max}	Time of the maximum measured plasma concentration
USP	United States Pharmacopeia

UV	Ultraviolet
XRD	X-ray diffraction
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pharmathen S.A. submitted on 9 June 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Aripiprazole Pharmathen, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 27 June 2013.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Aripiprazole Pharmathen is indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older.

Aripiprazole Pharmathen is indicated for 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.

Aripiprazole Pharmathen is indicated for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC)

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Abilify instead of non-clinical and clinical data unless justified otherwise.

Information on paediatric requirements

Not applicable

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:
  - Product name, strength, pharmaceutical form: Abilify, 5 mg, 10 mg, 15 mg, 30 mg, Tablet
  - Marketing authorisation holder: Otsuka Pharmaceutical Europe Ltd
  - Date of authorisation: 04-06-2004
  - Marketing authorisation granted by:
    - Community
      - Community Marketing authorisation number: EU/1/04/276/001-020
- Medicinal product authorised in the Community/Members State where the application is made or European

reference medicinal product:

- Product name, strength, pharmaceutical form: Abilify, 5 mg, 10 mg, 15 mg, 30 mg, Tablet
- Marketing authorisation holder: Otsuka Pharmaceutical Europe Ltd
- Date of authorisation: 04-06-2004
- Marketing authorisation granted by:
  - Community
    - Community Marketing authorisation number: EU/1/04/276/001-020

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Abilify, 10 mg, Tablet
- Marketing authorisation holder: Otsuka Pharmaceutical Europe Ltd
- Date of authorisation: 04-06-2004
- Marketing authorisation granted by:
  - Community
    - Community Marketing authorisation number: EU/1/04/276/007
- Bioavailability study number: BA13541220-01

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturers responsible for batch release

Pharmathen International S.A.
Industrial Park Sapes
Rodopi Prefecture
Block No 5
69300 Rodopi
Greece

Pharmathen S.A.
6 Dervenakion str.
Pallini
153 51 Athens
Greece

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP:

Rapporteur: Karsten Bruins Slot

- The application was received by the EMA on 9 June 2014.

- The procedure started on 23 July 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 October 2014.
- During the meeting on 6 November 2014 the Pharmacovigilance Risk Assessment Committee (PRAC) endorsed the PRAC Rapporteur's Risk Management Plan.
- During the meeting on 20 November 2014, the CHMP agreed on the consolidated List of Questions, which was circulated to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 December 2014.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 January 2015.
- During the meeting on 12 February 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) endorsed the PRAC Rapporteur's Risk Management Plan.
- During the CHMP meeting on 26 February 2015, the CHMP agreed on a List of Outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 23 March 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 27 March 2015.
- During the meeting on 10 April 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) endorsed the PRAC Rapporteur's Risk Management Plan.
- During their April 2015 meeting, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Aripiprazole Pharmathen.

2. Scientific discussion

2.1. Introduction

This application for a marketing authorisation for Aripiprazole Pharmathen concerns a generic medicinal product of the centrally authorised product Abilify, which, at the time of this report, was available as tablets (5 mg, 10 mg, 15 mg and 30 mg), orodispersible tablets (10 mg, 15 mg and 30 mg), oral solution (1 mg/ml) and solution for injection (7.5 mg/ml).

Aripiprazole is a quinolinone derivative, 7-{4-[4-(2, 3-dichlorophenyl)-1-piperazinyl]butyloxy}-3,4-dihydro-2(1H)-quinolinone, which exerts both agonistic and antagonistic activity at dopaminergic and serotonergic receptors, along with activities at other receptors. Abilify is approved for treatment of schizophrenia and manic episodes in Bipolar I Disorder as well as the prevention of manic episodes as follows:

> *ABILIFY is indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older.*

ABILIFY is indicated for 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.

ABILIFY is indicated for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.

The efficacy of aripiprazole in schizophrenia and Bipolar I Disorder is thought to be mediated through a combination of partial agonism at dopamine D2 and serotonin 5HT1a receptors and antagonism of serotonin 5HT2a receptors. For the treatment of schizophrenia, aripiprazole is given in an initial oral dose of 10 or 15 mg once daily. The recommended maintenance dose is 15 mg once daily. For the treatment of acute manic episodes in bipolar disorder, the recommended initial oral dose is 15 mg once daily as monotherapy, or combination therapy. For preventing recurrence of manic episodes, it is recommended to continue therapy at the same dose administered for treatment of acute episodes. The maximum daily dose should not exceed 30 mg.

The Applicant of Aripiprazole Pharmathen sought approval for 5 mg, 10 mg, 15 mg and 30 mg tablets (pack sizes of 14, 28 and 98 tablets) in the full range of indications approved for the reference product Abilify. The application was supported by one single dose bioequivalence (BE) study conducted under fasting condition. The study was carried out with the tablet strength of 10 mg instead of the highest strengths of 15 and 30 mg for safety reasons. For the remaining strengths, a biowaiver was requested.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as tablets containing 5 mg, 10 mg, 15 mg or 30 mg of aripiprazole as active substance.

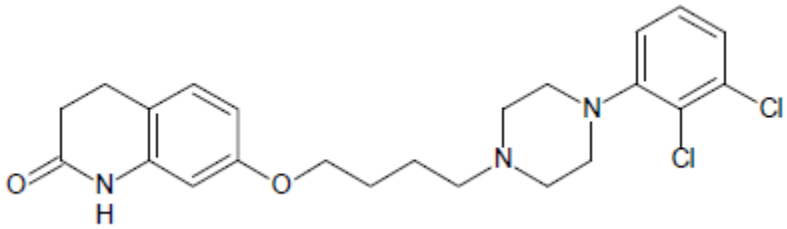
Other ingredients are: crystalline maltose, microcrystalline cellulose, pregelatinised starch, croscarmellose sodium, magnesium stearate in common for all tablets; indigo carmine (E132) for 5 mg tablets; iron oxide red (E172) for 10 mg and 30 tablets and iron oxide yellow (E172) for 15 mg tablets.

The product is available in PA/Alu/PVC/Alu blisters in carton box.

2.2.2. Active substance

General information

The chemical name of aripiprazole is 7-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy}-3,4-dihydroquinolin -2(1H)-one and has the following structure:



The structure has been confirmed using IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy, mass spectrometry and HPLC.

Aripiprazole is a white to off-white crystalline powder, freely soluble in N,N-dimethylformamide, soluble in dichloromethane, very slightly soluble in ethanol (96%). and practically insoluble in water. Solubility in water is increasing with lowering of pH within the physiological range.

Aripiprazole has a non-chiral molecular structure. Polymorphism has been observed for Aripiprazole. The active substance manufacturer consistently produces polymorphic form B, which has been demonstrated using XRPD method suitable for differentiating the polymorph form obtained from other forms reported. In addition, it has been demonstrated that polymorphic form does not change during manufacture and shelf-life of the finished medicinal product.

Manufacture, characterisation and process controls

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure. Aripiprazole is obtained from two manufacturing sites using a single ASMF.

Aripiprazole is synthesized in eight main steps using commercially available well defined starting materials with acceptable specifications. During the evaluation procedure, the active substance starting materials were redefined to ensure full control of the quality of the active substance in line with ICH Q11. Several genotoxic impurities are generated during the synthesis and satisfactory data is presented to demonstrate that the manufacturing proposed is capable of removing or purging these compounds to acceptable limits in line with current guidelines.

Due to regulatory starting material redefinition and consequential reclassification of intermediate manufacturers in relation to GMP applicability, CHMP recommended performing audits of the three new active substance intermediate manufacturers within the dates set in the submitted QP declaration/risk assessment reports that extended the validities of the last audits performed for these manufacturers.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Specification

The active substance specification includes tests for appearance (Ph. Eur.), solubility (Ph. Eur.), identity (Ph. Eur. and XRD), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), heavy metals (USP), assay (Ph. Eur.), impurities (HPLC and Ph. Eur.), residual solvents (GC) and particle size (laser diffraction).

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines.

Batch analysis data on three pilot scale batches and three commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three pilot scale batches of active substance from the proposed manufacturer stored in the intended commercial package for 40 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. Stability data on three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for 6 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. Results on stress conditions: water, acid, alkali, oxidation, UV, fluorescent, heat, and sunlight degradation were also provided for a single batch.

The following parameters were tested*:* appearance (Ph. Eur.), identity (Ph. Eur.), loss on drying (Ph. Eur.), assay (Ph. Eur.), and impurities (Ph. Eur.). The analytical methods used were the same as for release. Additional methods for description, solubility, identification (IR, XRD), water content, assay (HPLC), and impurities (HPLC) were used. It was demonstrated that the analytical methods were stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The aim of pharmaceutical development was to develop a stable tablet formulation that is bioequivalent to reference medicinal product Abilify tablets.

Tablets were selected as a pharmaceutical form as it is the same as in the reference medicinal product. Formulation development was based on studies investigating the physical and chemical properties of the active substance alone and combined with excipients. Due to low solubility, the active substance is micronised. Excipients that are soluble and enhance tablet dissolution were chosen. Further formulation studies were made to ensure the appropriate physico-chemical properties of the tablets and to optimise tablet manufacturability. Except for minor difference in pigment quantity (to match the colour of the reference medicinal product), the four strengths are dose proportional.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, USP standards (for crystalline maltose), USP standards and EC requirements (for iron oxide) or French pharmacopoeia and EC requirements (for indigo carmine (E132)).

The formulation is different than the reference medicinal product in these aspects: crystalline maltose and pregelatinised starch are used in Aripiprazole Pharmathen as a diluent, whilst lactose monohydrate and maize starch are used in the reference medicinal product, and croscarmellose sodium is used as a disintegrant in Aripiprazole Pharmathen, whilst hydroxypropylcellulose is used as a binder in the reference medicinal product. The differences in formulation between Aripiprazole Pharmathen and the reference medicinal product are not considered significant based on data presented with comparative dissolution profiles and demonstrated

bioequivalence. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The formulation used during clinical studies is the same that the used for marketing.

Bioequivalence study was performed showing bioequivalence between the clinical formulation and the proposed commercial formulation. This conclusion can be extrapolated to other strengths of Aripiprazole Pharmathen (5 mg, 15 mg and 30 mg tablets), as requirements for biowaiver specified in the Guideline on Investigation of Bioequivalence have been fulfilled.

The discriminatory power of the dissolution method has been demonstrated.

The primary packaging is PA/Alu/PVC/Alu blisters in carton box. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of seven main steps: first mixing, wet granulation, drying, dry granulation – sizing, second mixing, lubrication, and compression. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, average mass and uniformity of mass (Ph. Eur.), hardness (Ph. Eur.), disintegration (Ph. Eur.), friability (Ph. Eur.), loss on drying (Ph. Eur.), identification (HPLC, UV), assay (HPLC), related substances (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (HPLC), tightness of blister/ bottle, microbial contamination (Ph. Eur.), and visual inspection of the packaging. CHMP recommended to review and to tighten the specifications for total impurities at release and shelf life of finished medicinal product, when data collected from higher number of commercial scale batches is available.

Batch analysis results are provided for 3 batches per strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of 3 production scale batches per strength of finished product stored under long term conditions for 24 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for the same specifications as at release, except for uniformity of dosage units and visual inspection of the packaging. The analytical procedures used are stability indicating.

In addition, forced degradation (hydrogen peroxide, heat and acid hydrolysis and photo degradation (visual light and UV)) studies have been performed. Aripiprazole is stable during acid hydrolysis, visual light exposure, visual light and UV light exposure and heat according to the presented data. Oxidation of aripiprazole mainly degrades into impurity C.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. Specifications for total impurities at release and shelf life should be reviewed and tightened when data collected from higher number of commercial batches are available.

2. Audits of the three new active substance intermediate manufacturers should be performed within the dates set in the submitted QP declaration/risk assessment reports that extended the validities of the last audits performed for these manufacturers.

2.3. Non-clinical aspects

2.3.1. Introduction

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment (ERA) was submitted. This was justified by the applicant as the introduction of Aripiprazole Pharmathen is considered unlikely to result in any significant increase in the combined sales volumes for all aripiprazole containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion and conclusion on non-clinical aspects

For a generic of a reference medicinal product no toxicological and pharmacological tests are required. The CHMP concluded that no additional non-clinical data were required.

2.4. Clinical aspects

2.4.1. Introduction

The application concerned four strengths (5 mg, 10 mg, 15 mg and 30 mg) of Aripiprazole Pharmathen tablets. To support the application, the results of one single dose BE study under fasting condition using 10 mg tablets, instead of the higher strengths of 15 and 30 mg for safety reasons, were provided.

The Applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of a based on published literature. The SmPC is in line with the SmPC of the reference product.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

Good Clinical Practice (GCP)

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

The Applicant requested a biowaiver for the 5 mg, 15 mg and 30 mg strengths.

For the reference product Abilify, linear pharmacokinetics (PK) of aripiprazole in the therapeutic dose range of 5-30 mg has been established. Other criteria for biowaiver regarding the same manufacturing process and the qualitative composition/quantitative proportionality of the composition of all tablet strengths have also been fulfilled. In addition, similarity of dissolution profiles was demonstrated in line with the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) as described below.

Comparative in-vitro dissolution studies were performed at 3 dissolution media (i.e. at pH 1.2, 4.5 and 6.8). Twelve units of each Pharmathen product [Aripiprazole tablets 5mg, 10mg (reference), 15mg and 30mg] were

included in the dissolution studies in all three media. The Applicant also tested Aripiprazole Pharmathen against Abilify (both at 10mg).

Table 1. Dissolution parameters

Instrument	Distek Dissolution system 2100B
Paddles	Apparatus II
Rotation speed	50 rpm
Dissolution media	a) **Buffer pH= 1.2** (6.0ml HCL 37% + 2.0 gr NaCL) /L b) **Buffer pH=4.5** (2.99 g anhydrous sodium acetate + 14 ml acetic acid 2 M/L) c) **Buffer pH=6.8** (1 g KH_2PO_4 + 2 g K_2HPO_4 + 8.5 g NaCl/L)
Final volume of dissolution medium	900 ml
Temperature of dissolution medium	37 °C + 0.5 °C
Time points of sampling (min)	5, 10, 15, 20, 30, 45 min
Number of individual values for every time point (n)	12
Refill	3 ml

The dissolution samples were analysed using an high performance liquid chromatography method. Each dissolution sample was filtered through a 45 µm, 0.310" Filter Discs, ultra high molecular weight polyethylene.

The dissolution profiles for 5 mg, 15 mg and 30 mg tablets obtained at pH 1.2 and pH 4.5 were similar to those for 10 mg tablets. Since more than 85% of the drug was dissolved within 15 minutes at pH 1.2, calculation of the similarity factor (f_2) was not necessary and dissolution profiles were accepted as similar in line with the Guideline on the Investigation of Bioequivalence. As the dissolution rate was slower at pH 4.5, f_2 factors were calculated. All f_2 values were above 50 (61.1, 57.9 and 50.2 for 5mg, 15mg and 30mg Aripiprazole Pharmathen tablets as well as 50.9 for Abilify 10mg tablets), supporting similarity with Aripiprazole Pharmathen 10 mg tablets at this pH.

All four strengths of Aripipirazole Pharmathen as well as Abilify 10 mg tablets had very limited solubility at pH 6.8. The dissolved drug amount ranged from 1.9% to 8.1% within 45 min and a high variability in dissolution rate was observed. The f_2 factors could thus not be calculated. Aripiprazole is a drug with basic character (pKa: 7.6) with a pH-dependent solubility that decreases with increasing pH. As expected, both test and reference formulations showed very limited solubility at pH 6.8.

The Applicant justified the choice of the 10 mg tablet strength for the BE studies with the risk of life-threatening adverse events (AE) attributed to acute laryngeal dystonia which have been reported following administration of a single dose of 30 mg aripiprazole to healthy volunteers in BE studies. In section 4.8 of the SmPC of Abilify, dystonia is included as a class effect, stating that symptoms of dystonia may occur in susceptible individuals during the first few days of treatment. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Conclusions

The CHMP considered that the requirements for a biowaiver for the 5 mg, 15 mg and 30 mg strengths were met. Comparative in-vitro dissolution studies were performed in line with the Guideline on the Investigation of

Bioequivalence. Based on the result of these studies, similarity of the dissolution profiles of the 5 mg, 15 mg and 30 mg tablet strengths with the 10 mg tablets could be concluded.

The choice of the 10 mg tablets over the higher 15 and 30 mg strengths for the BE studies was also considered acceptable by the CHMP. In line with the Guideline on the Investigation of Bioequivalence, lower strengths may be selected for safety reasons. The CHMP considered that there was a risk of adverse reactions of dystonia, which increases with dose, thus justifying selection of the 10 mg tablet strength for the BE study in heathy subjects.

2.4.2. Pharmacokinetics

Study BA13541220-01: An open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study of Aripiprazole Tablets 10 mg of Pharmathen S.A., Greece and 'ABILIFY' (Aripiprazole) Tablets 10 mg of Otsuka Pharmaceutical Europe Ltd, UK in healthy adult human subjects under fasting conditions.

Methods

Study design

This was an open label, randomised, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral BE study in healthy, adult, human subjects under fasting conditions comparing 10 mg tablets of the test and reference products. The study was conducted at Cliantha Research Ltd., Ahmedabad, India.

In each study period, subjects were administered a single 10 mg oral dose of investigational product in the morning with approximately 240 ml of water after an overnight fasting of at least 8 hours. The washout period was at least 45 days which is more than 5 times the half-life of Aripiprazole (elimination half-life of 75 hours in extensive metabolisers of CYP2D6 and 146 hours in slow metabolisers of CYP2D6).

Blood samples were collected at pre-dose (0.0 hours) and at intervals over 72.0 hours after dosing in each period. A total of 26 venous blood samples were collected at pre-dose, and 0.5, 1.0, 1.5, 2.0, 2.25, 2.5, 2.75, 3.0, 3.25, 3.5, 3.75, 4.0, 4.5, 5.0, 5.5, 6.0, 7.0, 8.0, 10.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours post dose.

Test and reference products

Reference product-R

Formulation: ABILIFY (aripiprazole) Tablets 10 mg
Manufacturer: Bristol-Mayers Squibb
Marketing Authorization Holder: Otsuka Pharmaceutical Europe Ltd, UK
Batch No: 3A79832
Expiry Date: 06/2015

Test product-T
Formulation Aripiprazole (aripiprazole) 10 mg Tablets 10 mg
Manufacturer: Pharmathen S.A., Greece.
Batch No: 1204352

Batch size: 150,000 units
Manufacturing date: 10/01/2013
Expiry Date: 01/2016

Population studied

A total of 44 healthy volunteers aged 45-63 years were randomised to the study to ensure dosing of a total of 40 subjects. After administration of the dose in a sufficient number of subjects in Period I of the study, the remaining four subjects who were not dosed were checked out from the facility. The subjects included were all non-smoker Asian males.

Of the 40 subjects who were included in the study, 38 subjects completed both periods of the study, and received a single oral dose of the assigned formulation on day 1 and day 45. Two subjects withdrew from the study; one subject discontinued during Period II on his own accord, and one subject was withdrawn during Period I due to a single episode of vomiting.

Consequently, results from 38 subjects were included in the PK and statistical analysis.

Analytical methods

Concentrations of aripiprazole were determined using a validated high-performance liquid chromatography/electrospray ionization tandem mass spectrometry method with turbo ion source. A deuterated analogue of aripiprazole (aripiprazole-d8) was used as internal standard. The analyte aripiprazole and internal standard was extracted using a liquid-liquid extraction technique. Linearity of the method was shown in the range of 0.5-200 ng/ml. A linear regression model weighted 1/X2 was used to obtain the best fit of the data for the calibration curves.

A total of 2038 plasma samples obtained from 38 subjects were analysed. A total of 121 samples (5.94% of all samples) were re-analysed; 104 samples due to analytical batch failure, 16 samples due to inconsistent internal standard area, and 1 sample due to high baseline value. The re-analyses were performed and reported according to a predefined standard operation procedure.

The validation of the method and bioanalysis was conducted at Veeda Clinical Research Pvt. Ltd., Ahmedabad India.

PK variables

The primary PK parameters calculated were $AUC_{0\text{-}72h}$, c_{max} and t_{max}. The PK parameters were evaluated using a standard non-compartmental approach.

Statistical methods

Statistical comparison of the ln-transformed c_{max} and $AUC_{0\text{-}72h}$ was based on the ANOVA model, and was carried out using SAS® Version 9.2 (SAS Institute Inc., USA) by PROC MIXED. The treatment, period and sequence effects were included in the model as fixed effects, and subject within sequence as a random effect. All main effects were tested at the 0.05 level of significance using mean square error as the error term.

The 90% confidence intervals (CIs) of the relative mean of c_{max} and AUC_{0-72h} of the test and reference formulation for ln-transformed data should be within 80.00% to 125.00% for aripiprazole to establish bioequivalence.

Results

The results for the test product (Aripiprazole Pharmathen 10 mg tablets) and the reference product (Abilify 10 mg tablets) are summarised in table 2 and 3 below.

Table 2. Pharmacokinetic parameters for aripiprazole (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	aritmetric mean±SD	CV%	aritmetric mean±SD	CV%
$AUC_{(0-72h)}$	2251.4 ± 382.2	16.98%	2146.6 ± 465.5	21.6%
c_{max}	58.708 ± 12.82	21.8%	53.915 ± 13.30	24.6%
t_{max}*	3.125 (1.00 - 7.00)	-	3.125 (1.00 - 8.00)	-

AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours
c_{max}	maximum plasma concentration
t_{max}	time for maximum concentration [* median (range)]
CV	coefficient of variation

Table 3. Statistical analysis for aripiprazole (ln-transformed values))

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference (%)	Confidence Intervals	ANOVA CV%*
$AUC_{(0-72h)}$	105.87	100.83 - 111.16%	12.63
c_{max}	109.97	101.60 - 119.04%	20.64

* estimated from the Residual Mean Squares

The ANOVA test did not detect any statistically significant difference between the test and reference formulation for the PK parameters investigated. The 90% CIs of the geometric least square mean ratio for AUC_{0-72h} and c_{max} were within the acceptance range of 80-125%.

Safety data

A total of two adverse events (AEs) were reported in two subjects during the entire study. These were events of vomiting and headache. Both AEs were mild in nature. None of the AEs experienced by the subjects during this study were judged as serious. One subject discontinued due to AE of vomiting.

Both test and reference products were well tolerated by study subjects. There were no serious AEs reported during this study.

Conclusions

Based on the presented BE study, Aripiprazole Pharmathen 10 mg tablets are considered bioequivalent with Abilify 10 mg tablets. Furthermore, the results of study BA13541220-01 with the 10 mg tablet formulation can be extrapolated to the other strengths applied for, as relevant conditions provided for in the Guideline on the Investigation of Bioequivalence were met.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

The design of study BA13541220-01 was considered by the CHMP to be appropriate to investigate bioequivalence between immediate release formulations. The washout period, sampling period and analyte (patent compound) were considered adequate. Furthermore, since intake of aripiprazole tablets is recommended on an empty stomach, it was considered appropriate and in line with the Guideline on the Investigation of Bioequivalence that the study was conducted under fasting conditions. The population and sample size were considered acceptable.

The batch size of the test product was also acceptable, as it corresponded to 1/10 of the maximum proposed commercial size. The analytical method was adequately validated, including pre-study and within-study validations. Incurred samples re-analysis was performed and confirmed reliability of the initial results.

The PK parameters investigated were appropriate. Considering the long elimination half-life of aripiprazole and that the concentrations at 72 hours were quantifiable, it was considered by the CHMP to be sufficient to report AUC truncated at 72 hours. Individual plasma concentration curves obtained in the study revealed that the absorption and distribution phase was sufficiently covered within 72 hours post-dose.

Based on the results of the study, bioequivalence between the test and reference products has been adequately demonstrated with respect to the rate and extent of absorption. The CHMP however noted that both CIs lay completely in the upper part of the acceptance range. Furthermore, as there were concerns regarding reliability of the plasma concentrations used for calculation of the PK data for one subject, the 90% CIs for AUC_{0-72h} and c_{max} were re-calculated, using the original concentrations obtained. The re-calculated 90% CIs still lay within the acceptance range of 80-125%, confirming the bioequivalence of the test and reference products with respect to the rate and extent of absorption.

2.4.6. Conclusions on clinical aspects

Based on the available data, the CHMP concluded that bioequivalence of Aripiprazole Pharmathen 10 mg tablets to Abilify 10 mg tablets had been demonstrated. As all criteria for a biowaiver were met, the CHMP agreed that the results of the BE study could be extrapolated to the other tablet strengths applied for.

2.5. Pharmacovigilance

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version ARIPIP-v4-150415 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.
The CHMP endorsed the Risk Management Plan version ARIPIP-v4-150415 with the following content:

Safety concerns

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

Pharmacovigilance plan

Not applicable.

Risk minimisation measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Extrapyramidal symptoms (EPS), including tardive dyskinesia	SmPC sections 4.4, 4.6, 4.8 and 4.9 PIL sections 2 and 4 Prescription only medicine	Educational programme, in particular with respect to extrapyramidal symptoms, will be developed for healthcare professionals treating adolescent

		patients with bipolar mania and patients/caregivers.
Neuroleptic Malignant Syndrome (NMS)	SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None
Seizures	SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None
Hyperglycaemia/diabetes	SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None
Suicide-related events	SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None
Orthostatic hypotension	SmPC sections 4.4 and 4.8 Prescription only medicine	None
Dyslipidaemia	SmPC sections 4.8 and 5.1 Prescription only medicine	None
Cardiovascular related disorders	SmPC sections 4.4 and 4.8 PIL section 2 Prescription only medicine	None
Conduction abnormalities	SmPC sections 4.4, 4.5 and 4.8 PIL sections 2 and 4 Prescription only medicine	None
Weight gain	SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	Educational programme, in particular with respect to extrapyramidal symptoms, will be developed for healthcare professionals treating adolescent patients with bipolar mania and patients/caregivers.
Fatigue and somnolence	SmPC sections 4.2, 4.7 and 4.8 PIL section 4 Prescription only medicine	Educational programme, in particular with respect to extrapyramidal symptoms, will be developed for healthcare professionals treating adolescent patients with bipolar mania and patients/caregivers.
Dysphagia (primarily applies to schizophrenia population)	SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None
Increased mortality and cerebrovascular adverse reactions in elderly patients with dementia	SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine	None

Drug interactions	SmPC sections 4.2 and 4.5 PIL section 2 Prescription only medicine	None
Patients with ADHD comorbidity	SmPC section 4.4 Prescription only medicine	None
Aspartame (applicable only for orodispersible tablets)	SmPC sections 4.4 PIL section 2 Prescription only medicine	None
Growth	Innovator studies (Protocol numbers: 31-03-239, 31-03-241, 31-09-266 and 31-09-267). The results of these studies will be followed by the applicant. Prescription only medicine	None
Low prolactin in paediatric patients	SmPC sections 4.8 and 5.1 Prescription only medicine	None
Pathological gambling	SmPC section 5.1 Prescription only medicine	None
Serotonin syndrome	SmPC sections 4.5 and 4.8 PIL section 4 Prescription only medicine	None
Hepatic adverse events	SmPC section 4.8 PIL section 4 Prescription only medicine	None
Safety in pregnancy and lactation	SmPC sections 4.6 PIL section 2 Prescription only medicine	None
Safety in paediatric patients	SmPC sections 4.1, 4.2, 4.8 and 5.1 PIL section 2 Prescription only medicine	None

2.7. PSUR submission

At the time of granting the marketing authorisation, the submission of periodic safety update reports was not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal.

2.8. Product information

2.8.1. User consultation

The applicant has submitted a full user test for Aripiprazole Pharmathen 10 mg, 15 mg and 30 mg orodispersible tablets. The results of this user consultation 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.

No full user consultation with target patient groups on the package leaflet for Aripiprazole Pharmathen 5 mg, 10 mg, 15 mg and 30 mg tablets has been performed on the basis of a bridging report making reference to Aripiprazole Pharmathen orodispersible tablets. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of Aripiprazole tablets. The reference product Abilify is indicated for the 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 for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment as well as treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.

No non-clinical studies have been provided for this application but an adequate summary of the available non-clinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis of the application. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. The test formulation of Aripiprazole Pharmathen 10 mg tablets met the protocol-defined criteria for bioequivalence when compared with Abilify 10 mg tablets. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Aripiprazole Pharmathen in the *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 for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment as well as treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older* is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83 and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **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 agreeed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- 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 submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

In each Member State where Aripiprazole Pharmathen for the treatment up to 12 weeks of moderate to severe manic episode in Bipolar I Disorder in adolescents aged 13 years and older is launched the Marketing Authorisation Holder (MAH) shall agree an educational programme with the National Competent Authority. The MAH shall ensure that, following discussions and agreement with the National Competent Authorities in each Member State where Aripiprazole Pharmathen for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older is launched all healthcare professionals who are expected to prescribe Aripiprazole Pharmathen are provided with an information pack containing the following items:

- Summary of Product Characteristics (SmPC) and Package Leaflet
- Educational material for the healthcare professionals
- Educational material for the patients and their caregivers

<u>Key elements of the Healthcare Professional FAQ Brochure (Q&A format) intended for Healthcare Providers treating adolescent patients with bipolar mania:</u>

- 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 of 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

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.