EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 September 2015
EMA/CHMP/523618/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Aripiprazole Accord

International non-proprietary name: aripiprazole

Procedure No. EMEA/H/C/004021/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

AEs	Adverse events
Alu	Aluminium
ANOVA	Analysis Of Variance
ASMF	Active Substance Master File = Drug Master File
AUC_{0-72h}	Area under the plasma concentration versus time 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
CV	Coefficient of variation
CYP	Cytochrome P450 isoenzymes
EC	European Commission
EEA	European Economic Area
ERA	Environmental Risk Assessment
FT-IR	Fourier transform infrared spectroscopy
GC	Gas Chromatography
GC-MS	Gas chromatography mass spectrometry
GCP	Good clinical practice
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
KF	Karl Fischer titration
LC-MS	Liquid chromatography mass spectrometry
LC-MS/MS	Liquid Chromatography/ Tandem Mass Spectrometry
LLOQ	Lower limit of quantification
NMR	Nuclear Magnetic Resonance
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics

PPCRC	Polypropylene Child Resistant Closure
RH	Relative Humidity
SD	Standard Deviation
SmPC	Summary of product characteristics
tmax	Time of the maximum measured plasma concentration
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of toxicological concern
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare Ltd submitted on 1 August 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Aripiprazole Accord, 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 22 May 2014.

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

Aripiprazole Accord 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 Accord 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 two bioequivalence studies 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 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, 5 mg, Tablet
- Marketing authorisation holder: Otsuka Pharmaceutical Europe Ltd
- Date of authorisation: 04-06-2004
- Marketing authorisation granted by:
  - Community
  - Community Marketing authorisation number(s): EU/1/04/276/001-005
- Bioavailability study number(s): 463-12

■ 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(s): EU/1/04/276/006-010
- Bioavailability study number(s): 509-12

Licensing status

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

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: John Joseph Borg

The application was received by the EMA on 1 August 2014.

- The procedure started on 20 August 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 November 2014.
- During the meeting on 4 December 2014 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.

- During the meeting on 18 December 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 22 May 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 26 June 2015.
- During the meeting on 9 July 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the CHMP meeting on 23 July 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 22 August 2015.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 1 September 2015.
- During the meeting on 21-24 September 2015, 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 Accord.

2. Scientific discussion

2.1. Introduction

This Application for a marketing authorisation for Aripiprazole Accord 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). 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.*

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. 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 Accord sought approval for 5 mg, 10 mg, 15 mg and 30 mg tablets (pack sizes of 14x1, 28x1, 56x1 and 98x1 tablets for all strengths and 30 and 100 tablets in a bottle for all but the 30 mg strength) in the full range of indications approved for the reference product Abilify. The Application was supported by two bioequivalence (BE) studies. The studies were carried out with the tablet strengths of 5 and 10 mg, respectively, instead of the highest strengths of 15 and 30 mg. The Applicant justified the use of a lower strength with safety reasons including publically available literature and requested a biowaiver for the remaining strengths.

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.

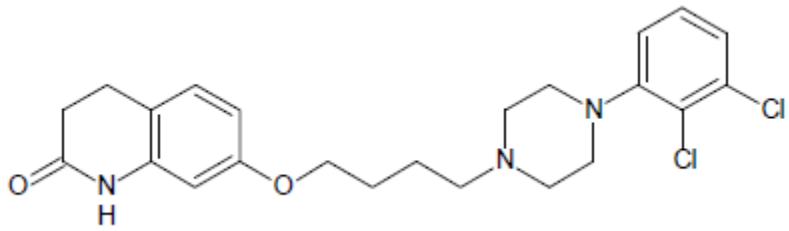
Other ingredients are: lactose monohydrate, microcrystalline cellulose, maize starch, hydroxypropylcellulose, magnesium stearate, indigo carmine aluminium lake (E132) for 5 mg tablets, iron oxide red (E172) for 10 mg and 30 mg tablets and iron oxide yellow (E172) for 15 mg tablets.

The product is available in aluminium/aluminium perforated unit dose blisters. Aripiprazole accord 5 mg, 10 mg and 15 mg tablets are also available in HDPE bottles with PPCRC closure.

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(1*H*)-one and has the following structure:



The structure has been confirmed by elemental analysis, ^{1}H-NMR and ^{13}C-NMR spectroscopy, mass spectrometry, FT-IR and UV spectroscopy.

The active substance is a white or almost white crystals or crystalline hygroscopic powder, practically insoluble in water, soluble in methylene chloride and very slightly soluble in ethanol (96 per cent). Its molecular weight is 448.4 $g \cdot mol^{-1}$, corresponding to the general molecular formula $C_{23}H_{27}Cl_2N_3O_2$.

Aripiprazole does not exhibit stereoisomerism, as it has no chiral centre. Polymorphism has been observed for this active substance. Aripiprazole is known in several polymorphic forms, i.e. hydrate-A, anhydride forms (classified as crystal B, C, D, E, F and G; or type I and type II crystals) and an amorphous form. It has been confirmed by P-XRD patterns that the active substance manufacturer consistently produces the same polymorphic form (anhydrous form B, Type-I crystals) and the stability data submitted demonstrate that humidity has no impact in the polymorphic form of aripiprazole and there is no interchangeability of the polymorphic form following storage.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Manufacture, characterisation and process controls

The active substance is synthesized in four main synthetic steps by a convergent route using well defined starting materials with acceptable specifications, followed by purification, drying, micronisation, and sifting. During the procedure, the CHMP requested to redefine one of the proposed starting materials to ensure that steps critical to the quality of the active substance are described in the dossier.

The description of the manufacturing process has been adequately described. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Although raw materials with potential genotoxic activity are used in the synthesis of aripiprazole, it has been demonstrated that their levels do not exceed 30% of the TTC limit in the final active substance.

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.

The active substance is packed in transparent polyethylene bags, tied with a plastic tag. This is placed in a black bag and tied with a plastic tag. This bag is placed in HDPE drum.

The polythene bags comply with EU directives 2002/72/EC as amended by 2004/1/EC, 2004/19/EC, 2005/79/EC, 2008/39/EC, 975/2009/EC, EU regulation 1282/2011 amended from 10/2011, the European guideline on plastic intermediate packaging materials (CHMP/QWP/4359/03) and Ph. Eur. requirements.

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 description (Ph. Eur.), solubility (Ph. Eur.), identification (IR, HPLC), appearance of solution (clarity and colour of the solution) (Ph. Eur.), polymorphism (XRD), hygroscopicity (KF), limit of chloride (turbidimetry), sulphated ash (Ph. Eur.), heavy metals (Ph. Eur.), related substances (HPLC, GC-MS, LC-MS), assay (Ph. Eur.), residual solvents (GC), loss on drying (Ph. Eur.), particle size (laser diffraction) and microbial examination (Ph. Eur.).

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

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

Stability

Stability data on commercial-scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions at 25 ºC / 60% RH (nine batches) and for up to 6 months under accelerated conditions at 40 ºC / 75% RH (three batches) according to the ICH guidelines were provided. The following parameters were tested*:* description, identification, polymorphism, loss on drying, water content, related substances and assay. The analytical methods used were the same as for release and were stability indicating. All results were within the proposed specifications and no negative trends were observed.

Forced degradation studies under exposure to heat (up to 105°C), humidity, light (according to ICH Q1B) in solid state, and water, acid or base hydrolysis, and oxidation in solution were also performed on one batch. Samples were tested for related substances and assay. Degradation was observed in the presence of hydrogen peroxide only. It is thus demonstrated that aripiprazole is photostable. The analytical methods have shown to be stability-indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable and justify the proposed retest period of 5 years in the proposed container with no special precautions for storage.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The aim of the pharmaceutical development was to obtain a stable generic formulation of aripiprazole bioequivalent to the reference medicinal product Abilify 5 mg, 10 mg 15 mg and 30 mg tablets.

Therefore, the four strengths of the reference product were characterised in order to establish the physical (appearance, average weight, thickness and disintegration time) and chemical (assay, related substances, impurities) characteristics of the reference product. The formulation approach for the different strengths was to develop a dose-weight proportional formulation for the 10 mg, 15 mg and 30 mg strengths, while maintaining the 5 mg tablets identical in weight to the 10 mg tablets.

During the formulation development, the finished product manufacturer studied key physicochemical characteristics of the active substance which could influence the performance of the finished product, including appearance, solubility, melting point, bulk density, compressibility, isomerism, polymorphism, hygroscopicity, particle size and pH solubility profile. From bulk density and compressibility studies it was concluded that aripiprazole (Type I) exhibits very poor flow properties. With regards to polymorphism, XRD analysis confirmed that the aripiprazole polymorph manufactured by the ASMF holder is aripiprazole anhydrous Type-I crystals. Additionally, the particle size distribution study concluded that since the drug substance is practically insoluble in water, its particle size should be controlled in order to achieve the desired dissolution profile. The results from the pH solubility study were used for the selection of the dissolution media.

The excipients used for the manufacture of Aripiprazole Accord tablets are the same used in the reference product, namely: lactose monohydrate (diluent), microcrystalline cellulose (diluent/disintegrant), maize starch (disintegrant), hydroxypropylcellulose (binder), magnesium stearate (lubricant) and ferric oxide red, ferric oxide yellow and carmine aluminium lake (colorants). All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards except for the colourants, which are described in the USP/USNF. The list of excipients is included in section 6.1 of the SmPC. Due to the low dose of the active substance, its static nature and its low particle size, which might lead to segregation and poor drug distribution, a wet granulation process was selected for the manufacture of the tablets.

A trial 10 mg tablet batch was initially manufactured, characterized and compared with the reference product. Based on the results from this study, the formulation development continued with the alteration of the levels of different excipients (e.g. cellulose microcrystalline, maize starch, magnesium stearate) and the manufacturing process itself until the physical characteristics of the tablets obtained were found to be satisfactory and the dissolution profile comparable to that of the reference medicinal product. Then, tablets of the other proposed strengths 5 mg, 15 mg and 30mg were manufactured and further formulation optimization was conducted.

Two bioequivalence studies were performed showing bioequivalence between aripiprazole 5 mg and 10 mg test products and the reference products Abilify 5 mg and 10 mg tablets, respectively. A request for a biowaiver for 15 mg and 30 mg strengths was submitted on the basis that: i) the 10 mg, 15 mg and 30 mg strengths are manufactured by the same manufacturer using the same manufacturing process, ii) the qualitative composition of the aripiprazole 15 mg and 30 mg is the same as that of aripiprazole 10 mg, iii) the composition of the 15 mg and 30 mg strengths are quantitatively proportional to the 10 mg strength, iv) aripiprazole exhibits linear pharmacokinetics, and v) the *in-vitro* dissolution profile is similar under identical conditions for 15 mg and 30 mg strengths and the strength of the batch used in the bioequivalence study (10 mg).

The dissolution profile of the different strengths of test and reference product strengths was subsequently studied in pH 1.2 HCl buffer, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. Although similarity of the dissolution profiles of the test and reference product for the 5mg and 10 mg strengths was not demonstrated in pH 4.5 acetate buffer, the similarity of the dissolution profiles for these tablets strengths was demonstrated at pH 1.2 and pH 6.8 buffers, and *in-vivo* bioequivalence was also demonstrated for these two strengths.

Similarity of dissolution profiles of the 10mg test product (biobatch) and the proposed additional strengths (15mg and 30mg) was demonstrated in pH 1.2, pH 4.5 and pH 6.8 buffers. Therefore, the biowaiver was considered acceptable.

The discriminatory power of the dissolution method was demonstrated.

The primary packaging for the four strengths is Aluminium-Aluminium (Alu-Alu) perforated unit dose blisters. These blisters replaced the original blisters proposed by the applicant, which were not considered acceptable by the CHMP as they were not peelable, did not include perforations, and were too hard to break through, and therefore could result in tablets break when forced out of the blister. In order to support this change of blister pack, the applicant submitted comparative studies between the two blister packs and stability data, which confirmed that both packagings have similar properties. Additionally, 5 mg, 10 mg and 15 mg tablets are also available in HDPE bottle with PPCRC closure. 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 for the tablets is a standard wet granulation process which consists of nine main steps: co-sifting, dry mixing, granulation/wet milling, drying, sifting/sizing, blending, lubrication, compression of tablets and packaging.

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.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, average weight of tablets, identification (HPLC, IR, UV), resistance to crushing of tablets (Ph. Eur.), friability (Ph. Eur.), water content (KF), dissolution (HPLC-UV), uniformity to dosage units (Ph. Eur.), related substances (HPLC-UV), assay (HPLC-UV) and microbial contamination (Ph. Eur.). The finished product is released on the market based on the above release specifications, through traditional final product release testing.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines.

Batch analysis data have been provided on two commercial scale batches of the 5 mg strength and 3 commercial scale batches of 10 mg, 15 mg and 30 mg strengths, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of two commercial scale batches of each strength of finished product stored under long term conditions for up to 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 aripiprazole tablets were identical to those proposed for marketing and were packed in a primary similar (Alu-Alu blister) or identical (HDPE bottles) to that proposed for marketing.

As mentioned above, additional stability data on one batch of 5 mg, 10 mg and 15 mg tablets packed in the Alu-Alu blisters to be marketed, stored for 6 months at accelerated and long term conditions were also provided in order to support the change of blister pack during the evaluation.

Samples were tested for description, resistance to crushing, water content, dissolution, related substances, assay and microbial examination. The analytical procedures used are stability indicating. All results were within specifications and no negative trends were observed.

In addition, one 10 mg strength batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The tablets were exposed to light unpacked, in the immediate pack and in the marketing pack. Samples were tested for description, assay and related substances. The results from this study demonstrated that the product is photostable in Alu-Alu packs and HDPE bottles.

Forced degradation studies were carried out to identify the likely degradation products. The following conditions were selected: acid hydrolysis, base hydrolysis, heat degradation (up to 60 °C), oxidation, UV and water hydrolysis. It was demonstrated that aripiprazole does not degrade significantly when exposed to stress conditions except for oxidation.

A thermal cycling study was performed to study the effect of transportation on stability of Aripiprazole tablets showing that all tested parameters remained within the specifications.

An in-use stability study was conducted on Aripiprazole 10 mg and 30 mg tablets packed in HDPE bottles. Results showed that all tested parameters remained within specifications 30 days (30 tablets HDPE bottle) and 100 days (100 tablets HDPE bottle) after breaking the seal of the container.

A polymorphism stability study was also conducted on the drug substance, placebo of the finished product and the 4 strengths of the finished product at 40 ^{0}C / 75% RH. It demonstrated that the polymorphic form remains stable and unchanged during manufacturing process of Aripiprazole tablets and upon storage.

Based on available stability data, a shelf-life of 2 years with no special storage conditions, as stated in the SmPC, is acceptable.

Adventitious agents

Lactose is the only excipient from animal or human origin used for the manufacture of the product. It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

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. As requested by the CHMP, the applicant redefined one of the proposed starting materials to ensure that all critical steps of the synthetic process are now described in the dossier. The concern regarding initially proposed blister pack, which was not peelable and was too hard to push the tablet through it, was also satisfactorily addressed. 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. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendations for future quality development

Not applicable.

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 justified that there was no need to

generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the Summary of Product Characteristics (SmPC) were 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 were 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 Accord was 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 risks to the environment were expected to remain the same.

2.3.3. Discussion and conclusions 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 needed.

2.4. Clinical aspects

Introduction

The Application concerned four strengths (5 mg, 10 mg, 15 mg and 30 mg) of Aripiprazole Accord tablets. To support the Application, the results of two single dose, cross-over BE studies under fasting conditions were provided using 5 and 10 mg tablets, respectively. The higher strengths of 15 and 30 mg were not used for safety reasons (see section on the biowaiver below)

The Applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of aripiprazole based on the reference product and published literature. The SmPC was 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 Applicant claimed that the clinical trials were performed in accordance with GCP.

The Applicant 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 (Biowaiver)

The Applicant justified the choice of the 5 and 10 mg tablet strengths for the BE studies since aripiprazole has been poorly tolerated by healthy volunteers, particularly at the higher dose levels. In a BE study, after administration of 30 mg oral aripiprazole, adverse effects leading to postural dizziness and blood pressure lowering were observed in some of the healthy volunteers (Mandal U et al. 2008). In another study in healthy volunteers, it was found that aripiprazole can affect cognitive function and alter frontal metabolic function linked

to greater D2 receptor occupancy, which in turn increases with the dose. Other studies with 30 mg aripiprazole revealed that adverse effects such as nausea, dyspepsia, vomiting, constipation, somnolence, accidental injury and akathisia occurred very commonly and led to dose reductions in several patients (Keck PE et al. 2003, Swainston HT et al. 2004).

For these reasons, the Applicant requested a biowaiver for the 15 mg and 30 mg tablet strengths.

For the reference product Abilify, linear pharmacokinetics (PK) of aripiprazole in the therapeutic dose range of 5-30 mg has been established. Other biowaiver criteria according to the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98), regarding the same manufacturer and manufacturing process and the qualitative composition/quantitative proportionality of the composition of all tablet strengths, have also been fulfilled.

To support the claim of a biowaiver, the Applicant furthermore conducted comparative *in-vitro* dissolution studies with the 10 mg (reference), 15 mg and 30 mg tablet strengths at 3 dissolution media (i.e. at pH 1.2, 4.5 and 6.8) using a paddle apparatus with a rotation speed of 50 rpm. Twelve units of each batch [10 mg tablets (reference), 15mg and 30mg] were included in the dissolution studies in all three media. The results of these studies showed similar dissolution profiles of the 15 mg and 30 mg tablet strengths compared to 10 mg tablets at all conditions tested.

Conclusions

The CHMP considered that the requirements for a biowaiver for the 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 (CPMP/EWP/QWP/1401/98 Rev 1). Based on the result of these studies, similarity of the dissolution profiles of the 15 mg and 30 mg tablet strengths with the 10 mg tablets could be concluded.

In line with the Guideline on the Investigation of Bioequivalence, lower strengths may be selected if higher strengths cannot be administered to healthy volunteers for safety/tolerability reasons. The CHMP considered that the risk of adverse reactions with aripiprazole increases with dose. In addition to the justification provided by the Applicant, the CHMP took into account the risk of acute laryngeal dystonia, a class effect of first generation antipsychotic drugs, whereby symptoms are known to occur more frequently and with greater severity with higher doses/potencies. Therefore, the choice of the 5 mg and 10 mg tablets for the BE studies over the higher tablet strengths of 15 and 30 mg was considered acceptable by the CHMP.

Pharmacokinetics (PK)

Two BE studies were provided in support of this Application:

Study 463-12: An open label, balanced, randomized, two treatment, two period, two sequence, crossover, single oral dose, bioequivalence study of two formulations of Aripiprazole tablets **5 mg** in healthy, elderly, human subjects under fasting conditions.

Study 509-12: An open label, balanced, randomized two treatment, two period, two sequence, crossover, single oral dose, bioequivalence study of two formulations of Aripiprazole tablets **10 mg** in healthy, elderly, human subjects under fasting conditions

Methods

Study design

Both studies were open label, randomised, two treatment, two period, two sequence, crossover, single oral dose, comparative oral bioavailability studies to establish comparative BE of Aripiprazole 5 mg tablets or 10 mg tablets (test product) and Abilify 5 mg or 10 mg tablets (reference product), respectively, in healthy, elderly, male human subjects under fasting conditions. The objective of the studies was to compare the rate and extent of absorption of both products and to monitor the adverse events (AE) to ensure the safety and tolerability of a single dose of Aripiprazole 5 mg/10 mg.

In each study period, following an overnight fast of at least 10 hours, each volunteer received a single 5 mg (study 463-12) or 10 mg (study 509-12) oral dose of test or reference product with 240 ml of water. Subjects were dosed while in sitting posture and were instructed to remain seated in an upright position for the first 8 hours following drug administration. Drinking water was not permitted one hour before dosing and until one hour post dose. Subjects were confined to the clinical facility from at least 12 hours prior to each drug administration until after the 72-hour blood sample collection in each study period.

In line with the randomisation scheme, subjects received either test of reference product in study period I and then crossed-over to receive the other product in period II. 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 Cytochrome P450 isoenzyme CYP2D6 and 146 hours in slow metabolisers of CYP2D6).

In study 463-12, blood samples were taken at the following time points: pre-dose and at 0 minutes, 0.5 minutes, 1, 1.5, 2, 2.5, 3, 3.333, 3.667,4, (lunch) 4.333, 4.667, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 24, 36, 48, 60 and 72 hours after dosing.

In study 509-12, blood samples were taken at the following time points: pre-dose and at 0.5 minutes, 1,1.5, 2, 2.33, 2.667, 3, 3.33, 3.667, 4, 4.333, 4.667, 5, 5.5, 6, 6.5, 7, 8, 10, 12,16, 24, 36, 48 and 72 hours after dosing. Blood sampling time adjustments are presented in the dossier.

Test and reference products

Study 463-12

Reference product

Formulation: ABILIFY (aripiprazole) 5 mg tablets
Manufacturer: Bristol-Mayers Squibb S.r.l, Italy
Marketing Authorization Holder (MAH): Otsuka Pharmaceutical Europe Ltd, UK
Batch No/Lot No: 1D67888
Expiry Date: 01/2014

Test product

Formulation: Aripiprazole (aripiprazole) 5 mg Tablets
Manufacturer: Intas Pharmaceutical Ltd India
Batch No/Lot No: PN00729
Batch size: 300,000 units (bio batch and commercial)
Expiry Date: 06/2014

Study 509-12

Reference product

Formulation: ABILIFY (aripiprazole) 10 mg tablets
Manufacturer: Bristol-Mayers Squibb S.r.l, Italy
MAH: Otsuka Pharmaceutical Europe Ltd, UK

Batch No/Lot No: 1G64617
Expiry Date: 01/2014

Test product

Formulation: Aripiprazole (aripiprazole) 10 mg Tablets
Manufacturer: Intas Pharmaceutical Ltd India
Batch No/Lot No: PN00870
Batch size: 300,000 units (bio batch and commercial)
Expiry Date: 07/2014

Population studied

Main inclusion criteria (both studies):

Healthy, elderly, non-smokers, non-alcoholics, human volunteers between 45 to 60 years of age (both inclusive), having a Body Mass Index between 18.0 to 30.0 kg/m^2 (both inclusive) and having given their written informed consent were enrolled for the studies. They did not have any significant diseases or clinically significant abnormal findings during screening, medical history, physical examination, laboratory evaluation, treadmill test, 12-lead electrocardiogram and Chest X-ray (postero-anterior view) recordings.

Study 463-12 (5 mg tablets) enrolled 43 healthy elderly male human subjects as per the protocol (including 2 extra subjects). The study started with 40 subjects (one patient discontinued on his own accords) and 29 completed the study. Amongst the 11 drop outs, 5 subjects withdrew during period I (3 on medical grounds, AE, and 2 due to emesis). The remaining subjects withdrew in or after period II based on medical grounds (1, AE), protocol deviation (2, alcohol consumption), and on their own accord (3).

Study 509-12 (10 mg tablets) enrolled 46 healthy elderly male human subjects as per the protocol (including 2 extra subjects). The study started with 44 subjects and 40 completed the study. Prior to dosing period I, two subjects did not want to participate in the study and were replaced by another two subjects who were already checked in as spares. Four subjects dropped out of the study in total. One drop out was during period I after an AE (emesis) and three subjects dropped out during period II. Two subjects left the study on their own accord and one subject dropped out due to an AE (emesis).

Analytical methods

The plasma samples of subjects were analysed using a validated LC-MS/MS method for aripiprazole. Calibration curves based on an 8-point calibration curve standard for aripiprazole (aripiprazole-d8) were used to determine the concentrations of aripiprazole in the human plasma samples obtained from the study subjects. All samples were immediately prepared for analysis and frozen at a temperature of -65 ± 10°C for interim storage till transfer to the bio-analytical facility. The longest storage period was 72 days and this covered by the stability data in the validation of the test method.

Method validation for study 463-12 (5 mg tablets) resulted in a lower limit of quantification (LLOQ) of this method for the estimation of aripiprazole concentrations in plasma was 0.498ng/ml (precision 0.9%; accuracy 100.7%). The linearity range of aripiprazole was from 0.498ng/ml to 50.147ng/ml (8 point curve).

Method validation for study 509-12 (10 mg tablets) resulted in a LLOQ of this method for the estimation of aripiprazole concentrations in plasma was 0.508 ng/ml (precision 1.4%; accuracy 97.3%). The linearity range of aripiprazole was from 0.508 ng/ml to 150.296 ng/ml (8 point curve).

All concentration values below the LLOQ were set to zero for the pharmacokinetic and statistical calculations.

PK variables

The primary PK parameters calculated for aripiprazole were:

- c_{max}: Maximum measured plasma concentration (ng/mL).
- t_{max}: Time of observing the peak concentration (h).
- AUC_{0-72h}: Area under the plasma concentration-time curve in ng*h /mL calculated by linear trapezoidal method.

Statistical methods

Descriptive statistics were computed and reported for all PK parameters of aripiprazole. ANOVA, power and ratio analysis for ln-transformed PK parameters c_{max} and AUC_{0-72h} were computed. The 90% confidence intervals (CI) for the ratio of the geometric least-squares means were calculated for the ln-transformed pharmacokinetic parameters c_{max} and AUC_{0-72h}.

Statistical comparison of the ln-transformed c_{max} and AUC_{0-72h} 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.

BE of the test versus the reference product was concluded if the 90% CI of the relative mean c_{max} and AUC_{0-72h} fell within the acceptance range of at least 80.00% and not more than 125.00% for ln-transformed data.

Results

- Study 463-12 (5 mg tablets)

The results for the test product (Aripiprazole Accord 5 mg tablets) and the reference product (Abilify 5 mg tablets) are summarised in **Table 1** and **Table 2** below.

Table 1 - PK Parameters (non-transformed values) for Aripiprazole 5 mg (Study 463-12)

	Arithmetic Means[2] (± SD)	
Pharmacokinetic Parameter	**Test Product**	**Reference Product**
AUC_{0-72h} (ng*h/ml)	864.381 ± 320.7829	806.927 ± 241.6949
c_{max} (ng/ml)	24.418 ± 7.0190	22.530 ± 4.4902
t_{max}[1] (h)	3.333 (1.000 – 7.000)	3.667 (1.000 – 4.667)

[1] Median (Min, Max)
[2] Arithmetic Means (±SD) may be substituted by Geometric Mean (±CV %)

Table 2 - Relative Bioavailability Results for Aripiprazole 5 mg (Study 463-12)

Parameters (Units)	**Geometric Least Squares Means**			**90 % CI**	**Power**
	Test Product – T	**Reference Product - R**	**Ratio (T/R)%**		
lnc_{max}	23.556	22.185	106.2	101.16 – 111.45	100.0
lnAUC_{0-72h}	820.194	776.928	105.6	101.85 – 109.43	100.0

None of the pre-dose samples was >5% c_{max}.

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%. There were no apparent major differences in t_{max} between test and reference product.

- Study 509-12 (10 mg tablets)

The results for the test product (Aripiprazole Accord 10 mg tablets) and the reference product (Abilify 10 mg tablets) are summarised in **Table 3**and **Table 4** below.

Table 3 - PK Parameters (non-transformed values) for Aripiprazole 10 mg (Study 509-12)

Pharmacokinetic Parameter	Arithmetic Means (± SD)	
	Test Product	Reference Product
AUC_{0-72h} (ng*h/ml)	1666.849 ± 330.3571	1583.623 ± 304.4343
c_{max} (ng/ml)	43.915 ± 10.6833	41.082 ± 10.9433
t_{max}[1] (h)	3.667 (1.000 - 8.017)	4.333 (1.000 - 10.000)

[1] Median (Min, Max)

Table 4 - Relative Bioavailability Results for Aripiprazole 10 mg (Study 509-12)

Parameters (Units)	Geometric Least Squares Means			90 % CI	Power
	Test Product – T	Reference Product - R	Ratio (T/R)%		
lnc_{max}	42.745	39.687	107.7	100.39-115.55	100.0
$lnAUC_{0-72h}$	1634.613	1553.073	105.3	100.91-109.78	100.0

None of the pre-dose samples was >5% c_{max}.

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%. There were no apparent major differences in t_{max} between test and reference product.

Safety data

In study 463-12, 37 subjects received test product and 33 received the reference product Abilify. A total of 7 AEs were reported by 7 subjects. Six AEs were reported in study period I and 1 AE was reported during post-study safety assessment. Five AEs were reported in subjects after administration of the test product and two AEs were reported in subjects after administration of the reference product. All AEs were mild in nature and the subjects were followed up until resolution. The causality assessment was judged 'possible' for 5 AEs and as unrelated for 2 AEs.

There were no deaths and serious AEs reported during the conduct of the study. However, four significant AEs were reported during the conduct of the study: ligament sprain (1), pyrexia each to subject (2) and toothache (1). All four subjects were withdrawn from the study on medical grounds. The causality assessment was judged as unrelated for two AEs (ligament sprain and toothache) and possible for other two AEs of pyrexia. The latter AEs occurred after administration of the test (1 subject) and the reference product (1 subject).

In study 509-12, 42 subjects received test product and 43 received the reference product (Abilify). Two AEs were reported by two subjects during the conduct of the study. One AE was reported in period I and the other in period II. Both AEs were cases of emesis that were reported in subjects after administration of the reference product. Both the AEs were mild in nature and the subjects were followed up until resolution. The volunteers that

encountered the AEs completely recovered before the end of the study. The causality assessment for both the AEs concluded that a relationship to the use of aripiprazole was possible. There were no deaths and serious/significant AEs during the conduct of the study.

In summary, both test and reference products were well tolerated, with no major side effects and no relevant differences were observed in safety profiles of the products.

Conclusions

Based on the presented BE studies, Aripiprazole Accord 5 mg tablets are considered bioequivalent with Abilify 5 mg tablets and Aripiprazole Accord 10 mg tablets are considered bioequivalent with Abilify 10 mg tablets.

Furthermore, the results of study 463-12 using the 10 mg tablet strength can be extrapolated to the other strengths applied for (15 and 30 mg), as relevant conditions as laid down in the Guideline on the Investigation of Bioequivalence were met.

Pharmacodynamics

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

Post marketing experience

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

Discussion on clinical aspects

The design of both studies 463-12 and 509-12 were considered by the CHMP to be suitable to investigate BE between immediate release formulations. The study population and sample size, washout period, sampling times 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.

Biobatch and commercial batch size were identical. The analytical methods were adequately validated and the PK parameters investigated were appropriate, including truncation of the AUC at 72 hours which is acceptable for immediate release formulations.

Based on the results of the studies, the CHMP considered that BE between the test and reference products has been adequately demonstrated for the 5 mg and 10 mg tablet strengths with respect to the rate and extent of absorption, as the 90% CIs of the ratios for AUC_{0-72h} and c_{max} were within the acceptance range of 80.00-125.00% and t_{max} was comparable. Furthermore, all requirements of the Guideline on the Investigation of Bioequivalence for a biowaiver were fulfilled. Adequate comparative *in-vitro* dissolution studies were carried out and the choice of lower strengths over the 15 and 30 mg tablets for the BE studies was agreed by the CHMP based on the justification presented by the Applicant. Consequently, the CHMP agreed that the results of the BE study with 10 mg tablets could be extrapolated to the 15 mg and 30 mg strengths.

Conclusions on clinical aspects

Based on the available data, the CHMP concluded that bioequivalence of Aripiprazole Accord 5 mg tablets to Abilify 5 mg tablets and Aripiprazole Accord 10 mg tablets to Abilify 10 mg tablets has been demonstrated. As

all criteria for a biowaiver were met, the CHMP agreed that the results of the BE study with the 10 mg tablet strength could be extrapolated to the 15 mg and 30 mg tablets. Taken together, the available clinical data were considered adequate to support the Application for Aripiprazole Accord 5 mg, 10 mg, 15 mg and 30 mg tablets as a generic medicinal product to Abilify tablets.

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 4 is acceptable.

The CHMP endorsed the Risk Management Plan version 4 with the following content:

Safety concerns

Important identified risks	• Extrapyramidal syndrome, including tardive dyskinesia • Neuroleptic Malignant Syndrome (NMS)
Important potential risks	• Seizures • Hyperglycemia/diabetes • Suicide-related events • Orthostatic hypotension • Dyslipidemia • Weight gain • Somnolence/fatigue
Missing information	• Safety in pregnancy and lactation • Safety in paediatrics

Pharmacovigilance plan

Not applicable.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risk: Extrapyramidal syndrome, including tardive dyskinesia	Section 4.4, 4.6, 4.8, 4.9 and 5.1 of proposed Aripiprazole Accord SmPC covers information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	Educational material concerning this risk will be distributed to healthcare professionals and patients.
Important Identified Risk: Neuroleptic Malignant Syndrome (NMS)	Section 4.4 and 4.8 of proposed Aripiprazole Accord SmPC covers information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	Currently available data does not support the need for additional risk minimization activities.
Important Potential Risk: Seizure	Section 4.4 and 4.8 of proposed Aripiprazole Accord SmPC covers information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	Currently available data does not support the need for additional risk minimization activities.
Important Potential Risk: Hyperglycemia/diabetes	Section 4.4 and 4.8 of proposed Aripiprazole Accord SmPC covers information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	Currently available data does not support the need for additional risk minimization activities.
Important Potential Risk: Suicide-related events	Section 4.4 and 4.8 of proposed Aripiprazole Accord SmPC covers information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	Currently available data does not support the need for additional risk minimization activities.
Important Potential Risk: Orthostatic hypotension	Section 4.4 and 4.8 of proposed Aripiprazole Accord SmPC covers information on this safety concern. Other routine risk minimisation measure includes the status of the product as	Currently available data does not support the need for additional risk minimization activities.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	"prescription only".	
Important Potential Risk: Dyslipidemia	Section 4.8 and 5.1 of proposed Aripiprazole Accord SmPC covers information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	Currently available data does not support the need for additional risk minimization activities.
Important potential risk: Weight gain	Section 4.2, 4.4, 4.8 and 5.1 of proposed Aripiprazole Accord SmPC covers information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	Educational material concerning this risk will be distributed to healthcare professionals and patients.
Important potential risk: Somnolence/fatigue	Section 4.2, 4.6, 4.7 4.8, 4.9 and 5.1 of proposed Aripiprazole Accord SmPC covers information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	Educational material concerning this risk will be distributed to healthcare professionals and patients.
Missing information: Safety in pregnancy and lactation	Section 4.6 and 5.3 of the proposed Aripiprazole Accord SmPC covers information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	Currently available data does not support the need for additional risk minimization activities.
Missing information: Safety in paediatrics	Section 4.2, 4.4, 4.7, 4.8, 5.1 and 5.2 of the proposed Aripiprazole Accord SmPC covers information on this safety concern. Other routine risk minimisation measure includes the status of the product as "prescription only".	Educational material concerning this risk will be distributed to healthcare professionals and patients.

2.7. PSUR submission

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any

subsequent updates published on the European medicines web-portal.

2.8. Product information

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Abilify 5/10/15/30 mg tablets and Solifenacin succinate 5/10mg film-coated tablets, the latter for design and layout. 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 nor 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.

Two bioequivalence studies were submitted in support of the Application. The studies' design was in line with the respective European requirements and adequate to evaluate bioequivalence of this formulation compared to the reference product. The test formulation of Aripiprazole Accord 5 mg tablets met the protocol-defined criteria for bioequivalence when compared with Abilify 5 mg tablets. The test formulation of Aripiprazole Accord 10 mg tablets met the protocol-defined criteria for bioequivalence when compared with Abilify 10 mg tablets. Bioequivalence of the two formulations was thus demonstrated. Furthermore, it was considered acceptable to extrapolate bioequivalence demonstrated for the 10 mg tablet strength to the 15 mg and 30 mg strengths as the requirements for a biowaiver as provided for in the Guideline on the Investigation of Bioequivalence were met.

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 Accord 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**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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 agreed 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.

- **Additional risk minimisation measures**

In each Member State where Aripiprazole Accord 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 Accord 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 Accord 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.