EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 April 2015
EMA/CHMP/232319/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Aripiprazole Zentiva

International non-proprietary name: aripiprazole

Procedure No. EMEA/H/C/003899/0000

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

Administrative information

Name of the medicinal product:	Aripiprazole Zentiva
Applicant:	Zentiva, k.s. U Kabelovny 130 Praha 10 102 37 Czech Republic
Active substance:	aripiprazole
International Non-proprietary 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; Orodispersible tablet
Strength(s):	Tablets: 5 mg, 10 mg, 15 mg and 30 mg Orodispersible tablets: 10 mg, 15 mg and 30 mg
Route(s) of administration:	Oral use
Packaging:	Blister OPA/alu/PVC/alu
Package size(s):	Tablets: 14, 28, 49, 56 and 98 tablets Orodispersible tablets: 14, 28 and 49 tablets

Table of contents

List of abbreviations

5-HT	5-hydroxytryptamine = serotonin
ABC	Aberrant Behaviour Checklist
AP	Applicant's Part (or Open Part) of a DMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ARP	aripiprazole
ASD	autism spectrum disorders
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
AUC	area under the curve
AUC0-∞	area under the curve from time zero to infinity
BE	Bioequivalence
BMI	body mass index
BP	British Pharmacopoeia
BPRS	brief psychiatric rating scale
CEP	Certificate of Suitability of the Ph.Eur.
CGI	clinical global impression
CGI-BV	clinical global impression bipolar version
CGI-S	clinical global impression - severity of illness
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
Cmax	peak plasma concentration
CMS	Concerned Member State
CNS	central nervous system
CoA	Certificate of Analysis
CRS	Chemical Reference Substance (official standard)
D2 / D3	dopamine receptor type 2 / dopamine receptor type 3
DA	dopamine autoreceptor
DCP	Decentralised Procedure

DMF Drug Master File = Active Substance Master File

DP Decentralised (Application) Procedure

DSC Differential Scanning Calorimetry

DSM-IV diagnostic and statistical manual of mental disorders

EC50 half maximal effective concentration

ECG electrocardiogram

EDQM European Directorate for the Quality of Medicines

EEG electroencephalogram

EPS extrapyramidal symptoms

ERP European Reference Medicinal Product

FGA first generation antipsychotics

GAF global assessment of functioning

GC gas chromatography

GMP Good Manufacturing Practice

HDPE High Density Polyethylene

HPLC High Performance Liquid Chromatography

IC50 half maximal inhibitory concentration

ICH International Conference on Harmonization

ICP-MS Inductively coupled plasma mass spectrometry

IPC In-process control

IR Infrared

ITT intention to treat

Kel elimination rate constant

Ki dissociation constant

LOA Letter of Access

LOCF last observation carried forward

LOD Limit of Detection

LoD Loss on Drying

LOQ Limit of Quantification/Quantitation,

LoQ List of Questions

MA Marketing Authorisation

MAA Marketing Authorisation Application

MADRS Montgomery-Asberg Depression Rating Scale

MAH Marketing Authorisation Holder

MDD Major depressive disorder

MS Mass Spectrometry

ND Not detected

NfG Notes for Guidance

NKEL Number of points used in calculation of terminal elimination rate constant

NLT Not less than

NMR Nuclear Magnetic Resonance

NMS neuroleptic malignant syndrome

NMT Not more than

NNH number of participants needed to harm

NNT number needed to treat

NOS Pervasive Developmental Disorder Not Otherwise Specified

ODT orodispersible tablets

OOS Out of Specifications

OPC aripiprazole major human metabolites (OPC-14857, OPC-3373)

PANSS positive and negative syndrome scale

PDE Permitted Daily Exposure

PE Polyethylene

Ph. Eur. European Pharmacopoeia

PL placebo

PL Package Leaflet

PP Polypropylene

PRL prolactin

PVC Poly vinyl chloride

QC Quality Control

QOS Quality Overall Summary

QP Qualified Person

QTc heartrate-corrected QT interval

RCT randomised controlled trial

RH Relative Humidity

RMS Reference Member State

RP Restricted Part (or Closed Part) of a DMF

RR relative risk

RRT Relative retention time

RSD Relative standard deviation

SAE serious adverse event

SF-12 short form health survey (short form of SFSF36)

SLS sodium lauryl sulphate

SmPC Summary of Product Characteristics

SPC Summary of Product Characteristics

TGA Thermo-Gravimetric Analysis

US NF Unites States National Formulary

USP United States Pharmacopoeia

UV Ultraviolet

XRD X-Ray Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Zentiva, k.s. submitted on 13 June 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Aripiprazole Zentiva, 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 21 November 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 Zentiva is indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older.

Aripiprazole Zentiva 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 Zentiva 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:

For tablets:

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/1/04/276/006-010
- Bioavailability study number: ARZ-BESD-03-ZNV/10

For orodispersible tablets:

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, 10 mg, 15 mg, 30 mg, orodispersible tablet
- Marketing authorisation holder: Otsuka Pharmaceutical Europe Ltd
- Date of authorisation: 04-06-2004
- Marketing authorisation granted by:
  - Community
    - Community Marketing authorisation number: EU/1/04/276/024-032

■ Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Abilify, 10 mg, 15 mg, 30 mg, orodispersible tablet
- Marketing authorisation holder: Otsuka Pharmaceutical Europe Ltd
- Date of authorisation: 04-06-2004
- Marketing authorisation granted by:
  - Community
    - Community Marketing authorisation number: EU/1/04/276/024-032

■ 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, orodispersible 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: ARZ-BESD-02-ZNV/10

Licensing status

Aripiprazole Zentiva was given a Marketing Authorisation in Turkey on 14 March 2013 (orodispersible tablets) and 22 May 2013 (tablets).

1.2. Manufacturers

Manufacturer responsible for batch release

Zentiva SA
50 Theodor Pallady Blvd.
District 3, 032266
Bucuresti
Romania

1.3. Steps taken for the assessment of the product

The Rapporteur and appointed by the CHMP and the evaluation team were:

Rapporteur: John Joseph Borg

- The application was received by the EMA on 13 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 22 December 2014.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 February 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 31 March 2015.
- During the meeting on 10 April 2015 the Pharmacovigilance Risk Assessment Committee (PRAC) endorsed the PRAC Rapporteur's Risk Management Plan.
- During the meeting on 23 April 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 Zentiva.

2. Scientific discussion

2.1. Introduction

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

This centralised application concerns a generic application according to article 10(1) of Directive 2001/83/EC for Aripiprazole Zentiva 5 mg, 10 mg, 15 mg and 30 mg tablets and Aripiprazole Zentiva 10mg, 15mg and 30mg orodispersable tablets.

The applicant, Zentiva k.s, provided the results of two bioequivalence studies using the originator as a reference product in order to support this application.

To support this application the applicant, Zentiva k.s, has performed two bioequivalence studies, one for each pharmaceutical from using the 10 mg strength in both cases. The applicant furthermore applied for a biowaiver for the 15mg and 30mg strength (orodispersable tablets) and for the 5mg, 15mg and 30mg (tablets).

The applicant has stated that according to the current GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr), a bioequivalence study investigating only one strength may be acceptable provided as the proposed aripiprazole tablets and orodispersible tablets fulfil the following 5 conditions:

- the pharmaceutical products are manufactured by the same manufacturing process;
- the drug pharmacokinetics is linear;
- the qualitative composition of the different strengths is the same;
- the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule);
- the dissolution profiles are similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.

Justifications of compliance with the five conditions as stated above have been provided. Comparative dissolution studies have been provided and a biowaiver was requested for the remaining strengths.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented in the form of 5 mg, 10 mg, 15 mg or 30 mg tablets and 10 mg, 15 mg or 30 mg orodispersible tablets (ODT), containing aripiprazole as active substance.

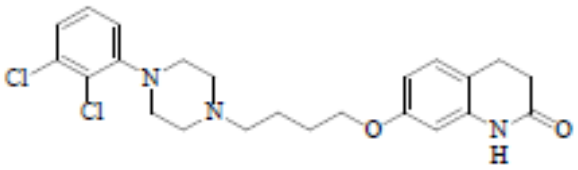
Other ingredients of the tablets are: lactose monohydrate, microcrystalline cellulose, crospovidone, hydroxypropyl cellulose, silica colloidal anhydrous, croscarmellose sodium and magnesium stearate. The orodispersable tablets contain, in addition, acesulfame potassium and mango flavour.

The product is available in OPA/Alu/PVC/Alu foil blisters (Alu-Alu blister) in a 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(1*H*)-one and has the following structure:



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

The active substance is a white to yellowish crystalline hygroscopic powder, which is practically insoluble in water, soluble in methylene chloride and very slightly soluble in ethanol (96 per cent).

Aripiprazole has a non-chiral molecular structure. Aripiprazole shows polymorphism. Several polymorphic forms have been identified: crystal forms A, B, C, D, E, F, G, and an amorphous form. It has been confirmed that the active substance manufacturers consistently produce the same crystal form B.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure. Two ASMFs have been submitted.

Manufacture, characterisation and process controls

Aripiprazole is synthesized in four main steps using commercially available well defined starting materials with acceptable specifications. In the original submission the applicant proposed a two-step synthesis. During the evaluation procedure the API starting materials were redefined by both ASMF holders to ensure full control of the quality of the active substance in line with ICH Q11. Although some of the starting materials proposed by the active substance manufacturers and some intermediates generated during the synthesis have a structural alert for genotoxicity, data presented demonstrate that the manufacturing process proposed by both ASMF holders is capable of removing or purging these compounds to acceptable limits.

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 both ASMFs and it was considered satisfactory.

Specification

The active substance specification includes tests for appearance, solubility, identification (IR, HPLC), assay (HPLC), related substances (HPLC), loss on drying (Ph. Eur.), sulphated ash (Ph. Eur.), polymorphism (XRD), appearance of solution (Ph. Eur.), residual solvents (GC), heavy metals (ICP-MS), bacterial endotoxins (Ph. Eur.), microbial contamination (Ph. Eur.) 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 3 pilot scale batches from each active substance manufacturer were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three pilot scale batches (from one of the active substance manufacturers) and three commercial scale batches (from the other proposed manufacturer of the active substance) stored in the intended commercial package for 12 or 9 months, respectively, 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. In addition, supportive stability studies from three commercial scale batches manufactured prior to process optimization (which involved minor changes on the crystallization and drying processes which were shown to have no impact on stability), and stored for 60 months at long term conditions and 6 months under accelerated conditions were provided.

The following parameters were tested: appearance, polymorphism, assay, related substances, loss on drying, particle size and microbial contamination.

All parameters remained within the proposed specification.

Photostability testing following the ICH guideline Q1B was performed on one batch from each same manufacturer, showing that the active substance is photostable.

Results from stress studies under heat, light, oxidizing, humidic, alkaline and acidic conditions were also provided on one batch from each manufacturer. Aripiprazole was found to be resistant against elevated temperature, basic conditions and light. Significant decomposition of aripiprazole occurred under oxidation and acidic conditions. The results from these studies confirmed the stability indicating nature of the HPLC method proposed for assay and related substances.

The analytical methods used were the same as for release and were stability indicating.

The stability results indicate that the drug substance manufactured by the proposed suppliers 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 product is presented in two pharmaceutical forms: 5 mg, 10 mg, 15 mg and 30 mg tablets; and 10 mg, 15 mg, and 30 mg orodispersible tablets.

The aim of the pharmaceutical development was to produce stable aripiprazole tablets and aripiprazole orodispersible tablets bioequivalent to the reference medicinal product Abilify tablets and Abilify orodispersible tablets, respectively.

The applicant conducted pre-formulation studies to evaluate key physicochemical characteristics of the active substance which could influence the performance of the finished product (particle size, solubility, stability, etc.). The solubility studies concluded that the drug substance shows a pH dependant solubility, which decreases when increasing the pH of the media. The solubility increases with the addition of sodium lauryl sulphate (SLS) up to the level when saturation is reached. Polymorphic screening studies concluded that the polymorphic form produced by both manufacturers, form B, is stable. No polymorphic form conversion of the drug substance supplied by any of the active substance manufacturers during the manufacturing of the finished product, or storage under different stress conditions in different primary packaging, was observed. In addition, no significant increase in the impurity levels of drug substance was detected, leading to the conclusion that aripiprazole is a stable active substance.

The selection of the excipients was primarily based on the composition of the reference medicinal product and on the results from compatibility studies of the active substance with individual excipients.

The qualitative composition of the different tablet and orodispersable tablet strengths are the same. The different tablet strengths are dose/weight proportional.

The excipients selected for the tablets are: lactose monohydrate (diluent), microcrystalline cellulose (diluent), hydroxy propyl cellulose (binder), magnesium stearate (lubricant), which are also present in the reference medicinal product and, crospovidone (disintegrant), croscarmellose sodium (disintegrant) and silica colloidal anhydrous (glidant).

The excipients selected for the orodispersible tablets are: microcrystalline cellulose, crospovidone, croscarmellose sodium, acesulfame potassium (sweetener), and magnesium stearate, which are also present in the reference medicinal product and, lactose monohydrate, hydroxy propyl cellulose, silica colloidal anhydrous (glidant) and mango flavour.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Different approaches were tried for the manufacture of Aripiprazole tablets. Based on the results from these studies wet granulation was selected for further development.

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

Results from two bioequivalence studies comparing the 10 mg tablets and 10 mg orodispersible tablets of the test and reference product were provided.

A request for a biowaiver for the other strengths (5mg, 15 mg and 30 mg tablets; and 15 mg and 30 mg orodispersible tablets) was submitted on the basis that: all the strengths are manufactured by the same manufacturer using the same manufacturing process, the qualitative composition of the different strengths is the same, the composition of the strengths are quantitatively proportional, formulation, aripiprazole exhibits linear pharmacokinetics in the proposed dose range, aripiprazole exhibits good solubility in the gastrointestinal pH range, and the similarity of the dissolution profiles of the different strengths as described below.

In this regard, data from *in vitro* dissolution tests at three different buffers (0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer) and the media intended for drug product release (QC media), obtained with biobatches

(10 mg) and additional strengths of both tablets (5mg, 15 mg and 30 mg) and ODT (15 mg and 30 mg) were also presented. The results from these studies demonstrated that dissolution profiles of all strengths in all dissolution media were similar since in 0.1 N HCl more than 85% of the active substance was released from the tablets and ODT within 15 min, and in pH 4.5 and 6.8 the similarity factor (*f*2) values obtained above 50.

The discriminatory power of the dissolution method was also demonstrated.

The primary packaging is Alu-Alu blisters in a 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 for both the tablets and the orodispersible tablets consists of seven main steps: dry mixing, wet granulation, drying, milling, lubrication, compression and packaging. 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.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, identification (HPLC, UV), weight, uniformity of mass (Ph. Eur.), uniformity of dosage units (Ph. Eur.), disintegration time (Ph. Eur.), water content (Karl Fisher), dissolution, assay (HPLC), related substances (HPLC), microbial contamination (Ph. Eur.). The specification of the orodispersible tablets also included fineness of dispersion.

Batch analysis results are provided for four batches of tablets per strength and two batches of orodispersible tablet 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 one pilot and two commercial scale batches of aripiprazole 5 mg and 30 mg tablets manufactured by the proposed finished product manufacturer and stored for 36 months under long term conditions at 25 ºC / 60% RH, for 12 months under intermediate conditions at 30 ºC / 65% RH, and for 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

Additional stability data from four commercial scale batches of aripiprazole 5 mg, 10 mg, 15 mg and 30 mg tablets stored for up to 12 months under long term and intermediate conditions and 6 months at accelerated conditions were also presented.

For the orodispersible tablets stability data of one pilot and two commercial scale batches of aripiprazole 10 mg and 30 mg orodispersible tablets manufactured by the proposed finished product manufacturer and stored for 36 months under long term conditions at 25 ºC / 60% RH, for 12 months under intermediate conditions at 30 ºC / 65% RH, and for 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

Additional stability data from two commercial scale batches of aripiprazole 10 mg, 15 mg and 30 mg orodispersible tablets stored for up to 6 months under long term, intermediate conditions and accelerated conditions were also presented.

The batches of aripiprazole tablets and orodispersible tablets were identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, disintegration, dissolution, assay, related substances, water content, fineness of dispersion (orodispersible tablets only) and microbial test. The analytical procedures used are stability indicating.

All results complied with the proposed specification at all-time points tested. Therefore, based on available stability data, the shelf-life as stated in the SmPC is acceptable.

Adventitious agents

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. 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. Recommendation(s) for future quality development

n/a

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 (ERA)

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Aripiprazole Zentiva 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 on non-clinical aspect

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

This is an application for 4 different strengths of aripiprazole tablets (5, 10, 15, 30 mg) and 3 different strengths of aripiprazole orodispersible tablets (10, 15, 30 mg). To support the marketing authorisation application the applicant conducted two bioequivalence studies with cross-over design under fasting conditions.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of aripiprazole 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.

For the clinical assessment the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98) in its current version is of particular relevance.

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

According to the current GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr), a bioequivalence study investigating only one strength for each pharmaceutical form may be acceptable if all of the following 5 conditions are fulfilled:

- the pharmaceutical products are manufactured by the same manufacturing process;
- the drug pharmacokinetics is linear;
- the qualitative composition of the different strengths is the same;

- the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule);
- the dissolution profiles are similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.

The applicant stated that the proposed aripiprazole tablets and oral dispersible tablets fulfil the above criteria since the manufacturing process for all the strengths for each pharmaceutical form are the same, the PK was linear, and the composition of the different strengths is the same and proportional, i.e. the ratio between amounts of active compound and excipients are identical for all the strengths.

Comparative dissolution studies with Aripiprazole 5 mg, 15 mg and 30 mg tablets against the bioequivalence study batch i.e. Aripiprazole 10 mg tablets were conducted in 0.1N HCL, pH 4.5, and pH 6.8 with F2 values above 50. The comparative dissolutions of Aripiprazole 15 mg and 30 mg orodispersible tablets against the bioequivalence study batch i.e. Aripiprazole 10 mg orodispersible tablets were conducted in 0.1N HCL, pH 4.5, and pH 6.8 with F2 values above 50. The drug input has been shown to be linear over the therapeutic range.

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

2.4.2. Pharmacokinetics

To support the application, the applicant has submitted two bioequivalence studies.

Study ARZ-BESD-03-ZNV/10

Methods

This was a randomised, open-label, two-period, two-sequence, single dose, two-way crossover comparative oral bioavailability study to establish comparative bioequivalence of Aripiprazole 10 mg tablets (Zentiva) and Abilify 10 mg tablets (Bristol Myers Squibb Italy) in 36 healthy, adult, male human subjects under fasting conditions. The objective of the study was to compare the rate and extent of absorption of both products and to monitor the adverse events to ensure the safety and tolerability of a single dose of Aripiprazole 10 mg.

Study design

Based on the randomised schedule and following an overnight fast of at least 6 hours in both periods each volunteer received a single oral dose of one Aripiprazole 10 mg tablet (either the reference or test product) with 200 ml of water in period I and in period II.

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.

The two periods were separated by a wash-out phase of at least 42 days.

Blood samples were taken at the following time points: pre-dose and at 10 minutes, 20minutes, 30 minutes,0.75, 1, 1.5, 2, 2.5, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.50, 4.75, 5, 5.5, 6, 9, 12, 24, 36, 48 and 72 hours after dosing. Blood sampling time adjustments are presented in the dossier.

Table 1 - Test and reference products

Product Characteristics	Test (T)	Reference (R)
Product Name	Aripiprazole 10 mg	Abilify 10 mg
Strength	10 mg	10 mg
Dosage Form	tablets	tablets
Manufacturer	[redacted]	Bristol-Myers Squibb, Italy
Batch/Lot No.		0E56649
Bio-batch Size		
Mesured content(s) (% of label claim)		[redacted]
Commercial Batch Size		
Expiry date		28/02/2013
Location of Certificate of Analysis		[redacted]
Member State where the reference product is purchased from:		Czech Republic
This product was used in the following trials:	ARZ-BESD-03-ZNV/10	

Population studied

36 healthy adult male human subjects were enrolled as per the protocol. The study started with 36 subjects and 35 completed the study.

Main inclusion criteria:

Healthy human adult literate male non-smoker subjects aged 45 years of age or older, having a body mass index (BMI) between 18.5 and 30 kg/m2 (inclusive) who had no evidence of underlying disease or clinically significant abnormal laboratory values at screening and who voluntarily consented to participate in the study in written form.

Protocol deviations;

Subject number 18 dropped out from the study for personal reasons. One minor deviation from the study protocol (one subject (2) took counteractive medication for headache) was the only registered deviation.

Analytical methods

Analysis of aripiprazole was performed using test method ARZ-BE-LCMSMS-01/10.

This HPLC/MS/MS method involved the extraction of aripiprazole and the internal standard aripiprazole-d8 from human plasma. Samples were kept frozen at -20ºC prior to analysis for a period of 48 days. During transport the samples were kept for 2 days at -70 ºC however this excursion is covered in the validation of the test method.

A total of 1846 blood samples were to be collected for the 35 subjects. 1 sample was re-assayed and 140 samples were identified for incurred sample reanalysis. 100.00% is the percentage of samples where the difference between the two values was less than 20% of the mean for chromatographic assays or less than 30% for the ligand binding assays.

The method has been validated (ARZ-BE-LCMSMS-01/10) and partially re-validated 4 times. The following parameters were addressed; selectivity of Aripiprazole and the internal standard (IS), calibration curve (linearity), carryover test, recovery of both the analyte and the internal standard, precision, accuracy, dilution integrity accuracy and precision, stability of the stock solution (short and long term stability in the biological matrix, bench top, freeze-thaw, auto sampler storage, and post-preparative stability), haemolysis effect accuracy and precision, ruggedness and matrix effect. Each parameter has been assessed and the limits are justified. This is deemed acceptable.

The effect of interfering drugs was also studied using the following commonly used medicines: caffeine, acetylsalicylic acid, tramadol, paracetamol, and ibuprofen. No effect on the determination of the analyte and the internal standard was observed.

The lower limit of quantification (LLOQ) of this method for the estimation of Aripiprazole concentrations in plasma was 0.250ng/ml (Precision 4.681%, Accuracy 117.733%). The linearity range of Aripiprazole was from 0.250g/ml to 100.000ng/ml. (8 point curve)

Pharmacokinetic (PK) variables

Primary parameters: AUC_{0-72} and C_{max}

Secondary parameters: T_{max}.

Bioequivalence criteria: The 90% confidence interval of the relative mean AUC_{0-72} and C_{max} of the test and reference product should be at least 80.00% and not more than 125.00% for log-transformed data.

Statistical methods

The 90% confidence interval of the relative mean AUC_{0-72} and C_{max} of the test and reference product should be at least 80% and not more than 125% for log-transformed data. ANOVA was performed on the log-transformed pharmacokinetic parameters - AUC_{0-72} and C_{max} of aripiprazole using General Linear Model (PROC GLM procedure) of SAS. The 90% confidence interval for the difference between the least square means (LSM) was calculated for the log-transformed pharmacokinetic parameters - AUC_{0-72} and C_{max} of aripiprazole. The number of observations,

arithmetic mean, standard deviation, coefficient of variation (CV %), minimum, median, maximum and geometric mean were calculated for all the pharmacokinetic parameters.

Results

The results are summarised in table 1 and 2 below.

Table 2 - Pharmacokinetic parameters for Aripiprazole 10mg (non-transformed values)

Pharmacokinetics Parameters	Arithmetic Mean (+/-SD)	
	Test product	Reference product
$AUC_{(0-72)}$ (ng·hr/mL)	1526.852± 525.840	1421.566± 563.550
Cmax (ng/mL)	42.401± 15.295	37.026± 15.433
Tmax (hr)[1]	2.000 [1.000-36.000]	3.000 [1.000-12.000]

[1]Median, (Min, Max)

Table 3 - Statistical analysis for Aripiprazole 10mg (ln-transformed values)

Pharmacokinetics parameter	Geometric Mean Ratio Test/Ref[1]	Confidence Intervals	CV%[2]
$AUC_{(0-72)}$ (ng·hr/mL)	107.997	103.960% - 112.191%	9.434
Cmax (ng/mL)	115.005	106.679% - 123.980%	18.729
$AUC_{(0-inf)}$ (ng·hr/mL)	-	-	-

[1] Calculated using least-squares means

[2] Estimated from the Residual Mean Squares. For replicate design studies report the within-subject CV% using only the reference product data.

Safety data

Both formulations were well tolerated, with no major side effects and no relevant differences in safety profiles were observed between the preparations.

Three adverse events out of which two of mild intensity and one of moderate intensity occurred in three subjects in the present study. These were not serious adverse events. The volunteers that encountered the adverse events completely recovered before the end of the study. No statistical significant differences between the test and reference treatments, for the incidence of subjects having experienced adverse events and for the incidence of adverse events were seen.

Study ARZ-BESD-02-ZNV/10

Methods

This was a randomised, open-label, two-period, two-sequence, single dose, two-way crossover comparative oral bioavailability study to establish comparative bioequivalence of Aripiprazole 10 mg orodispersable tablets (Zentiva) and Abilify 10 mg orodispersable tablets (Bristol Myers Squibb Italy) in 36 healthy, adult, male human subjects under fasting conditions. The objective of the study was to compare the rate and extent of absorption

of both products and to monitor the adverse events to ensure the safety and tolerability of a single dose of Aripiprazole 10 mg.

Study design

Based on the randomised schedule and following an overnight fast of at least 8 hours in both periods each volunteer received a single oral dose of Aripiprazole 10mg orodispersable tablet to be placed entirely in the mouth and allowed to disperse in saliva. Subjects received either one tablet of the reference or test product in period I and period II.

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.

The two periods were separated by a wash-out phase of at least 42 days.

Blood samples were taken at the following time points: pre-dose and at 10 minutes, 20minutes, 30 minutes, 0.75, 1, 1.5, 2, 2.5, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.50, 4.75, 5, 5.5, 6, 9, 12, 24, 36, 48 and 72 hours after dosing. Blood sampling time adjustments are presented in the dossier. A volume of 150 ml of blood was withdrawn in total from each patient per study period.

Table 4 - Test and reference products

Product Characteristics	Test (T)	Reference (R)
Product Name	Aripiprazole 10 mg	Abilify 10 mg
Strength	10 mg	10 mg
Dosage Form	orodispersible tablets	orodispersible tablets
Manufacturer	[redacted]	Bristol-Myers Squibb, Italy
Batch/Lot No.	[redacted]	9J50637
Bio-batch Size	[redacted]	
Mesured content(s) (% of label claim)	[redacted]	-
Commercial Batch Size	[redacted]	
Expiry date	[redacted]	06/2012
Location of Certificate of Analysis	[redacted]	[redacted]
Member State where the reference product is purchased from:		Slovac Republic
This product was used in the following trials:	ARZ-BESD-02-ZNV/10	

Population studied

A total of 36 healthy adult male human subjects were enrolled as per the protocol. The study started with 36 subjects and 36 completed the study.

Main inclusion criteria:

Healthy human adult literate male non-smoker subjects aged 45 years of age or older, having a body mass index (BMI) between 18.5 and 30 kg/m2 (inclusive) who had no evidence of underlying disease or clinically significant abnormal laboratory values at screening and who voluntarily consented to participate in the study in written form.

Analytical methods

Analysis of aripiprazole was performed using test method ARZ-BE-LCMSMS-01/10.

This HPLC/MS/MS method involved the extraction of aripiprazole and the internal standard aripiprazole-d8 from human plasma. Samples were kept frozen at -20ºC prior to analysis for a period of 48 days. During transport the samples were kept for 1 days at -70 ºC however this excursion is covered by sample stability data in the validation of the test method

A total of 1872 blood samples were to be collected for the 36 subjects. 1846 samples were collected. 7 samples were re-assayed and 144 samples were identified for incurred sample reanalysis. 100.00% is the percentage of samples where the difference between the two values was less than 20% of the mean for chromatographic assays or less than 30% for the ligand binding assays.

The method has been validated (ARZ-BE-LCMSMS-01/10) and partially revalidated 4 times. The following parameters were addressed; selectivity of Aripiprazole and the internal standard (IS), calibration curve (linearity), carryover test, recovery of both the analyte and the internal standard, precision, accuracy, dilution integrity accuracy and precision, stability of the stock solution (short and long term stability in the biological matrix, bench top, freeze-thaw, auto sampler storage, and post-preparative stability), haemolysis effect accuracy and precision, ruggedness and matrix effect. Each parameter has been assessed and the limits are justified. This is deemed acceptable.

The effect of interfering drugs was also studied using the following commonly used medicines: caffeine, acetylsalicylic acid, tramadol, paracetamol, and ibuprofen. No effect on the determination of the analyte and the internal standard was observed.

The lower limit of quantification (LLOQ) of this method for the estimation of Aripiprazole concentrations in plasma was 0.250ng/ml (Precision 3.646%, Accuracy 110.933%). The linearity range of Aripiprazole was from 0.250g/ml to 100.000ng/ml. (8 point curve).

PK Variables

Primary parameters: AUC_{0-72} and C_{max}

Secondary parameters: T_{max}.

Bioequivalence criteria: The 90% confidence interval of the relative mean AUC_{0-72} and C_{max} of the test and reference product should be at least 80.00% and not more than 125.00% for log-transformed data.

Statistical methods

The 90% confidence interval of the relative mean AUC_{0-72} and C_{max} of the test and reference product should be at least 80% and not more than 125% for log-transformed data. ANOVA was performed on the log-transformed pharmacokinetic parameters - AUC_{0-72} and C_{max} of aripiprazole using General Linear Model (PROC GLM procedure) of SAS. The 90% confidence interval for the difference between the least square means (LSM) was calculated for the log-transformed pharmacokinetic parameters - AUC_{0-72} and C_{max} of aripiprazole. The number of observations, arithmetic mean, standard deviation, coefficient of variation (CV %), minimum, median, maximum and geometric mean were calculated for all the pharmacokinetic parameters.

Results

Table 5 - Pharmacokinetic parameters for Aripiprazole 10mg (non-transformed values)

Pharmacokinetics Parameters	Arithmetic Mean (+/-SD)	
	Test product	Reference product
$AUC_{(0-72)}$ (ng·hr/mL)	1576.177± 466.811	1460.534± 423.215
Cmax (ng/mL)	43.368± 13.924	38.993± 12.262
Tmax (hr)[1]	2.250 [1.000-9.000]	3.125 [1.000-9.000]

[1]Median, (Min, Max)

Table 6 - Statistical analysis for Aripiprazole 10mg (ln-transformed values)

Pharmacokinetics parameter	Geometric Mean Ratio Test/Ref[1]	Confidence Intervals	CV%[2]
$AUC_{(0-72)}$ (ng·hr/mL)	107.322	100.648% - 114.438%	16.213
Cmax (ng/mL)	111.069	102.062% - 120.871%	21.461
$AUC_{(0-inf)}$ (ng·hr/mL)	-	-	-

[1] Calculated using least-squares means
[2] Estimated from the Residual Mean Squares. For replicate design studies report the within-subject CV% using only the reference product data.

Safety data

Both formulations were well tolerated, with no major side effects and no relevant differences in safety profiles were observed between the preparations. Five adverse events of moderate intensity occurred in two subjects in the study. These were not serious adverse events (Headache and Urticaria). The volunteers that encountered the adverse events completely recovered before the end of the study. No statistical significant differences between the test and reference treatments, for the incidence of subjects having experienced AEs and for the incidence of AEs were seen.

Conclusions

Based on the presented bioequivalence studies, Aripiprazole Zentiva 10mg orodispersable tablets and Aripiprazole Zentiva 10mg tablets are considered bioequivalent with Abilify 10mg orodispersable tablets and Abilify 10mg tablets of Bristol-Myers Squibb GmbH Italy, respectively.

The results for the 10 mg tablet and the 10 mg orodispersable tablet strengths can be extrapolated to the other respective strengths for each pharmaceutical form applied for, according to conditions provided for in the Guideline on the Investigation of Bioequivalence.

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

In support of this application,results from two bioequivalence (BE) studies were provided, one for the tablets and one for the orodispersible tablets, both using the 10 mg strength formulation. For all other strength a biowaiver was claimed.

The results of the two BE studies showed that both the 10mg tablet and orodispersible tablets were bioequivalent to the reference product Abilify. Results of study ARZ-BESD-03-ZNV/10 with the 10mg tablet formulation could be extrapolated to Aripiprazole 15mg and 30mg tablets and results of study ARZ-BESD-02-ZNV/10 with the 10 mg orodispersable tablet formulation could be extrapolated to Aripiprazole

30mg orodispersable tablet according to conditions in the Guideline on the Investigation Bioequivalence CPMP/EWP/QWP/1401/98 Rev 1. The 5mg tablet and the 15mg orodispersable tablet request for a biowaiver was also accepted as initially identified issues pertaining to dissolution concerns for those two pharmaceutical forms had been resolved at the time of this report.

2.4.6. Conclusions on clinical aspects

Based on the submitted bioequivalence study results, Aripiprazole 10 mg orodispersible tablets of Zentiva are considered bioequivalent with Abilify 10 mg orodispersible tablets of Bristol-Myers Squibb GmbH Italy and Aripiprazole 10 mg tablets of Zentiva are considered bioequivalent with Abilify 10mg tablets of Bristol-Myers Squibb GmbH Italy in healthy adult male patients under fasting conditions.

As all criteria for a biowaiver were met, the CHMP agreed that the results of study ARZ-BESD-03-ZNV/10 with the 10 mg tablet formulation can be extrapolated to Aripiprazole the 5mg, 15mg and 30mg tablets and the results of study ARZ-BESD-02-ZNV/10 with the 10 mg orodispersible tablet formulation can be extrapolated to Aripiprazole 15mg and 30mg orodispersible tablets according to conditions in the Guideline on the Investigation Bioequivalence CPMP/EWP/QWP/1401/98 Rev 1.

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 1.3 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed the Risk Management Plan version 1.3 with the following content:

Safety concerns

Applicable for both drug formulations.

Summary of safety concerns	
Important identified risks	• Extrapyramidal symptoms, including tardive dyskinesia • Neuroleptic malignant syndrome
Important potential risks	• Orthostatic hypotension • Seizures • Hyperglycaemia and diabetes mellitus • Suicidal behaviour • Dyslipidaemia
Missing information	• Safety in pregnancy and lactation • Safety in paediatric population

Pharmacovigilance plan

Not applicable.

Risk minimisation measures

Summary of proposals from MAH for risk minimisation measures has been updated as follows:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Extrapyramidal symptoms, including tardive dyskinesia	Proposed text in SmPC: Recommendation on posology in section 4.2 that aripiprazole daily dose in the treatment of manic episodes in Bipolar I Disorder in adolescents aged 13 years and older is 10 mg and that the treatment duration must not exceed 12 weeks. Doses higher than 10 mg/day are associated with a substantially higher incidence of significant undesirable effects including EPS related events. Warning in section 4.4 on possible risk of tardive dyskinesia and other extrapyramidal symptoms such as akathisia and parkinsonism. Information about the effect and the frequency in section 4.8 Pharmacodynamic properties are presented in section 5.1 Prescription only medicine	Educational Programme will be delivered to patients and prescribers at the time of marketing of the medicinal product. The national specialities must be adapted at national level with the national competent authorities as well as implementation plan. Objective of the Educational programme, in a form of Information Brochure pack for physicians and patients, will be to convey the following key messages regarding the safety profile of aripiprazole with respect to extrapyramidal symptoms in the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older: • treatment with aripiprazole has been associated with dose-related extrapyramidal symptoms such as akathisia, parkinsonism, and tardive dyskinesia • need for close monitoring and dosage adjustment if signs and symptoms of extrapyramidal symptoms appear in a patient taking Aripiprazole Zentiva • 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 for doses higher than 10 mg/day there is a greater potential for occurrence of adverse events
Neuroleptic malignant syndrome	Proposed text in SmPC: Warning in section 4.4 on possible risk of neuroleptic malignant syndrome during the treatment with aripiprazole. Listed among undesirable effects in section 4.8	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Prescription only medicine	
Orthostatic hypotension	Proposed text in SmPC: Listed among undesirable effects in section 4.8 Pharmacodynamic properties are presented in section 5.1 Prescription only medicine	None proposed.
Seizures	Proposed text in SmPC: Warning in section 4.4 on possible risk of seizures while treated with aripiprazole. Listed among undesirable effects in section 4.8 Prescription only medicine	None proposed.
Hyperglycaemia and diabetes mellitus	Proposed text in SmPC: Warning in section 4.4 that hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotic agents, including aripiprazole. Risk factors include obesity and family history of diabetes. Patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Listed in section 4.8 Prescription only medicine	None proposed.
Suicidal behaviour	Proposed text in SmPC: Warning in section 4.4 that suicidal behaviour has been observed early after initiation of the treatment. Close supervision should accompany	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	antipsychotic therapy. Listed in section 4.8 Prescription only medicine	
Dyslipidaemia	Proposed text in SmPC: Information about the effect and the frequency in section 4.8 Pharmacodynamic properties are presented in section 5.1 Prescription only medicine	None proposed.

Weight gain	Proposed text in SmPC:
	
	Recommendation on posology in section 4.2 that aripiprazole daily dose in the treatment of manic episodes in Bipolar I Disorder in adolescents aged 13 years and older is 10 mg and that the treatment duration must not exceed 12 weeks. Doses higher than 10 mg/day are associated with a substantially higher incidence of significant undesirable effects including weight gain.
	
	Warning in section 4.4 on possible risk of weight gain and predisposing factors such as history of diabetes, thyroid disorder or pituitary adenoma. Warning that weight gain should be monitored in adolescent patients with bipolar mania and if clinically significant, dose reduction should be considered.
	
	Information about the effect and the frequency in section 4.8
	
	Pharmacodynamic properties are presented in section 5.1
	
	Prescription only medicine
		Educational Programme will be delivered to patients and prescribers prior to the marketing of the medicinal product. Physicians will receive both educational packages. The patient's educational pack will be handed over by their treating physicians. The process should be very similar to the one used for the reference medicinal product.
		
		Objective of the Educational programme, in a form of Information Brochure pack for physicians and patients, will be to convey the following key messages regarding the safety profile of aripiprazole with respect to weight gain in the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older:
		• weight gain has been reported post-marketing among patients prescribed aripiprazole
		• significant risk factors are:
		  ○ history of diabetes
		  ○ thyroid disorder
		  ○ pituitary adenoma
		• need for close monitoring and dose reduction if weight gain is clinically significant
		• 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

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
		• Instructions that for doses higher than 10 mg/day there is a greater potential for occurrence of adverse events.
Somnolence and fatigue	Proposed text in SmPC: Recommendation on posology in section 4.2 that aripiprazole daily dose in the treatment of manic episodes in Bipolar I Disorder in adolescents aged 13 years and older is 10 mg and that the treatment duration must not exceed 12 weeks. Doses higher than 10 mg/day are associated with a substantially higher incidence of significant undesirable effects including somnolence and fatigue. Information in section 4.7 that some paediatric patients with Bipolar I Disorder have an increased incidence of somnolence and fatigue therefore should be cautioned about operating hazardous machines, including motor vehicles. Information about the effect and the frequency in section 4.8 Pharmacodynamic properties are presented in section 5.1 Prescription only medicine	Educational Programme will be delivered to patients and prescribers prior to the marketing of the medicinal product. Physicians will receive both educational packages. The patient's educational pack will be handed over by their treating physicians. The process should be very similar to the one used for the reference medicinal product. Objective of the Educational programme, in a form of Information Brochure pack for physicians and patients, will be to convey the following key messages regarding the safety profile of aripiprazole with respect to somnolence and fatigue in the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older: • in the paediatric population somnolence and fatigue were observed more frequently in patients with bipolar disorder compared to patients with schizophrenia • 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 for doses higher than 10 mg/day there is a greater potential for occurrence of adverse events
Safety in pregnancy and lactation	Proposed text in SmPC: Warning in section 4.6 that there are no adequate and well-controlled trials of aripiprazole in pregnant women. Congenital anomalies have been reported; however, causal relationship with aripiprazole could not be established. Due to insufficient safety this medicinal product should not be used in pregnancy unless the expected benefit clearly justifies the potential	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	risk to the foetus. Aripiprazole is excreted in human breast milk. Patients should be advised not to breast feed if they are taking aripiprazole. Prescription only medicine	

Safety in paediatric patients	Proposed text in SmPC:
	
	Therapeutic indications for paediatric patients in section 4.1 Aripiprazole Zentiva is indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older and for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.
	
	Information regarding posology in section 4.2 that Aripiprazole Zentiva is not recommended for use in patients with schizophrenia below 15 years of age due to insufficient data on safety and efficacy. In addition aripiprazole is not recommended for use in manic episodes in patients below 13 years of age due to increased risk of adverse events.
	
	Occurrence of undesirable effects in paediatric population is described in section 4.8.
	
	Pharmacodynamic properties are presented in section 5.1
	
	Prescription only medicine
		Educational Programme will be delivered to patients and prescribers at the time of marketing of the medicinal product. Core elements of these documents are attached in VII.10 Annex 10. The national specialities must be adapted at national level with the national competent authorities as well as implementation plan.
		
		Objective of the Educational programme, in a form of Information Brochure pack for physicians and patients, will be to convey the following key messages regarding the safety profile of aripiprazole with respect to extrapyramidal symptoms, weight gain and somnolence and fatigue in the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older:
		• treatment with aripiprazole has been associated with dose-related extrapyramidal symptoms such as akathisia, parkinsonism, and tardive dyskinesia
		• weight gain has been reported post-marketing among patients prescribed aripiprazole
		• significant risk factors for weight gain are:
		  ○ history of diabetes
		  ○ thyroid disorder
		  ○ pituitary adenoma
		• need for close monitoring and dosage adjustment if signs and symptoms of extrapyramidal symptoms and clinically significant weight gain appear in a patient taking Aripiprazole Zentiva
		• in the paediatric population somnolence and fatigue were observed more frequently in patients with bipolar

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
		disorder compared to patients with schizophrenia • 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 for doses higher than 10 mg/day there is a greater potential for occurrence of adverse events

2.7. PSUR submission

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.

2.8. Product information

2.8.1. User consultation

The applicant has submitted a full user test for Aripiprazole Zentiva 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 Zentiva 5 mg, 10 mg, 15 mg and 30 mg tablets has been performed on the basis of a bridging report making reference to Aripiprazole Zentiva 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 and Aripiprazole orodispersable 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 nonclinical studies have been provided for this application but an adequate summary of the available nonclinical 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 two bioequivalence studies formed the pivotal basis of the application. The study designs were considered adequate to evaluate the bioequivalence of the two formulations applied for and were in line with the respective European requirements.

The test formulations of Aripiprazole Zentiva 10 mg tablets and Aripiprazole Zentiva 10 mg orodispersable tablets met the protocol-defined criteria for bioequivalence when compared with respectively Abilify 10 mg tablets and Abilify 10 mg orodispersable 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 Zentiva 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 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.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

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

Not applicable.