CBG MEB

Public Assessment Report

Scientific discussion

Aripiprazol Doc Generici 5 mg, 10 mg and 15 mg, tablets
Aripiprazol Doc Generici 10 mg and 15 mg, orodispersible tablets

(aripiprazole)

NL/H/3203/001-003+005-006/DC

Date: 16 August 2016

This module reflects the scientific discussion for the approval of Aripiprazol Doc Generici 5 mg, 10 mg and 15 mg, tablets and Aripiprazol Doc Generici 10 mg and 15 mg, orodispersible tablets. The procedure was finalised on 12 June 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Aripiprazol Doc Generici 5 mg, 10 mg and 15 mg, tablets and 10 mg and 15 mg, orodispersible tablets from Doc Generici S.r.l.

These products are indicated for the treatment:

- Of schizophrenia in adults and in adolescents aged 15 years and older.
- 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.
- Up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Abilify 5 mg, 10 mg and 15 mg tablets and 10 mg and 15 mg orodispersible tablets, which have been registered in the European Union by Otsuka Pharmaceutical Europe Ltd. since 4 June 2004 by the centralised procedure EMEA/H/C/000471.

The concerned member states (CMS) involved in this procedure was Italy.

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

Scientific advice regarding the bioequivalence study of aripiprazole tablets was given by the MEB of the Netherlands on 6 December 2012 and 21 January 2014. For the bioequivalence study of the aripiprazole orodispersible tablets, the MEB provided the MAH with scientific advice on 6 December 2012. Scientific advice was given by the regulatory authorities of Spain and Germany as well.

II. QUALITY ASPECTS

II.1 Introduction

- Aripiprazol Doc Generici 5 mg, tablets is round, white and with “ARZ” engraved on one side and “5” on the other side. Each tablet contains 5 mg of aripiprazole.
- Aripiprazol Doc Generici 10 mg, tablets is oblong, pink (possibly with dark dots), with “ARZ” and “10” engraved on one side. Each tablet contains 10 mg of aripiprazole.
- Aripiprazol Doc Generici 15 mg, tablets is round, yellow (possibly with dark dots), and with “ARZ” and “15” engraved on one side. Each tablet contains 15 mg of aripiprazole.
- Aripiprazol Doc Generici 10 mg, orodispersible tablets is round and pink (possibly with dark dots), with “AD10” engraved on one side. Each orodispersible tablet contains 10 mg of aripiprazole.
- Aripiprazol Doc Generici 15 mg, orodispersible tablets is round and yellow (possibly with dark dots), with “AD15” engraved on one side. Each orodispersible tablet contains 15 mg of aripiprazole.

The tablets are packed in Aluminium//PVC/aluminium/oPA blisters.
The orodispersible tablets are packed in Aluminium//PVC/aluminium/oPA blisters, either as push-through or peel-off blister.

All tablets contain: sodium starch glycolate, microcrystalline cellulose, lactose monohydrate, hydroxypropylcellulose and magnesium stearate.
To create different colors for each strength, the 10 mg tablets (pink) contain as extra ingredient red iron oxide (E172(ii)) and the 15 mg tablets (yellow) contain yellow iron oxide (E172(iii)).

All orodispersible tablets contain: lactose monohydrate, magnesium stearate, colloidal anhydrous silica, croscarmellose sodium, crospovidone, microcrystalline cellulose, vanilla, aspartame (E951), acesulfame potassium (E950) and tartaric acid.
To create different colors for each strength, the 10 mg tablets (pink) contain as extra ingredient red iron oxide (E172(ii)) and the 15 mg tablets (yellow) contain yellow iron oxide (E172(iii)).

Except for some slight qualitative and quantitative differences in the colouring agents and the amount of sodium starch glycolate present in the tablets, all tablet strengths are quantitatively proportional.

Except for a slight difference in the type and quantity of iron oxide used, the 10 mg and 15 mg orodispersible tablets are fully dose-proportional.

II.2 Drug Substance

The active substance is aripiprazole, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Aripiprazole is a white or almost white powder and practically insoluble in water. Aripiprazole does not exhibit optical isomerism. The substance shows polymorphism and is manufactured as polymorphic Form II.
The Active Substance Master File (ASMF) procedure is used for both manufacturers of the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The drug substance is supplied by two manufacturers. Both manufacturers do not use heavy metal catalysts/reagents or class I organic solvents in the process. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with appropriate additional tests. The in-house methods have been adequately validated. Batch analytical data demonstrating compliance with this specification have been provided for one full scale batch for each supplier.

Stability of drug substance
Manufacturer one
Stability data on the active substance have been provided for 4 pilot scale and 3 full scale batches in accordance with applicable European guidelines, stored for36 months (25°C/60% RH) and 6 months (40°C/75% RH). Based on the data submitted, a retest period could be granted of 36 months with the storage condition: 'Store in the original package below 25°C'.

Manufacturer two
Stability data on the active substance have been provided for 13 batches (pilot and full scale) in accordance with applicable European guidelines. The active substance was stored for up to 60 months at25°C/60% RH and for 6 months at 40°C/75% RH. Based on the data submitted, a retest period could be granted of 60 months with storage condition: 'Preserve in tight containers, packed with desiccant, at 25°C'.

II.3 Medicinal Product

Aripiprazol Doc Generici 5 mg, 10 mg and 15 mg tablets

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were the characterisation of the

innovator product, optimization of the composition and the performance of comparative dissolution studies complementary to the bioequivalence study with the 10 mg product strength and in support of the biowaiver for the additional strengths. Comparative dissolution testing was performed between the test and reference formulations, and between the 10 mg biobatch and the 5 mg and 15 mg strengths at pH 1.2, 4.5 and 6.8. Results were satisfactory, as similarity was demonstrated. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The main steps of the manufacturing steps are wet granulation, final blending and compression. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three commercial scale batches per strength from one manufacturer and for two commercial scale batches for the 5 mg and 10 mg strengths and for one commercial size scale batch of the 15 mg strength batches from the other manufacturer, in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients

The excipients comply and are tested in accordance with the respective Ph.Eur., United States Pharmacopeia or National Formulary monographs. These specifications are acceptable. For the iron oxides compliance with the purity criteria of Regulation EU 231/2012 is confirmed.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification and includes tests for description, dissolution, identification, assay, uniformity of dosage units, related substances and microbial purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data have been provided from three commercial scaled batches per strength from one proposed production site. From the other production site, data from two commercial size batches of the 5 mg, 10 mg and 15 mg strengths. It demonstrates compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three commercial batches of the 5 mg and 10 mg strengths and two commercial scale batches of the 15 mg strength in accordance with the ICH stability guideline. The data cover 24-36 months stored at 25°C/60% RH and 6 months stored at 40°C/75% RH., Results of a photostability study show that the drug product is not sensitive to light. Based on the stability data, the proposed shelf-life of 36 months without special storage requirements is acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Lactose monohydrate is the only material of animal origin that is used in the manufacture of the drug product. A BSE statement for lactose monohydrate has been provided, stating that it has been produced from milk sourced from healthy cows in the same conditions as milk collected for human consumption and is produced without the use of other ruminant material than calf rennet.

Aripiprazol Doc Generici 10 mg 15 mg, orodispersible tablets

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The excipients are well known. The development is comparable to that of the immediate release tablets described above.

The main development studies were the characterisation of the reference product, dissolution method development, optimization of the formulation, the development of the manufacturing process and the performance of comparative dissolution studies complementary to the bioequivalence study with the 15 mg product strength and in support of the biowaiver for the additional strength. The comparative dissolution studies between the test and reference batch in pH 1.2, 4.5 and 6.8 dissolution media confirm their similarity. The test batch used in the bioequivalence study was manufactured according

to the finalized manufacturing process and composition. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps of the manufacturing process are the mixing of excipients, final blending and compression. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three commercial scale batches in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full-scaled batches will be performed post authorisation.

Control of excipients
The excipients comply and are tested in accordance with the respective Ph.Eur., United States Pharmacopeia or National Formulary monographs. These specifications are acceptable. For the iron oxides compliance with the purity criteria of Regulation EU 231/2012 is confirmed.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, dissolution, disintegration time, identification, assay, water content, uniformity of dosage units, impurities and microbial quality. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data have been provided from three commercial scaled batches per strength from the proposed production site demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three commercial scaled batches per strength in accordance with the ICH stability guideline. The data cover 12 months stored at 25°C/60% RH and 6 months stored at 40°C/75% RH. The batches were stored in the proposed blisters. The stability data show no clear changes or trends were observed in any of the tested parameters. Results of a photostability study show that the drug product is not sensitive to light. The proposed shelf-life of 24 months with the storage condition: “Store in the original package in order to protect from moisture” is acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is the only material of animal origin that is used in the manufacture of the drug product. A BSE statement for lactose monohydrate has been provided, stating that it has been produced from milk sourced from healthy cows in the same conditions as milk collected for human consumption and is produced without the use of other ruminant material than calf rennet.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Aripiprazol Doc Generici 5 mg, 10 mg and 15 mg, tablets and 10 mg and 15 mg, orodispersible tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Aripiprazol Doc Generici is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Abilify, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Aripiprazole is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies, one study for the 10 mg tablet form and one for the 15 mg orodispersible tablet form, which are discussed below.

IV.2 Pharmacokinetics

Aripiprazol Doc Generici tablets

The MAH conducted one bioequivalence study to demonstrate that the proposed Aripiprazol Doc Generici 10 mg tablets (Doc Generici S.r.l., NL) is bioequivalent with Abilify 10 mg tablets (Otsuko Pharmaceutical Europe Ltd., UK).
The choice of the reference product in the bioequivalence study is accepted, as Abilify has been registered through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
The MAH applied for a biowaiver for the 5 mg and 15 mg strengths in accordance with the Guideline on the Investigation of Bioequivalence. The tablet strengths are dose-proportional, contain the same excipients and are manufactured by the same manufacturing process.
Results of *in vitro* dissolution studies were submitted. At pH 1.2,dissolution was very fast (more than 85% within 15 minutes) for all the different strengths. At pH 4.5, the f2 values between 10 mg and the other strengths were between 50 and 100. Dissolution in pH 6.8 was poor and dose-dependent for all strengths. The f2-values were between 50 and 100. However, considering the solubility of aripiprazole is pH-dependent and the profiles indicate comparative similarity, these results were acceptable. Overall, the dissolution data conducted to waive the 5 mg and 15 mg strengths are considered acceptable.

Bioequivalence study
Design
A single-dose, open label, randomised, two-period, laboratory-blinded, crossover bioequivalence study was carried out under fasted conditions in 24 healthy subjects (10 males, 14 females), aged 45-61 years. Each subject received a single dose (10 mg tablet) of one of the 2 aripiprazole formulations. The tablet was orally administered with 200 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 42 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 24, 32, 48 and 72 hours after administration of the products.

The overall study design is acceptable. Considering that aripiprazole is a drug with low solubility, in principle, the highest strength should be used to show bioequivalence. A lower strength was used due to serious safety consideration of healthy volunteers, as the highest strength cannot be administered

to healthy volunteers for safety/tolerability reasons. Based on the justification provided by the MAH, the choice of 10 mg strength for the bioequivalence study is considered justified.
As the half-life of aripiprazole is about 90 hours, estimation of the extent of absorption over a period of 72 hours is acceptable. Also the washout period is acceptable. The product can be taken regardless of food intake, therefore a study under fasting conditions is justified.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
No subjects withdrew from the study, all 24 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of aripiprazole under fasted conditions.

Treatment N=24	AUC_{0-72} ng/ml/h	C_{max} ng/ml	t_{max} h
Test	1561 ± 387	44.5 ± 12	2.5 (1-12)
Reference	1543 ± 420	42.0 ± 12	3.0 (1-14)
***Ratio (90% CI)**	1.02 (0.96 – 1.09)	1.07 (0.97 – 1.19)	--

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

**ln-transformed values*

Safety
Twelve (12) subjects experienced a total of 35 mild to moderate adverse events over the course of the study (i.e. weakness, nausea, vomiting, collapse and asymptomatic hypotension). In total, there were 17 adverse events considered related to the test product and 14 adverse events considered related to the reference product. No serious adverse event appeared during the course of the study.

Aripiprazol Doc Generici orodispersible tablets

The MAH has submitted results from one bioequivalence study to demonstrate that the proposed Aripiprazol Doc Generici 15 mg orodispersible tablets (Doc Generici S.r.l., NL) are bioequivalent with Abilify 15 mg orodispersible tablets (Otsuko Pharmaceutical Europe Ltd., UK)

The choice of the reference product in the bioequivalence study is accepted, as Abilify has been registered through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
For the 10 mg strength, the MAH applied for a biowaiver. The 10 mg and 15 mg products are manufactured by the same manufacturing process, the qualitative composition of the different strengths is the same and they are dose-proportional in composition.
At pH 1.2 and 4,5 the dissolution was very fast (more than 85% within 15 minutes) in the two strengths and at 6.8, the f2 values were higher than 50 between 10 mg and the additional strength 15 mg. The dissolution data provided justify a biowaiver for the 10 mg strength.

Bioequivalence study
Design
An open label, randomized, two-treatment, two-period, single-dose, crossover, bioequivalence study was carried out under fasted conditions in 40 healthy male and female subjects, aged 45-55 years. Each subject received a single dose (15 mg) of one of the 2 aripiprazole formulations. The tablet was

orally administered; it was placed on the tongue after a fasting period of at least 10 hours. Before dosing, 20 ml of water was administered to moisten the buccal cavity. The subjects were asked to close their mouth in a natural way, without chewing, biting or breaking the orodispersible tablets. Once the tablet was completely dissolved, the subjects swallowed the saliva. There were 2 dosing periods, separated by a washout period of 42 days.

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

The design of the study is acceptable. The proposed tablets can be taken with or without food. Thus, a study in fasting conditions is appropriate. Administration of the tablets under thirsting conditions is adequate as the orodispersible tablets may be taken with or without water. Considering the half-life of aripiprazole the estimation of the extent of absorption over a period of 72 hours is acceptable. The wash-out period of 42 days is sufficient.
The MAH performed the bioequivalence study with the 15 mg strength, in line with the MEB's scientific advise. A study with the higher strength is appropriate since aripiprazole is a low solubility drug.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
Two subjects withdrew from the study on their own accord and one subject due to an accidental injury. Therefore, 37 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=37	**AUC_{0-72}** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h
Test	2773 ± 657	69.5 ± 20	4.5 (2-24)
Reference	2979 ± 658	73.9 ± 18	4.5 (2-9)
***Ratio (90% CI)**	0.92 (0.88 – 0.97)	0.93 (0.86 – 1.01)	--

AUC_{072} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

**ln-transformed values*

Safety
One subject experienced a single adverse event (accidental injury) over the course of the study, which was mild in nature and not related to the oral administration of test aripiprazole 15 mg orodispersible tablet. No serious adverse event appeared during the course of the study.

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for AUC_{0-72h} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Aripiprazol Doc Generici tablets and orodispersible tablets are considered bioequivalent with Abilify tablets and orodispersible tablets.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Aripiprazol Doc Generici.

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

As an additional risk minimisation measure the MAH should provide educational material. This should contain the following key elements:

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

- Brief introduction to aripiprazole indication and the purpose of the tool
- Instructions reinforcing that the indicated age range is 13-17 years and that aripiprazole is not recommended for use in patients below 13 years of age due to safety concerns
- Instructions that the recommended dose is 10 mg/day and that enhanced efficacy at higher doses has not been demonstrated
- Information regarding the safety and tolerability profile of aripiprazole, in particular potential consequences regarding adverse effects at doses higher than 10 mg/day, in particular with respect to:
    - Weight gain, including a recommendation to monitor patients
    - Extrapyramidal symptoms
    - Somnolence
    - Fatigue

- Reminder to educate patients/caregivers and distribute the Patient/Caregiver Information Brochure

Key elements of the Patients/Caregiver Information Brochure:

- Brief introduction to aripiprazole indication and the purpose of the tool
- Information that the indicated age range is 13-17 years and that aripiprazole is not recommended for use in patients below 13 years of age
- Information that aripiprazole can cause adverse effects at doses higher than 10 mg/day, in particular with respect to:
  - Weight gain, including a recommendation to monitor patients
  - Extrapyramidal symptoms
  - Somnolence
  - Fatigue
- Request to inform the physician of all medical conditions before treatment
- The importance of not attempting to self-treat any symptoms without consulting their Healthcare professional

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator products Abilify tablets and Abilify orodispersible tablets No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference products. Risk management is adequately addressed. These generic medicinal products can be used instead of the reference products.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Abilify (EMEA/H/C/000471). The bridging report submitted by the MAH has been found acceptable. The wording of the two leaflets is the same.
To support the changes made to the proposed package leaflet compared to the originator package leaflet (administrative data, design, layout) a user test of the package leaflet of Eplerenone 25 mg and 50 mg film-coated tablets has been submitted. This user test confirms that the MAH's house style does not affect the readability of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Aripiprazol Doc Generici 5 mg, 10 mg and 15 mg tablets and Aripiprazol Doc Generici 10 mg and 15 mg orodispersible tablets have a proven chemical-pharmaceutical quality and are generic forms of respectively Abilify 5 mg, 10 mg and 15 mg tablets and Abilify 10 and 15 mg orodispersible tablets.. Abilify is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Aripiprazol Doc Generici with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 June 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier	NL/H/3203/ 1-6/IB/001	IB	07-03-2016	06-04-2016	Approval	N
Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a Union referral procedure; Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006; Implementation of wording agreed by the competent authority.	NL/H/3203/IA/002/G	IA/G	25-02-2016	26-03-2016	Approval	N
Deletion of a strength; 20 mg tablet.	NL/H/3203/ 1-4/IB/003/	IB	31-05-2016	30-06-2016	Approval	N
Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006; implementation of wording agreed by the competent authority.	NL/H/3203/ 1-6/IA/003/	IA	14-07-2016	21-07-2016	Approval	N