22 October 2015
EMA/49072/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Aripiprazole Mylan

International non-proprietary name: aripiprazole

Procedure No. EMEA/H/C/004236/0000

Note

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

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1. Recommendation

Based on the CHMP review of the data on quality, safety and efficacy, the CHMP considers that the generic application for **Aripiprazole Mylan 5 mg, 10 mg, 15 mg, 30 mg tablets and** for **Aripiprazole Mylan 10mg and 15 mg orodispersible tablets** in the claimed indication:

- 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
- Treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older<is approvable. The CHMP considers some points could be resolved after the marketing authorisation (see section 5).

is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time.

In addition, satisfactory answers must be given to "other concerns".

Questions to be posed to additional experts

N/A

Inspection issues

GMP inspection(s)

The Committee for Medicinal Products for Human Use has requested an inspection of the manufacturing facilities at Mylan Laboratories Ltd., Plot No H12 & H13 MIDC Waluj Industrial Estate, 431 136 Aurangabad INDIA, in accordance with Regulation (EC) No. 726/2004, Art 19(3).

GCP inspection(s)

No GCP inspections are deemed necessary at this stage within the scope of this MAA evaluation procedure.

2. Executive summary

2.1. Problem statement

This is an abridged application under Article 10(1) of Directive 2001/83/EC as amended, i.e. a generic application referring to a reference medicinal product.
The chosen reference medicinal product with recognized efficacy and an acceptable level of safety is Abilify 5 mg, 10 mg, 15 mg, 30 mg tablets and Abilify 10 mg and 15 mg orodispersible tablets from Otsuka Pharmaceutical Europe Ltd. The reference medicinal product was first authorized in the European Union (EU) on 4th June 2004 via the centralized procedure.

2.2. About the product

According to the CHMP guidance on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1 Cor**) the Applicant has generated comparative dissolution profiles of the generic Aripiprazole 5 mg, 10 mg, 15 mg and 30 mg tablets and the respective strengths of the EU reference product ABILIFY® tablets of Otsuka Pharmaceutical Europe Ltd, United Kingdom, in different dissolution media, in order to apply for a waiver of a bioequivalence study for the additional strengths.

A comparison of the qualitative composition of the reference medicinal product (ABILIFY tablets) and the Applicant´s product Aripiprazole Mylan tablets is provided below:

	Abilify 10 mg tablets	Aripiprazole Mylan tablets 5 mg/10mg/15 mg/30 mg
Active substance	Aripiprazole	Aripiprazole
Excipients	Lactose monohydrate	-
	Maize starch	-
	Microcrystalline cellulose	Microcrystalline cellulose
	Hydroxypropyl cellulose	-
	Magnesium stearate	Magnesium stearate
	Red iron oxide (E172)	-
		Mannitol
		Croscarmellose sodium

According to the CHMP guidance on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1 Cor**) the Applicant has generated comparative dissolution profiles of the generic Aripiprazole 10 mg and 15 mg orodispersible tablets and the respective strengths of the EU reference product ABILIFY® orodispersible tablets of Otsuka Pharmaceutical Europe Ltd in different dissolution media, in order to apply for a waiver of a bioequivalence study for the additional strength.

A comparison of the qualitative composition of the reference medicinal product (ABILIFY orodispersible tablets) and the Applicant´s product Aripiprazole Mylan Orodispersible tablets is provided below:

	Abilify 10 mg orodispersible tablets	Aripiprazole Mylan orodispersible tablets 10mg
Active substance	Aripiprazole	Aripiprazole
Excipients	Calcium silicate	-
	Croscarmellose sodium	Croscarmellose sodium
	Silicon dioxide	Silica, colloidal anhydrous
	Xylitol	-
	Microcrystalline cellulose	Microcrystalline cellulose
	Aspartam (E951)	Aspartam (E951)
	Acesulfame potassium	
	Vanilla flavour (including vanillin and ethyl vanillin)	Vanilla flavour
	Tartaric acid	-
	Magnesium stearate	Magnesium stearate
	Red iron oxide (E172)	-
	-	Mannitol (E421)

The active ingredients and the route of administration are the same for both products (ABILIFY tablets/orodispersible tablets and Aripiprazole Mylan tablets/orodispersible tablets).

The proposed SmPC for Aripiprazole Mylan tablets/orodispersible tablets is based on the SmPC for ABILIFY® tablets/orodispersible tablets.

Aripiprazole is used for the treatment of schizophrenia or bipolar disorder.

Pharmacological class: Antipsychotics
ATC code: N05AX12
Mechanism of action

It has been proposed that aripiprazole's efficacy in schizophrenia and Bipolar I Disorder is mediated through a combination of partial agonism at dopamine D2 and serotonin 5HT1a receptors and antagonism of serotonin 5HT2a receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity. Aripiprazole exhibited high binding affinity in vitro for dopamine D2 and D3, serotonin 5HT1a and 5HT2a receptors and moderate affinity for dopamine D4, serotonin 5HT2c and 5HT7, alpha-1 adrenergic and histamine H1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

Aripiprazole doses ranging from 0.5 to 30 mg administered once a day to healthy subjects for 2 weeks produced a dose-dependent reduction in the binding of 11C-raclopride, a D2/D3 receptor ligand, to the caudate and putamen detected by positron emission tomography.

Pharmacokinetic properties
Absorption
Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3-5 hours after dosing. Aripiprazole undergoes minimal pre-systemic metabolism. The absolute oral bioavailability of the tablet formulation is 87%. There is no effect of a high fat meal on the pharmacokinetics of aripiprazole.

Distribution
Aripiprazole is widely distributed throughout the body with an apparent volume of distribution of 4.9 l/kg, indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and dehydro-aripiprazole are greater than 99% bound to serum proteins, binding primarily to albumin.

Biotransformation
Aripiprazole is extensively metabolised by the liver primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on in vitro studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalysed by CYP3A4. Aripiprazole is the predominant medicinal product moiety in systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

Elimination
The mean elimination half-lives for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6.

The total body clearance of aripiprazole is 0.7 ml/min/kg, which is primarily hepatic.

Following a single oral dose of [14C]-labelled aripiprazole, approximately 27% of the administered radioactivity was recovered in the urine and approximately 60% in the faeces. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% was recovered unchanged in the faeces.

Pharmacokinetics in special patient groups

Paediatric population

The pharmacokinetics of aripiprazole and dehydro-aripiprazole in paediatric patients 10 to 17 years of age were similar to those in adults after correcting for the differences in body weights.

Older people

There are no differences in the pharmacokinetics of aripiprazole between healthy elderly and younger adult subjects, nor is there any detectable effect of age in a population pharmacokinetic analysis in schizophrenic patients.

Gender

There are no differences in the pharmacokinetics of aripiprazole between healthy male and female subjects nor is there any detectable effect of gender in a population pharmacokinetic analysis in schizophenic patients.

Smoking and Race

Population pharmacokinetic evaluation has revealed no evidence of clinically significant race-related differences or effects from smoking upon the pharmacokinetics of aripiprazole.

Renal impairment

The pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to young healthy subjects.

Hepatic impairment

A single-dose study in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C) did not reveal a significant effect of hepatic impairment on the pharmacokinetics of aripiprazole and dehydro-aripiprazole, but the study included only 3 patients with Class C liver cirrhosis, which is insufficient to draw conclusions on their metabolic capacity.

According to the submitted SmPC, the following indications are proposed:

- Aripiprazole Mylan is indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older.
- Aripiprazole Mylan 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 (see section 5.1).
- Aripiprazole Mylan 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 (see section 5.1).

Posology and method of administration

Posology

Adults

Schizophrenia: the recommended starting dose for Aripiprazole Mylan is 10 or 15 mg/day with a maintenance dose of 15 mg/day administered on a once-a-day schedule without regard to meals. Aripiprazole Mylan is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 15 mg has not been demonstrated although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Manic episodes in Bipolar I Disorder: the recommended starting dose for Aripiprazole Mylan is 15 mg administered on a once-a-day schedule without regard to meals as monotherapy or combination therapy (see section 5.1). Some patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg.

Recurrence prevention of manic episodes in Bipolar I Disorder: for preventing recurrence of manic episodes in patients, who have been receiving aripiprazole as monotherapy or combination therapy, continue therapy at the same dose. Adjustments of daily dosage, including dose reduction should be considered on the basis of clinical status.

Paediatric population
Schizophrenia in adolescents aged 15 years and older: the recommended dose for Aripiprazole Mylan is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using aripiprazole oral solution 1 mg/ml) for 2 days, titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg. When appropriate, subsequent dose increases should be administered in 5 mg increments without exceeding the maximum daily dose of 30 mg (see section 5.1).

Aripiprazole Mylan is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated although individual patients may benefit from a higher dose.

Aripiprazole Mylan is not recommended for use in patients with schizophrenia below 15 years of age due to insufficient data on safety and efficacy (see sections 4.8 and 5.1).

Manic episodes in Bipolar I Disorder in adolescents aged 13 years and older: the recommended dose for Aripiprazole Mylan is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using aripiprazole oral solution 1 mg/ml) for 2 days, titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg.

The treatment duration should be the minimum necessary for symptom control and must not exceed

12 weeks. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated, and a daily dose of 30 mg is associated with a substantially higher incidence of significant undesirable effects including EPS related events, somnolence, fatigue and weight gain (see section 4.8). Doses higher than 10 mg/day should therefore only be used in exceptional cases and with close clinical monitoring (see sections 4.4, 4.8 and 5.1).

Younger patients are at increased risk of experiencing adverse events associated with aripiprazole. Therefore, Aripiprazole Mylan is not recommended for use in patients below 13 years of age (see sections 4.8 and 5.1).

Irritability associated with autistic disorder: the safety and efficacy of Aripiprazole Mylan in children and adolescents aged below 18 years have not yet been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Patients with hepatic impairment: no dosage adjustment is required for patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In these patients dosing should be managed cautiously. However, the maximum daily dose of 30 mg should be used with caution in patients with severe hepatic impairment (see section 5.2).

Patients with renal impairment: no dosage adjustment is required in patients with renal impairment.

Older people: the effectiveness of Aripiprazole Mylan in the treatment of schizophrenia and Bipolar I Disorder in patients aged 65 years and older has not been established. Owing to the greater sensitivity of this population, a lower starting dose should be considered when clinical factors warrant (see section 4.4).

Gender: no dosage adjustment is required for female patients as compared to male patients (see section 5.2).

Smoking status: according to the metabolic pathway of Aripiprazole Mylan no dosage adjustment is required for smokers (see section 4.5).

Dose adjustments due to interactions:

When concomitant administration of potent CYP3A4 or CYP2D6 inhibitors with aripiprazole occurs, the aripiprazole dose should be reduced. When the CYP3A4 or CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased (see section 4.5).

When concomitant administration of potent CYP3A4 inducers with aripiprazole occurs, the aripiprazole dose should be increased. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced to the recommended dose (see section 4.5).

2.3. The development programme/Compliance with CHMP Guidance/Scientific Advice

Scientific advice

No scientific advice was given by the EMA for this medical product.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

A QP declaration (dated 02/11/2015) on behalf of all involved QPs responsible for the finished product manufacture and release of the drug product has been provided by batch releaser Mylan Hungary, stating that the active ingredient aripiprazole manufactured by Mylan Laboratories Limited (Unit 3, Jeedimetla), India, is manufactured in accordance with GMP; the declaration is based on an on-site audit by Mylan Laboratories Limited on 5-6 September 2013.

The Qualified Person of Mylan Hungary confirmed GMP compliance for the drug substance manufacturer Mylan Laboratories Limited (Unit 3, Jeedimetla), India, as well as for the intermediate manufacturer Rampex Labs Pvt Ltd., India, based on audits performed on-site.

For the drug product manufacturer Mylan Laboratories Limited (Unit-3, Jeedimetla Hyderabad, India a GMP certificate has been provided dated 15/07/2013 (expiry date 08/02/2016) issued by Department of Health and Ageing, Therapeutic Goods Administration, Australian Government.

For all sites which are involved in the manufacture of the drug product respective manufacturing authorizations and certificates of GMP compliance have been provided in Module 1.

GCP

The applicant confirms that the studies were conducted in accordance with the protocol and all other pertinent requirements of the Ethical guidelines for Biomedical Research on Human Participants, ICMR (2006), ICH (Step 5) "Guidance on Good Clinical Practice", Schedule Y (amended version, 2013) of CDSCO, "Good Laboratory Practice" "Good Clinical Practices for Clinical Research in India'" Guidelines,

Good Clinical Laboratory Practice (GCLP), Declaration of Helsinki (Seoul 2008), EMA guidelines and meets the ethical requirements of Directive 2001/20/EC.

Moreover that "clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC". A copy of the declaration signed by the sponsor's representative was provided.

2.5. Type of application and other comments on the submitted dossier

- Legal basis

This application concerns a centralised procedure under Article 10(1) of Directive 2001/83/EC as amended, i.e. a generic application referring to a reference medicinal product.

For this application, the reference medicinal product authorized in the Community/Member State not less than 10 years ago, with recognized efficacy and an acceptable level of safety, is Abilify 5 mg, 10 mg, 15 mg, 30 mg Tablets as well Abilify 10 mg and 15 mg orodispersible tablets of Otsuka Pharmaceutical Europe Ltd. The medicinal product was first authorized in the EU on 4th June 2004 via the centralized procedure.

This application is for a generic form of Aripiprazole tablets in strengths of 5 mg, 10 mg, 15 mg, 30 mg as well Aripiprazole orodispersible tablets in strengths 10 mg and 15 mg. The active ingredient and the route of administration are the same for both products.

Background information:

During evaluation of the clinical studies ARIP-1K-537-13 and ARIP-1K-653-13 provided in support of the former Aripiprazole Mylan application (EMEA/H/C/003926) the CHMP had questioned whether the bioequivalence studies had been carried out in accordance with Good Clinical Practice (GCP). Following the triggered GCP inspection, the Applicant (Generics (UK) Limited) officially notified the CHMP of their wish to withdraw the application for a marketing authorisation for this product.

The new bioequivalence studies submitted in support of the current application (EMEA/H/C/004236) were performed by different contract research organisations. The dissolutions profiles submitted in this procedure are the same as those in the previous application EMEA/H/C/003926. In addition, the MAH generated a dissolution profile of the Abilify 10 mg tablets (reference product Batch No. 3M55103) used in the current bioequivalence study, performed in one medium (i.e. 0.1N hydrochloric acid) at 60 rpm and a dissolution profile of the Abilify 10 mg orodispersible tablets (reference product Batch No. 4E79057) used in the current bioequivalence study, in one buffer (i.e. pH 4.0 acetate buffer; release media) at 75 rpm.

3. Scientific overview and discussion

3.1. Introduction

This abridged application is for a generic form of Aripiprazole tablet in the strengths of 5 mg, 10 mg, 15 mg and 30 mg as well as Aripiprazole orodispersible tablets in the strengths of 10 and 15 mg, submitted under Article 10(1) of Directive 2001/83/EC.

3.2. Quality aspects

3.2.1. Introduction

The applied drug products are immediate release tablets respectively immediate release orodispersible tablets containing the single active substance aripiprazole.

3.2.2. Active Substance

General Information

Aripiprazole is a drug substance that is described in the Ph. Eur. The active ingredient is manufactured by Mylan Laboratories Limited, India, and is documented via EDQM certificate of suitability CEP 2013-330, issued in 2/2015. Therefore, no separate assessment on the drug substance has been conducted except stability data due to non-declaration of a re-test period on the CEP.

Specification

An API specification was provided by the applicant, showing compliance with the Ph. Eur. monograph #04/2014:2617 for aripiprazole.

Stability

Stability of the API has been tested due to non-declaration of a re-test period on the CEP. Regarding API stability there are some open issues, i.e. impurity results above Ph. Eur. qualified thresholds, and unproven applicability of the Ph. Eur. related substances method for an in-house impurity, which should be clarified.

Comparability exercise for Active Substance

Not applicable.

3.2.3. Finished Medicinal Product

Aripiprazole Mylan tablets and orodispersible tablets

Description of the product and Pharmaceutical Development

The drug product Aripiprazole Mylan tablet is an immediate release tablet containing the active substance aripiprazole and it is available in four strengths of 5 mg, 10 mg, 15 mg and 30 mg, which are proportional in composition.

The drug product Aripiprazole Mylan orodispersible tablet is an immediate release orodispersible tablet containing the active substance aripiprazole and it is available in strengths of 10 mg and 15 mg, which are proportional in composition.

The pharmaceutical development and the optimizations performed during manufacturing process development have been discussed satisfactorily.

Manufacture of the product and process controls

Detailed descriptions of the manufacturing process which is conducted by direct compression and performed in-process controls have been provided.

Product specification

The release and shelf-life specifications of the drug products contain adequate parameters for a tablet respectively for an orodispersible tablet.

Stability of the product

Aripiprazole Mylan tablets

Stability studies have been performed on batches of all strengths packed in HDPE bottles, cold form blister and simulated bulk shipment pack (which only differ in dimensions with respect to bulk shipment pack).

Long-term stability data of 24 months have been provided. For the drug product packed in bulk shipment pack a shelf life of 12 months is declared without any special storage condition which is accepted.

A shelf-life of 36 months has been proposed for the drug product packed in HDPE bottles and cold form blister pack without any special storage condition. Based on available stability data the extrapolation of the shelf-life to 36 months is acceptable. For the drug product packed in bulk shipment pack a shelf life of 12 months is declared without any special storage condition which is accepted.

According to results of the in-use stability study Aripiprazole Mylan tablets are stable up to 100 days after opening the HDPE bottle pack. According to the application form/SmPC/package leaflet/labelling a package size of 500 tablets in HDPE bottles is intended for the tablet strengths 10 mg, 15 mg and 30 mg. The in-use stability study only covers 100 days and the dose range of aripiprazole is 10 to 30 mg per day. Taken this into consideration the discrepancy between the covered period of the performed in-use stability study and the proposed package size of 500 tablets in HDPE bottles should be explained.

Aripiprazole Mylan orodispersible tablets

Stability studies have been performed on batches of all strengths packed in cold form blister and simulated bulk shipment pack (which only differ in dimensions with respect to bulk shipment pack).

Long-term stability data of 24 months have been provided. For the drug product packed in bulk shipment pack a shelf life of 12 months is declared without any special storage condition which is accepted.

A shelf-life of 36 months has been proposed for the drug product packed in cold form blister pack without any special storage condition. Based on available stability data the extrapolation of the shelf-life to 36 months is acceptable.

Comparability exercise for Finished Medicinal Drug Product

Not applicable.

Adventitious agents

Not applicable.

3.2.4. Discussion on chemical, pharmaceutical and biological aspects

Drug Substance

The active ingredient manufactured by Mylan Laboratories Limited, India, is documented via EDQM certificate of suitability CEP 2013-330, issued in 2/2015. No assessment on the drug substance has been conducted except stability data due to non-declaration of a re-test period on the CEP; some concerns on drug substance stability remain.

Drug Product

There are some "other concerns" identified for the drug products. Apart from the raised concerns the documentation of the drug products is adequate and the proposed shelf-life of 36 months without any special storage condition for Aripiprazole Mylan tablets and Aripiprazole Mylan orodispersible tablets is acceptable.

3.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

There are a few "other concerns" regarding the drug substance and the drug product. From the quality point of view Aripiprazole Mylan tablets and Aripiprazole Mylan orodispersible tablets could be recommended for approval provided the questions regarding the drug substance and drug product can be resolved and the requested information is provided.

3.3. Non clinical aspects

3.3.1. Pharmacology, Pharmacokinetics & Toxicology

A non-clinical overview on pharmacology, pharmacokinetics and toxicology has been provided, which 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 non-clinical overview report refers to 25 publications up to year 2014.

The CHMP considers that the non-clinical overview is based on up-to-date and adequate scientific literature. It is agreed that no further non-clinical studies are required.

3.3.2. Ecotoxicity/environmental risk assessment

The applicant states that an environmental risk assessment according to CHMP guideline CPMP/SWP/4447/00 (Note for Guidance on the Environmental Risk Assessment of Medical Products for Humane Use) has not been provided.

This application is for a generic version of Abilify® (aripiprazole) 5 mg, 10 mg, 15 mg and 30 mg tablets as well Abilify® (aripiprazole) 10 mg and 15 mg orodispersible tablets, the products that were registered in the EU since 2004. Aripiprazole Mylan 5 mg, 10 mg, 15 mg and 30 mg tablets as well Aripiprazole Mylan 10 mg and 15 mg orodispersible tablets contain an identical amount of aripiprazole drug substance and has been formulated with a range of commonly used excipients to be pharmaceutically equivalent to Abilify® 5 mg, 10 mg, 15 mg and 30 mg tablets, and Abilify® 10 mg and 15 mg orodispersible tablets, respectively, and as such are not considered to pose any greater environmental risk than the reference products.

Furthermore, given that Aripiprazole Mylan 5mg, 10mg, 15mg and 30mg tablets and Aripiprazole Mylan 10 mg and 15 mg orodispersible tablets are aimed at replacing rather than increasing prescriptions of Abilify® 5 mg, 10 mg, 15 mg and 30 mg tablets and Abilify® 10 mg and 15 mg orodispersible tablets, respectively, no increased environmental burden is expected from the marketing of these generic products.

3.3.3. Conclusion on non-clinical aspects

There are no objections to approval of Aripiprazole Mylan 5 mg, 10 mg, 15 mg, 30 mg tablets and Aripiprazole Mylan 10 mg and 15 mg orodispersible tablets from a non-clinical point of view.

3.4. Clinical aspects

Tabular overview of clinical studies

Type of Study	Study Identifier	Objective(s) of the study	Study Design and Type of control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy subjects or Diagnosis of patients	Duration of Treatment
BE	14-VIN-657	To compare the rate and extent of absorption of Aripiprazole orodispersible tablets 10mg of Mylan Laboratories Limited and ABILIFY® (aripiprazole) 10 mg orodispersible tablets of Otsuka Pharmaceutical Europe Ltd. In healthy, adult, human subjects under fasting condition. To evaluate the safety and tolerability of Aripiprazole orodispersible tablets 10 mg in healthy human subjects.	An open label, balanced, randomized, single-dose, two-treatment, single-period, parallel bioequivalence study in healthy, adult, human subjects under fasting condition. Treatment controlled	One tablet formulation, single dose, oral administration	Enrolled: 60 (+3 extra) Completed: 60 Total subjects analysed for pharmacokinetics and statistical analysis: 60	Healthy adult human Subjects	Single dose
BE	BA141017 95-01	The objectives of this study were to compare and evaluate the oral bioavailability of Aripiprazole Tablets 10 mg with that of 'ABILIFY' (Aripiprazole) 10 mg Comprimes (Tablets) in healthy, adult, human subjects under fasting conditions and to monitor the safety of the subjects.	An open label, randomized, single-period, two-treatment, parallel, balanced, single dose oral bioequivalence study in healthy, adult, human subjects under fasting conditions.	**Test Product-T:** Aripiprazole Tablets 10 mg, Dosage Regimen: 10 mg **Route of administration:** Oral **Reference Product-R** ABILIFY® (Aripiprazole Tablet) 10 mg, Dosage Regimen: 10 mg **Route of administration:** Oral	No. of subjects dosed Group-I**:** 36 Group-II: 24 Completed-57 Subjects considered for pharmacokinetic and statistical analysis-57 (28 subjects in Test treatment and 29 subjects in Reference treatment)	Healthy Subjects	Single dose

BE: Bioequivalence

3.4.1. Pharmacokinetics

To support the application, the Applicant has submitted **two** bioequivalence studies.

Tablets
An open label, randomized, single-period, two-treatment, parallel, balanced, single dose oral bioequivalence study of Aripiprazole Tablets 10 mg and 'ABILIFY' (Aripiprazole) 10 mg comprimes (tablets) in healthy adult human subjects under fasting conditions (**Study Report No. BA14101795-01**).

Orodispersible Tablets:
An open label, balanced, randomized, single-dose, two-treatment, single-period, parallel bioequivalence study of Aripiprazole orodispersible tablets 10 mg of Mylan Laboratories Limited, India and ABILIFY® (aripiprazole) 10 mg orodispersible tablets of Otsuka Pharmaceutical Europe Ltd. in healthy, adult, human subjects under fasting condition (**Study Report No. 14-VIN-657**).

3.4.1.1. Aripiprazole Mylan Tablets

Study No. BA14101795-01

Study Title:

Single dose oral bioequivalence study of Aripiprazole Mylan Tablets 10 mg and Abilify (Aripiprazole) 10 mg comprimes (tablets) in healthy adult human subjects under fasting conditions.

Study design

An open label, randomized, single-period, two-treatment, parallel, balanced, single dose oral bioequivalence study.

The study was designed based on the known pharmacokinetics of aripiprazole and generally accepted standards for the conduct of bioequivalence studies.

Study Centres (Clinical, Analytical, Pharmacokinetics and Statistical):

Clinical: Cliantha Research Limited
Analytical: Mylan Laboratories Limited
Pharmacokinetics and Statistical: Cliantha Research Limited

The study was conducted with 60 (57 completed) healthy, adult, human subjects in accordance with the protocol. During the study, a single 10 mg oral dose of investigational product was administered to the subjects following an overnight fast of at least 8 hours. The test formulation was Aripiprazole tablets 10 mg and the reference formulation was ABILIFY (aripiprazole) 10 mg comprimes (tablets). The subjects received one tablet of either test product or reference product; the order of administration was according to the randomization schedule.

During the study, a single 10 mg oral dose of investigational product was administered to the subjects under fasting condition. Total duration of the treatment from first subject dosed to last subject completed was 06 days.

During the study, total 19 venous blood samples were collected in vacutainers containing K3EDTA at pre-dose (0.00 hour) and at 0.50, 1.00, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 9.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00, 60.00 and 72.00 hours post dose.

The CHMP noted that, according to EMA Guidance (CPMP/EWP/QWP/1401/98 Rev.1 Cor**), if two formulations are compared a randomised, two-period, two-sequence single dose crossover design is

recommended. Under certain circumstances, provided the study design and the statistical analyses are scientifically sound, alternative well-established designs, such as parallel design for substances with very long half-life and replicate designs e.g. for substances with highly variable pharmacokinetic characteristics, could be considered.

Even though the bioequivalence (BE) guideline opens up for the possibility of choosing the parallel study design under certain circumstances, the choice is somewhat surprising given that in the previous MAA BE studies with the standard cross over design had in principle proven suitable for showing BE for aripiprazole. The guideline further details that "…in parallel design studies, the treatment groups should be comparable in all known variables that may affect the pharmacokinetics of the active substance (e.g. age, body weight, sex, ethnic origin, smoking status, extensive/poor metabolic status). This is an essential pre-requisite to give validity to the results from such studies." Therefore, the cHMP requested a discussion and justification in line with above guideline requirements to support adequacy of the chosen design.

Blood samples were collected at pre-dose (0.00 hours) and at intervals over 72.00 hours after administration of dose. The sampling period is sufficient to characterize the plasma concentration-time profile. Blood sampling points were considered by the CHMP to be appropriate to allow an accurate measurement of T_{max} (time of the maximum measured plasma concentration).

The study was conducted under fasting conditions. Since there is no evidence of a significant food effect in the literature and the SmPC of the reference product gives no recommendation for administration of the drug in relation to food and as food intake does not affect the absorption of the active substance, this was considered adequate by the CHMP.

Aripiprazole exhibits linear pharmacokinetics within the 5-30 mg range and in principle, the bioequivalence study should be conducted at the highest strength. However, due to well-known serious safety concerns the highest strength cannot be administered to healthy volunteers. Therefore, the dose selection (10 mg) was considered acceptable by the CHMP.

Test and reference products

Product Characteristics	Reference product	Test Product
Name	ABILIFY®	Aripiprazole
Strength	10 mg	10 mg
Dosage form	Tablets	Tablets
Manufacturer	Otsuka Pharmaceutical Europe Ltd. Hunton House Highbridge Estate, Oxford Road Uxbridge-Middlesex UB8 1LX –United Kingdom	Mylan Laboratories Limited, H-12 & H-13, MIDC, Waluj Industrial Area, Aurangabad-431136, Maharashtra, India.
Batch number / Lot Number	3M55103	2001593
Batch size (Biobatch)	-	190000
Measured content(s) (% of label claim)	100.6 %	102.4 %
Commercial Batch Size	--	--
Expiry date (Retest date)	Aug 2016	Nov 2015
Location of Certificate of Analysis	5312-compar-ba-be-stud-rep, Appendix-16.1.6	5312-compar-ba-be-stud-rep, Appendix-16.1.6
Member State where the reference product is purchased from:	UK	--
This product was used in the following trials:	Study no.: BA14101795-01	Study no.: BA14101795-01

Certificates of analysis of the test and reference product were provided by the applicant. The batch size of the test product (190 000 Units) was considered acceptable by the CHMP.

The applicant confirmed that the composition and manufacturing process of the test product formulation used in the bio-equivalence study and the formulation proposed for commercial supplies to the European Economic Area is the same.

The CHMP noted, that the location of Certificate of Analysis given by the applicant in the table above was incorrect and should be revised.

Population(s) studied

The study was conducted in Asian male population. The 60 subjects (male) who participated in this study were healthy, in the age range of 45 to 60 years (mean age 50 years), a weight range of 45.6 to 84.2 kg (mean weight 61.1 kg), a height range of 146.0 to 180.0 cm (mean height 163.9 cm) and Body Mass Index (BMI) range of 18.7 to 29.3 kg/m2 (mean BMI 22.7 kg/m^2).

A total of **47** healthy, adult, human subjects in Group-I and **31** in Group-II meeting the inclusion and exclusion criteria as mentioned in the protocol were enrolled in to the study to ensure the dosing of 60 subjects.

*Group	Check-In	Dosing	Check-Out
Group-I	10 Mar 15	13 Mar 15	16 Mar 15
Group-II	13 Mar 15	16 Mar 15	19 Mar 15
*Note: Subjects were dosed in two different groups. Two Groups were as; Group-I was conducted with Subjects 01-36 and Group-II was conducted with Subjects 37-60.			

Group I

Twelve subjects were enrolled as extra subjects (Subjects E1 to E12) in this group.

Subject 34 was replaced by Subject E1 prior to check-in to the facility (i.e. 10 Mar 15). Subjects 28, 10, 04, 09, 15, 25, and 35 were replaced by Subject E2, E3, E5, E6, E7, E9, and E10, respectively. Subject 28 was checked out from the facility on the day of check in (i.e. 10 Mar 15). Subjects 10, 04, 09, 15, 25, 35, E4 & E8 were checked out from the facility prior to dosing (i.e. 12 Mar 15).

After dosing of a sufficient number of subjects in Group-I, two extra subjects (E11 & E12) were not dosed & checked out on the day of dosing (i.e. 13 Mar 15).

No. of subjects dosed: 36

Group II

Eight subjects were enrolled as extra subjects (Subjects E13 to E20) in this group.

Subject 41 was replaced by Subject E13 prior to check-in to the facility (i.e. 13 Mar 15). Subject 39 was replaced with Subject E14 and further the same Subject E14 was replaced with Subject E15. Subjects 45 & 55 were replaced by Subjects E16 & E17, respectively. Subject 39 was checked out from the facility prior to dosing (i.e. 14 Mar 15). Subject E14, 45 & 55 were checked out from the facility prior to dosing (i.e. 15 Mar 15).

After dosing of sufficient number of subjects in Group-II, three extra subjects (E18, E19 & E20) were not dosed & checked out on the day of dosing (i.e. 16 Mar 15).

No. of subjects dosed: 24

Subjects discontinued:

Subject 06 was discontinued after dosing on his own accord, as he did not want to participate further in the study due to personal reason. Subject was dosed with the reference product in the study.

Subject 11 was discontinued after dosing on medical ground, as he had single episode of Vomiting. Subject was dosed with the test product in the study.

Subject 54 was discontinued after dosing on medical ground, as he had single episode of Vomiting. Subject was dosed with the test product in the study.

Total 57 subjects completed the study and were included in pharmacokinetic and statistical analysis.

Based on the above, the CHMP considered that the study population chosen was appropriate and in line with current bioequivalence guidance. Since literature reports no gender-related differences in

aripiprazole pharmacokinetics, inclusion of only male subjects is acceptable. The in- and exclusion criteria were considered adequate.

Analytical methods

Sponsor of the study: Mylan Laboratories Limited

Clinical center: Cliantha Research Limited

Bioanalytical center: CRC – Mylan Laboratories Limited

The analytical part of the study lasted from April 13th 2015 till April 17th 2015; study samples were obtained stored at a nominal temperature of -70ºC.

1098 samples (theoretical amount 1140 samples from 60 subjects; 1110 samples obtained) from 59 evaluable subjects (19 time-points per subject, 1 period) were analysed; 3 from 60 subjects (#6, 11, 54) dropped out and therefore 30 samples were missing.

Analytical Methods

The analyte is aripiprazole, internal standard was Aripiprazole-d8; samples were extracted from a 200 µL aliquot of K_3 EDTA human plasma by liquid-liquid extraction. The extracted samples were injected into a liquid chromatograph.

The detection method used was tandem mass spectrometry detector.

Quantitation is determined by peak area ratio method. A weighted (1/x) linear regression is performed to determine the concentration of the analytes.

The validated calibration range for the assay of Aripiprazole is from 0.500 ng/mL (LLOQ) to 100.053 ng/mL.

Validation of the analytical methods

Results obtained from this validation are presented.

Table 1: Study No. BA14101795-01 – outcome of validation of the analytical methods

Parameter	Acceptance criterion	Found value	acceptable (yes/no)
Selectivity	6 individual sources, response is <20% of LLOQ and <5% of IS	14 lots, no significant response	yes
LLOQ	Min 5 times the signal of a blank sample; <5% of Cmax	0.500 nm/mL; complies	yes
Range	LLOQ – ULOQ (Σ=6 calibrators) ±20% for LLOQ ±15% for >LLOQ – ULOQ 75% of ≥6 calibration standards must fulfill	9 calibrators all ±15%	yes
Accuracy Intra batch	≥5 samples at ≥4 concentration levels each (low QC, medium QC, high QC), ±20% for LLOQ ±15% for >LLOQ – ULOQ	Low, medium, high QC within ±15%	yes
Accuracy Inter batch	Low, medium and high QC from ≥3 runs at ≥2 days ±20% for LLOQ ±15% for >LLOQ – ULOQ	Low, medium, high QC within ±15%	yes
Precision Intra batch	≥5 samples at ≥4 concentration levels each, ±20% for LLOQ ±15% for >LLOQ – ULOQ	Low, medium, high QC within ±15%	yes
Precision Inter batch	≥5 samples at ≥4 concentration levels each, ±20% for LLOQ ±15% for >LLOQ – ULOQ	Low, medium, high QC within ±15%	yes
Dilution integrity	Accuracy and precision should be within the set criteria, i.e. within ±15%	Dilution factor 2 & 4; complies	yes
Matrix effects	normalized MF calculated from the 6 lots of matrix ≤15 % for low and high concentration level	6 lots, no significant matrix effect	yes
Carry over	response is <20% of LLOQ and <5% of IS	complies	yes

Other validation parameters comprise recovery, ruggedness, haemolysis effect, injector carry-over.

Long-term stability of analyte in matrix was shown over 67 days – clinical phase started on March 13th 2015, analytical phase ended on April 17th 2015.

Observations and comments

Sample reassays for aripiprazole were not done, only a single discrete sample was repeated (Code A/bad chromatography – IS peak was not properly integrated).

Incurred sample reanalysis (ISR) of Aripiprazole has been performed on 108 samples (~10% of total samples analysed, subjects 1, 2, 4, 6, 8, 11, 12, 14, 15, 16, 17, 20, 23, 24, 27-29, 31, 33, 36, 41, 45-48, 50, 52, 54-60 not included); all ISR samples were within 20% from the mean value.

Representative chromatograms were provided for sample runs from 14 (#1-5, 7-10, 12-14) out of 60 subjects (above 20%).

The CHMP considered that the analytical method for the determination of aripiprazole in human plasma as well as respective validations (including partial validations) had been adequately described; the validations were basically performed according to the requirements of the EMA "Guideline on bioanalytical method validation" (EMEA/CHMP/EWP/192217/2009). Acceptance criteria are in a plausible range.

Regarding long-term stability, which is indicated as 67 days, the respective data in partial validation 00-01 could not be found – this should be clarified.

A single re-assay has been performed (initial value: ~860 ng/mL; re-assay: ~14 ng/mL) – the reason is mentioned as "Code A (bad chromatography)" due to difficulties with IS peak integration; this should be explained in more detail. For this repeat, reference was also made to Standard Operation procedure (SOP) "CRCBL026" – this SOP should be provided.

Pharmacokinetic variables

Pharmacokinetic parameters: The following pharmacokinetic parameters were determined from the time and concentration data using a non-compartmental analysis of WinNonlin® professional software (Version: 6.3 Pharsight Corporation, USA).

AUC_{72}: The area under the curve (AUC - calculated by the linear trapezoidal rule) from time zero to 72 hours. However, if the concentration at the 72-hour plasma draw is below the limit of quantification, then AUC_{72} was calculated from time zero up to the sampling time for which the last measured concentration was equal to or larger than the limit of quantification.

C_{max}: Maximum measured plasma concentration over the time span specified.

T_{max}: Time of the maximum measured plasma concentration. If the maximum plasma concentration occurs at more than one time point, the first was chosen as T_{max}.

T/R (Test/Reference) ratio was reported for AUC_{72} and C_{max}.

The CHMP considered that the pharmacokinetic variables were adequate. According to the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr** in studies with a sampling period of 72 h, and where the concentration at 72 h is quantifiable, $AUC_{0-\infty}$ and residual area do not need to be reported. It is sufficient to report AUC_{0-72h}. The applicant did not report any additional parameters such as the terminal rate constant or $t_{1/2}$; this is acceptable.

Statistical methods

Based on literature and sponsor's in-house estimate on aripiprazole the maximum inter-subject variability observed among primary pharmacokinetic parameters was found to be ~26%. Hence, considering the coefficient of variation (CV) of ~26%, the following estimates were considered for the computation of sample size:

T/R ratio = 95 – 105%

Inter-Subject CV (%) ~ 26%

Significance Level = 5%

Power >= 80%

Bioequivalence Limits = 80 – 125% (C_{max} and AUC_{72})

Based on the above estimate, a **sample size of 29 subjects** were to be sufficient (**for each arm**) to establish bioequivalence between aripiprazole formulations under fasting conditions with adequate power. However, considering the dropouts, a sample size of 60 subjects was considered for the study

Descriptive statistics:

Mean, standard deviation, coefficient of variance, median, maximum and minimum for all pharmacokinetic parameters were calculated.

Statistical analysis:

Statistical analysis was performed on pharmacokinetic data of subjects using SAS® statistical software (Version: 9.3 SAS Institute Inc, USA).

Analysis of Variance:

Ln-transformed data of C_{max} & AUC_{72} were evaluated statistically using the PROC GLM from SAS® for difference due to treatment as a fixed effect. The treatment effects were tested at 5% level of significance.

Two One-Sided test for bioequivalence:

Two one-sided 90% confidence intervals for the ratio of means between drug formulations were calculated for Ln-transformed data of C_{max} and AUC_{72}.

Power:

The power of the ANOVA test to detect a 20% mean difference between test reference formulations was reported.

The 90% confidence intervals of the relative mean C_{max} and AUC_{72} of the test to reference formulation for Ln-transformed data was to be within 80.00% to 125.00% for Aripiprazole to establish bioequivalence.

The CHMP considered that the statistical evaluation of the pharmacokinetic parameters and the acceptance ranges for bioequivalence are in accordance with the bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev.1 Cor**). The statistical methods are considered adequate.

Results

Tables 2 and 3: Descriptive statistics of Test and Reference treatment for aripiprazole

Treatment=T

Variable	N	Mean	Std Dev	Coeff of Variation	Minimum	Maximum	Median
Cmax	28	44.863	9.371	20.888	23.846	72.150	43.152
AUC72	28	1721.004	330.439	19.200	1350.692	2854.092	1629.424
Tmax	28	3.000	1.587	52.899	1.000	9.000	2.000

Treatment=R

Variable	N	Mean	Std Dev	Coeff of Variation	Minimum	Maximum	Median
Cmax	29	41.073	8.913	21.702	26.617	64.644	40.844
AUC72	29	1662.675	334.356	20.110	1122.618	2415.607	1670.025
Tmax	29	4.416	2.720	61.592	1.000	10.000	3.000

Tables 4 and 5: Summary of statistical analysis of aripiprazole data

PARAMETER	REFERENCE LEAST SQUARE MEANS	TEST LEAST SQUARE MEANS	REFERENCE GEOMETRIC MEAN	TEST GEOMETRIC MEAN
LnCmax	3.693	3.783	40.178	43.934
LnAUC72	7.397	7.435	1630.963	1695.043

PARAMETER	INTER-SUBJECT CV (%)	RATIO OF GEOMETRIC MEANS	90% CONFIDENCE INTERVAL	POWER
LnCmax	21.372	109.35%	(99.57%;120.09%)	0.9877
LnAUC72	18.795	103.93%	(95.69%;112.88%)	0.9969

Details of p-value:

Parameters	Cmax	AUC72
group*treatment	0.6057	0.9352

The analysis of the plasma Aripiprazole, data resulted in no statistically significant, $\alpha = 0.05$, difference between group*treatment for natural log-transformed Cmax (p=0.6057) and AUC72 (p=0.9352).

Details of p-value:

Parameters	Cmax	AUC72
Treatment	0.1162	0.4384

The analysis of the plasma Aripiprazole, data resulted in no statistically significant, $\alpha = 0.05$, difference between treatment for log-transformed Cmax and AUC72.

After applying the Grubb's outlier test, Subject#16 was detected as an outlier in Cmax and Subject#01 was detected as an outlier in AUC72 for Aripiprazole data. Statistical analysis also performed after excluding subject#01 & 16.

For the log transformed Aripiprazole data of excluding outlier subject#01 & 16, the 90% confidence intervals about the ratio of the Test geometric mean to Reference geometric mean are within the 80.00% to 125.00% limits for Cmax (100.97%;119.48%) and AUC72 (95.04%;111.11%).

The CHMP considered that the statistical analysis was performed on the pharmacokinetic data for 57 subjects (28 subjects on test treatment and 29 subjects on reference treatment).

No statistically significant treatment effects were observed for AUC_{0-72} or C_{max}.

The 90% confidence interval of the test/reference ratio from the ANOVA of the log-transformed

AUC_{0-72} and C_{max} were within the acceptance criteria of 80.00-125%. Although it is not described in a very comprehensive and transparent way, it is understood that a second analysis was performed excluding pharmacokinetic outliers. From the little information provided it appears that the reasons for exclusion and handling of the two outliers are not conform to the BE guideline. This analysis is thus regarded as irrelevant, but in view of the BE conclusion in the complete data set no concern is raised.

Safety data

A total of four adverse events (AE) were reported by four subjects during the entire study. All AEs were mild in nature. Two subjects (No.: 11 and 54) were analyzed in the bioanalytical laboratory for safety reasons.

There were two AEs (Vomiting) which were considered possibly related to the oral administration of test product T (Aripiprazole tablets 10 mg). There were two AEs (lood Glucose Increased, White Blood Cell Count Increased) which were considered unlikely/remotely related to the oral administration of test product T (Aripiprazole Tablets 10 mg).

Overall, a single oral dosage (1 × 10 mg) of Aripiprazole tablets administered under fasting condition were well tolerated in both test and reference formulation.

The CHMP noted that four adverse events were reported in the study. Overall, the two formulations were well tolerated, with no apparent differences in safety profiles.

Justification for requesting biowaiver for additional strengths

Aripiprazole Mylan is applying for a marketing authorisation for 4 different strengths of aripiprazole tablets (5, 10, 15, 30 mg). According to the current BE guideline, a bioequivalence study investigating only one strength may be acceptable if all of the following 5 conditions are fulfilled:

- the pharmaceutical products (all the strengths) are manufactured by the same manufacturer at the same manufacturing site using similar manufacturing process;
- 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 drug pharmacokinetics is linear;
- 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 states that the proposed aripiprazole tablets fulfil the above criteria since the process for all the strengths are the same, the composition of the different strengths is the same and proportional, i.e. the ratio between amounts active compound and excipients are identical for all the strengths.

The Applicant has performed one bioequivalence study, using the 10 mg strength of Aripiprazole tablets, and is applying for a biowaiver for the 5 mg, 15 mg and 30 mg tablets.

For this reason the justification of compliance with the five conditions as stated in the BE Guideline has been provided.

Table 6: Unit composition for Aripiprazole Mylan 5mg, 10mg, 15mg and 30mg tablets

Name of the Ingredient	mg / tablet				% w/w	Pharmaceutical Function	Reference to Standards
	5mg	10mg	15mg	30mg			
Active Ingredient							
Aripiprazole*	5.000	10.000	15.000	30.000	11.11	Active ingredient	Ph. Eur.
Inactive Ingredients							
Mannitol	9.500	19.000	28.500	57.000	21.11	Diluent	Ph. Eur.
Cellulose, microcrystalline (PH 112)@	27.500	55.000	82.500	165.000	61.11	Diluent	Ph. Eur.
Croscarmellose sodium	2.500	5.000	7.500	15.000	5.56	Disintegrant	Ph. Eur.
Magnesium stearate	0.500	1.000	1.500	3.000	1.11	Lubricant	Ph. Eur.
Total tablet weight	**45.000**	**90.000**	**135.000**	**270.000**	**100.00**	-	-

Notes:

* : The quantity of Aripiprazole Ph. Eur. is based on based on 100 %w/w assay on dried basis/anhydrous and nil Loss on Drying/water content.

@ : The quantity of Cellulose, microcrystalline is adjusted based on the actual quantity of Aripiprazole Ph. Eur. taken to maintain constant unit weight.

Linear pharmacokinetics of aripiprazole:

Aripiprazole exhibits linear pharmacokinetics in the dosing range of 5 to 30 mg/day, i.e. across the range of strengths of application from 5 mg to 30 mg tablet formulations.

The most commonly reported adverse reactions associated with aripiprazole are restlessness, insomnia, anxiety, extrapyramidal disorder, akathisia, tremor, dizziness, somnolence, sedation, headache, blurred vision, dyspepsia, vomiting, nausea, constipation, salivary hypersecretion and fatigue. On the basis of safety information available for aripiprazole the adverse event somnolence has been observed upon escalating the dose.

In the dose range of 10 to 30 mg/day aripiprazole tended to slightly shorten the QTc interval.

Discontinuation due to adverse events increases with increasing dose.

Also as per the reported data, aripiprazole has been poorly tolerated by healthy volunteers in bioequivalence studies, particularly at the 15 and 30 mg dose levels.

Life-threatening adverse events attributed to acute laryngeal dystonia have been reported following administration of a single dose of 30 mg aripiprazole to healthy volunteers in bioequivalence studies. Such events have not been reported at doses lower than 30 mg. Considering this situation, ethically, the lowest available strength would be appropriate for a bioequivalence study in healthy volunteers.

Based on the above cited safety and tolerability reasons and considering the linear kinetics characteristics of the drug the most suitable strength for investigation of bioequivalence would be 5 mg in healthy volunteers, but as the exposure levels/plasma levels of aripiprazole after administration of 5 mg strength would not be adequate for detecting the difference between products, the likely selection can be either (2 x 5 mg) dose or (1 x 10 mg) dose. Hence, among the available marketed strengths of 5, 10, 15 and 30 mg for aripiprazole, the strength/dose decided upon for the investigation of bioequivalence was 10 mg, administered as a single dose.

Comparative Dissolution Studies

The applicant considered that the generated dissolutions profiles are the same as those submitted within the previous application EMEA/H/C/003926. In addition, the applicant presented a dissolution profile of the reference product Abilify 10 mg tablets (Batch No. 3M55103) used in the current BE study, performed in one medium (0.1N hydrochloric acid) at 60 rpm. More than 85% of the labeled

amount of drug (aripiprazole) was released within 15 minutes from reference product. Therefore, the applicant stated that, as per the provisions mentioned in BE guideline, the dissolution profiles can be considered as similar without further mathematical calculations.

CHMP discussion

The comparative dissolution profiles have been updated (as compared to the previous marketing authorization application, EMEA/H/C/003926) with one dissolution profile of the reference product Abilify 10 mg tablets (Batch No. 3M55103) used in the current BE study in one buffer (i.e. 0.1N hydrochloric acid) at 60 rpm. More than 85% of the labeled amount of drug (aripiprazole) released within 15 minutes from reference product. However, the agitation speed is different to the current recommendation (for paddle apparatus is usually 50 rmp). This should be justified. Moreover, *in vitro* dissolution profiles of the EU reference product (Batch No. 3M55103) should be investigated within the range of pH 1 – 6.8. Therefore additional dissolution profiles under other recommended conditions (pH 4.5 and pH 6.8) should be performed and submitted. All non-compliances with the current BE sguideline should be also sufficiently discussed and justified.

Since the other dissolution profiles are the same as those summited within the previousl application of Aripiprazole Mylan (EMEA/H/C/003926) and the major objection as well as a point for clarification have been not yet been resolved by the applicant, the following issues are still valid and outstanding:

The 5 minutes sampling time have not been included to calculate the f2 similarity factor. If the 5 minutes sample were considered, the dissolution profiles would be considered similar only for the 5 mg strength. Therefore, the biowaiver to extrapolate the bioequivalence study to the additional strengths of 15 mg and 30 mg is presently not acceptable.

The applicant should justify that the dissolution profile comparison is conducted with adequate sampling times to characterize completely all relevant parts of the curve (ascending part) and that the shown differences are mainly related to the absence of sink conditions due to the pH dependent active pharmaceutical ingredient solubility. Therefore, the applicant should demonstrate that:

a) the same differences occurs with the corresponding reference strengths when compared to the reference biobatch, or

b) the dissolution profiles are similar when the same amount of drug is included per vessel (e.g. one tablet of 30 mg vs. three tablets of 10 mg and two tablets of 15 mg vs. three tablets of 10 mg).

All dissolution profiles have been performed at 60 rpm for tablets. According to the current Guideline, the agitation speed, in dissolution testing, for paddle apparatus is usually 50 rmp. Any deviation from the current Guideline should be adequately justified.

Therefore, a biowaiver for the additional strengths is not considered acceptable at present.

CHMP Conclusion

Although the bioequivalence study appears to have been well conducted, some outstanding issues should be clarified:

A discussion and justification to support adequacy of the chosen design according to guideline requirements is requested.

A waiver cannot yet be granted, since the 5 minutes sampling time has not been included to calculate the f2 similarity factor. If the 5 minutes sample were considered, the dissolution profiles would be considered similar only for the 5 mg strength. Therefore, the biowaiver to extrapolate the bioequivalence study to the additional strengths of 15 mg and 30 mg is not acceptable at present. This was considered a major objection in the previous application and has remained unresolved.

Furthermore the rotation speed used is 60 rpm while in the BE guideline 50 rpm is recommended. Moreover, additional dissolution profiles under the two other recommended conditions (pH 4.5 and pH 6.8) of the reference product Abilify 10 mg comprimés tablets (batch No. 3M55203*)* used in the BE study were not presented and need to be submitted.

Regarding long-term stability, which is indicated as 67 days, the respective data in partial validation 00-01 could not be found – this should be clarified.

A single re-assay has been performed (initial value: ~860 ng/mL; re-assay: ~14 ng/mL) – reason is mentioned as Code A (bad chromatography)" due to difficulties with IS peak integration; this should be explained in more detail. For this repeat, reference was also made to SOP "CRCBL026" – this SOP should be provided.

3.4.1.2. Aripiprazole Mylan Orodispersible Tablets

Study No.: 14-VIN-657

Study Title:

An open label, balanced, randomized, single-dose, two-treatment, single-period, parallel bioequivalence study of Aripiprazole orodispersible tablets 10 mg of Mylan Laboratories Limited, India and ABILIFY® (aripiprazole) 10 mg orodispersible tablets of Otsuka Pharmaceutical Europe Ltd. in healthy, adult, human subjects under fasting condition.

Study design

An open label, randomized, single-period, two-treatment, parallel, balanced, single dose oral bioequivalence study.

Clinical centre and Pharmacokinetic and Statistical centre:	Veeda Clinical Research Pvt. Ltd
Bioanalytical centre:	Mylan Laboratories Ltd.

The study was conducted in two groups and in each group, the subjects received either test or reference products randomly. Randomization was carried out using SAS (SAS® Institute Inc., USA) Version 9.2. Randomization was done in blocks using PROC PLAN such that the design is balanced. The order of receiving the test and reference formulations for each subject in the study was determined according to randomization schedule.

Subjects were fasted overnight for at least 10 hours before dosing. Following steps were followed for dosing. Investigator remains present during dosing activity.

- Just prior to drug administration (within 5 minutes), each subject was instructed to rinse their mouth for approximately 5 seconds with approximately 20 mL of room temperature water, and then swallowed this water.
- Subsequently, the investigational product (allocated as per the randomization schedule) was placed on subject's tongue at scheduled dosing time.
- Subjects were also instructed not to chew or crush the investigational product and allowed to disperse the tablet for maximum of 60 seconds after being placed on the tongue. Subjects were also instructed not to swallow the tablet / dispersed particles / saliva during this period.

- After 60 seconds, subjects were instructed to swallow the dispersed medication along with the saliva.
- Subjects were asked to move their tongue around the mouth (front and back part of the gum, tooth and palate) to ensure that all remaining medication has been swallowed.
- Following the administration of the drug, mouth was checked with the help of disposable spatula and torch in order to confirm the consumption of the medication.
- No water (except for the approximately 20 mL of room temperature water provided to subjects just prior to dosing) was provided with the administration of the drug.

A total of nineteen (19) blood samples were collected during study period. The pre-dose (0.00 hour) blood sample of 5.0 mL was collected within one hour before dosing. The post-dose blood samples of 5.0 mL each was drawn at 0.50, 1.00, 2.00, 3.00, 4.00, 5.00, 6.00, 7.00, 8.00, 9.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00, 60.00 and 72.00 hours following drug administration in study period.

Study Period:	**Clinical Phase**	07 Mar 2015 to 17 Mar 2015
	Group 01	
	Check-in	07 Mar 2015
	Dosing	08 Mar 2015
	Check-out	11 Mar 2015
	Group 02	
	Check-in	13 Mar 2015
	Dosing	14 Mar 2015
	Check-out	17 Mar 2015
	Bioanalytical Phase	
	Start date	06 Apr 2015
	End date	13 Apr 2015

The CHMP noted that, according to the BE guideline, "if two formulations are compared, a randomised, two-period, two-sequence single dose crossover design is recommended. Under certain circumstances, provided the study design and the statistical analyses are scientifically sound, alternative well-established designs could be considered such as parallel design for substances with very long half-life and replicate designs e.g. for substances with highly variable pharmacokinetic characteristics".

Even though the BE guideline opens up for the possibility of choosing the parallel study design under certain circumstances, the choice is somewhat surprising given that in the previous application BE studies with the standard cross over design had in principle proven suitable for showing BE for aripiprazole. The guideline further details that "…in parallel design studies, the treatment groups should be comparable in all known variables that may affect the pharmacokinetics of the active substance (e.g. age, body weight, sex, ethnic origin, smoking status, extensive/poor metabolic status). This is an essential pre-requisite to give validity to the results from such studies." A discussion and justification on the adequacy of the chosen design in line with above guideline requirements was requested from the applicant.

The orodispersible tablets were taken without water (20 ml water was given to the subjects to wet the mouth). This is in the line with BE guideline since the reference medical product can be taken with or without water.

Blood samples were collected at pre-dose (0.00 hours) and at intervals over 72.00 hours after administration of dose. The sampling period were considered by the CHMP to be sufficient to

characterize the plasma concentration-time profile. Blood sampling points were appropriate to allow an accurate measurement of T_{max}.

The study was conducted under fasting conditions. Since there is no evidence of a food effect in the literature and the SmPC of the reference product gives no recommendation for administration of the drug in relation to food, and as food intake does not affect the absorption of the active substance, this was considered adequate by the CHMP.

Aripiprazole exhibits linear pharmacokinetics within the 5-30 mg range and in principle, the bioequivalence study should be conducted at the highest strength. However, due to well-known serious safety concerns the highest strength cannot be administered to healthy volunteers. Therefore, the dose selection (10 mg) was considered acceptable by the CHMP.

Test and reference products

Product Characteristics	Test product	Reference Product
Name	Aripiprazole Orodispersible Tablets 10 mg	ABILIFY® (aripiprazole) 10 mg orodispersible tablets
Strength	10 mg	10 mg
Dosage form	Orodispersible Tablets	Orodispersible Tablets
Manufacturer/ MAH	Mylan Laboratories Limited, Plot No.H-12 & H-13, MIDC, Waluj Industrial Area, Aurangabad - 431 136, Maharashtra India.	Otsuka Pharmaceutical Europe Ltd. Gallions, wexham springs, frame wood road, wexham, SL3 6PJ-United Kingdom
Batch number /Lot number	2001816	4E79057
Batch size (Biobatch)	141000	
Measured content (s) (% of label claim)	99.1 %	100.8 %
Commercial Batch Size		
Expiry date (Retest date)	Dec 2015	Mar 2017
Location of Certificate of Analysis	5312-compar-ba-be-stud-rep, Appendix-16.1.6	5312-compar-ba-be-stud-rep, Appendix-16.1.6
Member State where the reference product is purchased from:	--	UK
This product was used in the following trials:	Study no.: 14-VIN-657	Study no.: 14-VIN-657

Certificates of analysis of the test and reference product were provided by the applicant. The batch size of the test product (141 000 Units) were considered acceptable by the CHMP.

The applicant confirmed that the composition and manufacturing process of the test product formulation used in the bioequivalence study and the formulation proposed for commercial supplies to European Economic Area is the same.

The CHMP however requested that the location of Certificate of Analysis given by the applicant in the table above should be corrected.

Population(s) studied

Healthy volunteers of age between 45 and 65 years (both inclusive) were selected on the basis of laboratory evaluations during screening, medical history, clinical examination (including physical examination and systemic examination), Chest X-ray (PA view), ECG recordings and measuring the concentration of Aripiprazole during screening.

In the bioequivalence study, including Group-I and Group-II, a total of 60 (+3 extra up to period 01 dosing) healthy volunteers were enrolled. A total of 39 subjects were dosed in Group-I and 21 subjects were dosed in Group-II in the study.

Group-I - 40 Subjects Enrolled**, 39 Subjects dosed**

From Group-I, one subject self-withdrawn prior dosing, hence the subject was not dosed in group-I of the study. The un-dosed subject was replaced by another subject during group-II of the study.

Group-II - 20 (+03 extra up to dosing) enrolled, **21 subjects dosed** including replacement subject (see above)

All 60 subjects completed the study as per protocol.

The CHMP was of the view that the study population chosen was appropriate and in line with the bioequivalence guideline. Since literature reports no gender-related differences in aripiprazole pharmacokinetic inclusion only male subjects is acceptable. The inclusion and exclusion criteria were considered adequate.

Analytical methods

Sponsor of the study: Mylan Laboratories Limited

Clinical center: Veeda Clincal Research Pvt. Ltd.

Bioanalytical center: Mylan Laboratories Limited

The analytical part of the study lasted from April 6th 2015 till April 13th 2015; study samples were obtained stored at a nominal temperature of -70ºC.

1140 samples (theoretical amount 1140 samples from 60 subjects; 1140 samples obtained) from 60 evaluable subjects (19 time-points per subject, 1 period) were analysed.

Analytical Methods
The analyte is aripiprazole, internal standard was Aripiprazole-d8; samples were extracted from a 200 µL aliquot of K_3 EDTA human plasma by liquid-liquid extraction. The extracted samples were injected into a liquid chromatograph.

The detection method used was tandem mass spectrometry detector.

Quantitation is determined by peak area ratio method. A weighted (1/x) linear regression is performed to determine the concentration of the analytes.

The validated calibration range for the assay of Aripiprazole is from 0.500ng/mL (LLOQ) to 100.053ng/mL.

Validation of the analytical methods
Results obtained from this validation are presented below.

Table 7: Study No. 14-VIN-657– outcome of validation of the analytical methods

Parameter	Acceptance criterion	Found value	acceptable (yes/no)
Selectivity	6 individual sources, response is <20% of LLOQ and <5% of IS	14 lots, no significant response	yes
LLOQ	Min 5 times the signal of a blank sample; <5% of Cmax	0.500 nm/mL; complies	yes
Range	LLOQ – ULOQ (Σ=6 calibrators) ±20% for LLOQ ±15% for >LLOQ – ULOQ 75% of ≥6 calibration standards must fulfill	9 calibrators all ±15%	yes
Accuracy Intra batch	≥5 samples at ≥4 concentration levels each (low QC, medium QC, high QC), ±20% for LLOQ ±15% for >LLOQ – ULOQ	Low, medium, high QC within ±15%	yes
Accuracy Inter batch	Low, medium and high QC from ≥3 runs at ≥2 days ±20% for LLOQ ±15% for >LLOQ – ULOQ	Low, medium, high QC within ±15%	yes
Precision Intra batch	≥5 samples at ≥4 concentration levels each, ±20% for LLOQ ±15% for >LLOQ – ULOQ	Low, medium, high QC within ±15%	yes
Precision Inter batch	≥5 samples at ≥4 concentration levels each, ±20% for LLOQ ±15% for >LLOQ – ULOQ	Low, medium, high QC within ±15%	yes
Dilution integrity	Accuracy and precision should be within the set criteria, i.e. within ±15%	Dilution factor 2 & 4; complies	yes
Matrix effects	normalized MF calculated from the 6 lots of matrix ≤15 % for low and high concentration level	6 lots, no significant matrix effect	yes
Carry over	response is <20% of LLOQ and <5% of IS	complies	yes

Other validation parameters comprise recovery, ruggedness, haemolysis effect, injector carry-over.

Long-term stability of the analyte in matrix was shown over 67 days – clinical phase started on March 7th 2015. The analytical phase ended on April 13th 2015.

Observations and comments

Sample re-assays for aripiprazole were done on 77 samples (6.75%), out of them 76 due to a rejected analytical run; a single discrete sample was repeated (Code F/sample processing error). The discrete re-assay is in accordance with the presented SOP and the relevant guideline.

Incurred sample reanalysis (ISR) of Aripiprazole has been performed on 112 samples (~10% of total samples analysed, subjects 1, 8, 9, 11-14, 17, 19, 21-24, 26-28, 31-33, 36, 37, 43, 44, 46, 48, 50, 52, 55-58, 60 not included); all samples were within 20% from the mean value.

Representative chromatograms were provided for sample runs from 12 (#1-12) out of 60 subjects (20%).

The CHMP considered that the analytical method for the determination of Aripiprazole in human plasma as well as the respective validations (including partial validations) were adequately described; the validations were basically performed according to the requirements of the EMA Guideline on

bioanalytical method validation (EMEA/CHMP/EWP/192217/2009). Acceptance criteria were in a plausible range.

Regarding long-term stability, which is indicated as 67 days, the respective data in partial validation 00-01 could not be found – this should be clarified.

Pharmacokinetic variables

The following pharmacokinetic parameters for Aripiprazole were estimated using WinNonlin® Enterprise Software Version 5.3 (Pharsight Corporation, USA) for both the formulations [Reference (R) and Test (T)]:

C_{max}	:	Maximum measured plasma concentration over the time span specified
T_{max}	:	Time of the maximum measured plasma concentration. If the maximum-value occurs at more than one time point, Tmax is defined as the first time-point with this value.
AUC_{0-72}	:	The area under the plasma concentration versus time curve, from time 0 to 72 hours (last measurable concentration) calculated using linear trapezoidal method.
K_{el}	:	The elimination rate constant associated with the terminal (loglinear) portion of the curve. Estimated by linear regression of time vs. log concentration.
$t_{½}$	:	The terminal elimination half-life, calculated as ln(2)/Kel
Volume of distribution (Vd)	:	Drug quantity in the body/drug concentration in blood

The primary pharmacokinetic variables were C_{max} and AUC_{0-72}

The CHMP considered that the pharmacokinetic variables were adequate. According to the BE guideline, in studies with a sampling period of 72 h and where the concentration at 72 h is quantifiable, $AUC_{0-\infty}$ and residual area do not need to be reported; it is sufficient to report AUC_{0-72h}.

Statistical methods

The estimation of the pharmacokinetic parameters C_{max}, AUC_{0-72}, T_{max}, $t_{1/2}$, Vd and K_{el} was planned to be done using a non-compartmental model by using WinNonlin® Enterprise Software Version 5.3 (Pharsight Corporation, USA).

The statistical comparison of the ln-transformed C_{max} and AUC_{0-72} was planned to carry out using SAS® Version 9.2 (SAS Institute Inc., USA).

Analysis of variance was planned to carry out using SAS® Version 9.2 (SAS Institute Inc., USA) for ln-transformed C_{max} and AUC_{0-72} using PROC GLM.

The ANOVA model included the fixed effect of group, treatment, and group by treatment as the fixed-effects.

If there is no significant group by treatment interaction, the bioequivalence analysis was planned to perform using data from all groups with the group by treatment term dropped from the ANOVA model.

The formulation effect was tested at the 0.05 level of significance against the residual error (mean square error/MSE) from the ANOVA as the error term.

Geometric least square means of pharmacokinetic parameters C_{max} and AUC_{0-72} were planned to be computed and reported.

The ratio of geometric least squares means was planned to be calculated and reported for parameters C_{max} and AUC_{0-72}.

Two-one sided 90% confidence intervals for the geometric least square mean ratio (T/R) obtained from the analysis of ln-transformed parameters C_{max} and AUC_{0-72}, was planned to construct using root mean square error computed by PROC GLM.

Criteria for bioequivalence:
Based on the statistical results of 90% confidence intervals for the geometric least square mean ratio for the pharmacokinetic parameters C_{max} and AUC_{0-72} for aripiprazole the conclusions were drawn whether test formulation is bioequivalent to reference formulation under fasting condition. Acceptance range for bioequivalence is 80.00% - 125.00% for 90% confidence intervals of the geometric least square means ratio for C_{max} and AUC_{0-72} for aripiprazole.

The CHMP considered that the statistical evaluation of the pharmacokinetic parameters and the acceptance ranges for bioequivalence wer in accordance with the bioequivalence guideline. The statistical methods are considered adequate.

Results

Table 8: Summary of statistical analysis of aripiprazole data

Parameters (Units)	Arithmetic Mean ± SD (%CV)	
	Reference Product (R) (N = 30)	Test Product (T) (N = 30)
C_{max} (ng/mL)	40.592 ± 8.6060 (21.20%)	41.318 ± 10.5808 (25.61%)
T_{max} (hr)[#]	4.000 (2.00 - 12.00)	5.000 (2.00 - 10.00)
AUC_{0-72} (hr*ng/mL)	1685.512 ± 426.0371 (25.28%)	1682.872 ± 396.2429 (23.55%)
$t_{½}$ (hr)	85.103 ± 40.7175 (47.84%)	66.974 ± 19.8393 (29.62%)
K_{el} (1/hr)	0.0098 ± 0.00410 (41.69%)	0.0113 ± 0.00347 (30.74%)
Vd (mL)	315474.794 ± 73383.4279 (23.26%)	301321.551 ± 79274.2094 (26.31%)

[#] For T_{max} median (min – max),

The geometric least squares mean of Test Formulation (T) and Reference Formulation (R), its ratio (T/R)% and 90% confidence intervals the Geometric least square mean ratio (T/R) obtained from the analysis of ln-transformed parameters C_{max} and AUC_{0-72} are summarized in the following table.

PK Parameters (Unit)	Geometric Least Square Means and It's Ratio			Inter subject CV%	90% CI	Power (%)
	Test Product (T) (N = 30)	Reference Product (R) (N = 30)	(T/R) (%)			
C_{max} (ng/mL)	40.057	39.896	100.40	24.87	90.32% - 111.61%	96.56
AUC_{0-72} (hr*ng/mL)	1620.828	1622.273	99.91	23.43	90.42% - 110.40%	97.83

Main Effects	p-value for pharmacokinetic parameters	
	LnC_{max}	$LnAUC_{0-72}$
Formulation	0.9495	0.9882
Group	0.7207	0.2349

From the above table, formulation and group effects for ln-transformed C_{max} and AUC_{0-72} were found statistically insignificant.

The statistical analysis on the pharmacokinetic data was performed for 60 subjects (30 subjects in Test treatment and 30 subjects in Reference treatment). No statistically significant treatment or group effects were observed for AUC_{0-72} or C_{max}.

The 90% confidence interval of the test/reference ratio from the ANOVA of the log-transformed AUC_{0-72} and C_{max} were within the acceptance criteria of 80.00-125%.

Safety data

The Aripiprazole orodispersible tablets 10 mg was well tolerated by the all subjects. None of the subject reported any adverse event during the conduct of the study.

The CHMP considered that, overall, the two formulations were well tolerated, with no apparent differences in safety profiles.

Justification for requesting biowaiver for additional strength(s)

Aripiprazole Mylan is applying for a marketing authorisation for 2 different strengths of aripiprazole orodispersible tablets (10 mg and 15 mg) According to the current BE guideline, a bioequivalence study investigating only one strength may be acceptable if all of the following 5 conditions should be fulfilled:

- the pharmaceutical products (all the strengths) are manufactured by the same manufacturer at the same manufacturing site using similar manufacturing process;
- 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 drug pharmacokinetics is linear;
- 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 states that the proposed aripiprazole orodispersible tablets fulfil the above criteria since the process for all the strengths are the same, the composition of the different strengths is the same and proportional, i.e. the ratio between amounts active compound and excipients are identical for all the strengths.

The applicant has performed one bioequivalence studies, using the 10 mg strength of Aripiprazole orodispersible tablets and is applying for a biowaiver for the 15 mg tablets.

For this reason the justification of compliance with the five conditions as stated in the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr Section 4.1.6.) has been provided.

Table 9: The unit composition for Aripiprazole Mylan 10 mg and 15 mg

Name of the Ingredient	mg / tablet		% w/w	Pharmaceutical Function	Reference to Standards
	10mg	15 mg			
Active Ingredient					
Aripiprazole*	10.000	15.000	12.50	Active ingredient	Ph. Eur.
Inactive Ingredients – Core					
Cellulose, microcrystalline (PH 112)@	47.500	71.250	59.38	Diluent	Ph. Eur.
Mannitol	12.000	18.000	15.00	Diluent	Ph. Eur.
Croscarmellose sodium	5.000	7.500	6.25	Disintegrant	Ph. Eur.
Silica, colloidal anhydrous	2.000	3.000	2.50	Glidant	Ph. Eur.
Vanilla 501441 AP2004 (Nature identical flavourings, Natural flavours, Maize maltodextrin, INS 1450 modified corn starch and INS 1518 Triacetin)	0.500	0.750	0.62	Flavour	IH
Aspartame	2.000	3.000	2.50	Sweetener	Ph. Eur.
Magnesium stearate	1.000	1.500	1.25	Lubricant	Ph. Eur.
Total weight (mg)	**80.000**	**120.000**	**100.000**	-	-

Notes:

* : The quantity of Aripiprazole Ph. Eur. is based on 100% w/w assay on dried basis/anhydrous basis and nil loss on drying/water content.

@ : The quantity of Cellulose microcrystalline is adjusted based on the actual quantity of Aripiprazole Ph. Eur. taken to maintain constant unit weight.

Linear pharmacokinetics of aripiprazole:

Aripiprazole exhibits linear pharmacokinetics in the dosing range of 5 to30 mg/day, i.e. across the range of strengths of application from 5 mg to 30 mg tablet formulations.

The most commonly reported adverse reactions associated with aripiprazole are restlessness, insomnia, anxiety, extrapyramidal disorder, akathisia, tremor, dizziness, somnolence, sedation, headache, blurred vision, dyspepsia, vomiting, nausea, constipation, salivary hypersecretion and fatigue.

On the basis of safety information available for Aripiprazole the adverse event somnolence has been observed upon escalating the dose.

In the dose range of 10 to 30 mg/day aripiprazole tended to slightly shorten the QTc interval.

Discontinuation due to adverse events increases with increasing dose.

Also as per the reported data, aripiprazole has been poorly tolerated by healthy volunteers in bioequivalence studies, particularly at the 15 and 30 mg dose levels.

Life-threatening adverse events attributed to acute laryngeal dystonia have been reported following administration of a single dose of 30 mg aripiprazole to healthy volunteers in bioequivalence studies. Such events have not been reported at doses lower than 30 mg. Considering this situation, ethically, the lowest available strength would be appropriate for a bioequivalence study in healthy volunteers.

Based on the above cited safety and tolerability reasons and considering the linear kinetics characteristics of the drug the most suitable strength for investigation of bioequivalence would be 5 mg in healthy volunteers, but as the exposure levels/plasma levels of aripiprazole after administration of 5 mg strength would not be adequate for detecting the difference between products, the likely selection can be either (2 x 5 mg) dose or (1 x 10 mg) dose.

Hence, among the available marketed strengths of 10 mg and 30 mg for aripiprazole, the strength/dose decided upon for the investigation of bioequivalence was 10 mg, administered as a single dose.

Comparative Dissolution Studies

The generated dissolutions profiles are the same as those submitted within the previous application EMEA/H/C/003926.

In addition, the applicant presented a dissolution profile of the reference product Abilify 10 mg orodispersible tablets (Batch No. 4E79057) used in the current BE study, performed in one medium, i.e. 4.0 Acetate buffer (Release media) at 75 rpm.

The similarity factor (f2 value) between the test product and EU reference product (batch number 4E79057) is found to be 43. However, the applicant stated that, as bioequivalence has been proved between the test batch (B. No.: 2001816) and reference product (B. No. 4E79057), the f2 value of less than 50 is insignificant.

CHMP discussion

The comparative dissolution profiles have been updated (as compared to the previous procedure EMEA/H/C/003926) with one dissolution profile of the reference product (Batch No. 4E79057) used in the current BE sudy, in one buffer, i.e. pH 4.0 acetate buffer (release media) at 75 rpm. The similarity factor (f2 value) between the test product (Aripiprazole Mylan 10 mg orodispersible tablets B. No: 2001816) and EU reference product Abilify® (aripiprazole) 10 mg orodispersible tablets (Batch No. 4E79057) at pH 4.5 acetate buffer was found to be less than 50. However, the exactly same batch of reference product and test product were used in the BE study and are proven to be bioequivalent. According to the guideline on bioequivalence, where the results of similarity in vitro do not reflect bioequivalence as demonstrated in vivo, the latter prevails and thus the difference in dissolutions profiles between the 10 mg batches is not considered critical.

However, the agitation speed is different from the current recommendation (for paddle apparatus it is usually 50 rmp). This should be justified. Moreover, *in vitro* dissolution profiles of the EU reference product (Batch No. 4E79057) should be investigated within the range of pH 1 – 6.8. Therefore additional dissolution profiles under other recommended conditions (pH 1.2 and pH 6.8) should be submitted. Possible non-compliance with the current BE guideline should be also sufficiently discussed and justified.

The other dissolution profiles are the same as those submitted within the previous application for Aripiprazole Mylan (EMEA/H/C/003926). The former points for clarification had not been resolved by the Applicant. Therefore, the following issue is still valid and outstanding: All dissolution profiles have been performed at 75 rpm for orodispersible tablets. According to the current Guideline, the agitation speed in dissolution testing for paddle apparatus is usually 50 rmp. Any deviation from the current guideline should be adequately justified.

Therefore, until these issues are properly clarified and the missing data submitted a biowaiver for the additional strengths is not considered acceptable.

CHMP conclusions
Although the bioequivalence study appears to have been well conducted some outstanding issues should be clarified.

A discussion and justification on the adequacy of the chosen parallel group study design, in line with guideline requirements, is requested.

A waiver cannot yet be granted as the rotation speed used is 75 rpm while 50 rpm is the speed recommended in the BE guideline. Moreover, additional dissolution profiles under two other recommended conditions (pH 1.2 and pH 6.8) of the reference product Abilify 10 mg orodispersible tablets (B. No. 4E79057*)* used in the BE study need to be submitted.

Regarding long-term stability, which is indicated as 67 days, the respective data in partial validation 00-01 could not be found – this should be clarified.

3.4.2. Additional data

The applicant is requesting additional pack-sizes and types to the registered packaging configurations of the reference product. More specifically, in addition to the unit dose presentations of 14 x 1 tablets,

28 x 1 and 49 x 1 tablets in perforated unit dose blisters, the applicant is proposing additional packages of 56 and 98 tablets and pack types of unperforated (random) blisters and HDPE containers of 500 tablets. The difference in the proposed pack-sizes and types is due to the marketing strategy of the applicant. The additional packaging configurations are requested to better meet the commercial needs of individual European markets, in keeping with the marketing strategy of the applicant.

The CHMP was of the view that the proposed additional presentation (in the meaning of "pack size") did not pose any safety or efficacy concerns.

3.4.3. Post marketing experience

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

3.4.4. Discussion on clinical aspects

The Applicant conducted two studies investigating bioequivalence of Aripiprazole Mylan 10 mg tablets and orodispersible tablets versus Abilify (aripiprazole) 10 mg tablets and orodispersible tablets, respectively, in healthy adult subjects under fasting conditions. The choice of the 10 mg strength is acceptable. The studies were open label, randomized, single-period, two-treatment, parallel, balanced, single dose oral bioequivalence studies.

According to the BE guideline, if two formulations are compared, a randomised, two-period, two-sequence single dose crossover design is recommended. Under certain circumstances, provided the

study design and the statistical analyses are scientifically sound, alternative well-established designs could be considered such as parallel design for substances with very long half-life and replicate designs e.g. for substances with highly variable pharmacokinetic characteristics". The guideline further details that "…in parallel design studies, the treatment groups should be comparable in all known variables that may affect the pharmacokinetics of the active substance (e.g. age, body weight, sex, ethnic origin, smoking status, extensive/poor metabolic status). This is an essential pre-requisite to give validity to the results from such studies." A discussion and justification on the adequacy of the chosen design in line with guideline requirements as outlined above is requested.

3.4.5. Conclusions on clinical aspects

Although the bioequivalence studies appear to have been well conducted, the applicant should justify that the chosen study design (parallel group) is adequate.

The biowaiver to extrapolate the bioequivalence conclusion from study BA14101795-01 with the 10mg Aripiprazole Mylan tablets to the 15 mg and 30 mg strengths is presently not acceptable. Moreover, some issues with regard to the biowaiver for the additional strengths of the Aripiprazole Mylan orodispersible tablets in Study 14-VIN-657 require further clarification.

3.5. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant is acceptable.

3.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted risk management plan (RMP):

The PRAC considered that the RMP version 1.0 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC Rapporteur final assessment report on RMP.

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the RMP cannot be agreed at this stage.

4. Benefit/risk assessment

Although the bioequivalence studies appear to have been well conducted, some outstanding issues should be clarified. The applicant should justify that the chosen parallel group study design is adequate. The waiver for the 15 mg and 30 mg Aripiprazole Mylan tablets and for the additional strengths of the Aripiprazole Mylan orodispersible tablets is not acceptable at present.

4.1. Conclusions

The application is presently not approvable. A benefit/risk ratio comparable to the reference product can only be concluded once all outstanding issues have been resolved.