20 November 2014
EMA/CHMP/705827/2014
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal Assessment report

Aripiprazole Mylan

International non-proprietary name: aripiprazole

Procedure No. EMEA/H/C/003926

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 clinical, the CHMP considers that the generic application for Aripiprazole Mylan 5 mg, 10 mg, 15 mg, 30 mg Tablets and Aripiprazole Mylan 10 mg and 15 mg Orodispersible Tablets in the treatment of

- schizophrenia in adults and in adolescents aged 15 years and older
- moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment
- up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older

is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions.

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.

Questions to be posed to additional experts

N/A

Inspection issues

GMP inspection(s)

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

GCP inspection(s)

A request for GCP inspection is made for the following clinical studies: **ARIP-1K-537-13** and **ARIP-1K-653-13**.

The outcome of these inspections and the satisfactory responses to its findings are part of the responses to the LoQ and will be needed by Day 121.

Rationale: **ARIP-1K-537-13: Orodispersible Tablets**
Pre-dose drug concentrations greater than 5% of C_{max} were found for three subjects (S02, S03 and S10) previous to administration of study drug in period I; the applicant did not provide any explanation for this unexpected finding.

Rationale: **ARIP-1K-653-13: Tablets**
Pre-dose drug concentrations greater than 5% of C_{max} were found for three subjects (S26, S33 and S36) previous to administration of study drug in period I; the applicant did not provide any explanation for this unexpected finding.

Various reasons (e.g. mix-up of samples from different periods, mislabeling, analytical problems, false data entry into the chromatography system, violation of inclusion criteria, etc.) could be envisioned,

many of them suggesting GCP non-compliance. As long as these issues are not sufficiently clarified, the validity of the entire BE-studies is questionable.

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. generic application referring to a reference medicinal product. In 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. The reference medicinal product was first authorized in the community on 04th June 2004 via the centralized procedure.

2.2. About the product

According to the CPMP 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/Aripiprazole 10 mg and 15 mg Orodispersible Tablets against EU reference product ABILIFY® tablets/ABILIFY® Orodispersible Tablets of Otsuka Pharmaceutical Europe Ltd, United Kingdom in different dissolution media, to waive bioequivalence studies for the addition strengths.

The active ingredient and the route of administration are the same for reference and generic products (ABILIFY tablets/ Orodispersible tablets and Aripiprazole Mylan tablets/ Orodispersible tablets).

A comparison of the qualitative composition of the reference medicinal products (ABILIFY tablets/ orodispersible tablets) and the applicant´s products Aripiprazole Mylan (tablets/orodispersible 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

	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	Vanilla flavour

	vanillin and ethyl vanillin)	
	Tartaric acid	-
	Magnesium stearate	Magnesium stearate
	Red iron oxide (E172)	-
	-	Mannitol (E421)

Additionally, the proposed SPC for Aripiprazole Mylan (tablets/ orodispersible tablets) is based on the SPC 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 ^{11}C-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 metabolizers of CYP2D6 and approximately 146 hours in poor metabolizers 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 schizophrenic 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.
- 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.

Posology and method of administration

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. 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.

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.

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 aripirazole 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. Doses higher than 10 mg/day should therefore only be used in exceptional cases and with close clinical monitoring.
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.

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.

Tics associated with Tourette's disorder: the safety and efficacy of ABILIFY in children and adolescents 6 to 18 years of age 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.

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.

Gender: no dosage adjustment is required for female patients as compared to male patients.

Smoking status: according to the metabolic pathway of Aripiprazole Mylan no dosage adjustment is required for smokers.

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.
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.

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

Scientific advice

Formal scientific advice was not sought in the development of this medical product.

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

GMP

Active ingredient aripiprazole

A QP declaration () on behalf of all involved QPs responsible for the finished product manufacture and release of the drug product has been provided by batch releaser, stating that the active ingredient aripiprazole, is manufactured in accordance with GMP; the declaration is based on an on-site audit .

Due to the requested redefinition of one of the starting materials in the drug substance manufacture (see confidential part of the ASMF AR), new QP declarations regarding the manufacturer(s) have to be provided

For the drug substance manufacturer a GMP certificate has been provided issued by the competent authority of AustriaFor the drug product manufacturer a GMP certificate has been provided issued by Department of Health and Ageing, Therapeutic Goods Administration, Australian Government.

GCP

The applicant confirms that the BE-study was conducted as per the Ethical guidelines for biomedical research on human participants, ICMR (2006), ICH (Step 5) 'Guidance on Good Clinical Practice', Schedule Y (amended version, 2005) of CDSCO, 'Good Laboratory Practice', 'Good Clinical Practices for Clinical Research in India' Guidelines, Good clinical laboratory practice (GCLP), Declaration of Helsinki (Seoul 2008) and EMA guidelines and by adhering to the Standard Operating Procedures laid down by Micro Therapeutic Research Labs Private Limited.

A list of Good Clinical Practice (GCP) inspections conducted by other regulatory authorities related to the trial sites involved is found in Annex I (as attachment to the cover letter, Module I).

However, two major concerns with regard to the validity of the BE studies are raised at present and therefore, a GCP inspection is requested.

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. generic application referring to a reference medicinal product.

For this application, the reference medicinal products authorized in the Community/Member State not less than 10 years ago, with recognized efficacy and an acceptable level of safety, are ABILIFY® 10 mg, 15 mg Orodispersible Tablets and ABILIFY® 5 mg, 10 mg, 15 mg, 30 mg Tablets. The medicinal products were first authorized in the community on 04th June 2004 via the centralized procedure.

This application is for a generic form of Aripiprazole Tablets in strengths of 5mg, 10mg, 15mg and 30mg and Orodispersible Tablets in strengths of 10mg and 15 mg. The reference products used in the BE studies are ABILIFY® Tablets/Orodispersible Tablets 10 mg of Otsuka Pharmaceutical Europe Ltd. Hunton House, Highbridge Business Park, Oxford Road Uxbridge - Middlesex UB8 1HU. The active ingredient and the route of administration are the same for both products.

3. Scientific overview and discussion

This abridged application is for a generic form of Aripiprazole Tablets in strengths of 5 mg, 10 mg, 15 mg and 30 mg and Aripiprazole Orodispersible Tablets in strengths of 10 mg and 15 mg, submitted under Article 10.1 of Directive 2001/83/EC.

The original products are ABILIFY® (Aripiprazole) Tablets and ABILIFY® (Aripiprazole) Orodispersible Tablets of Otsuka Pharmaceutical Europe Ltd. Hunton House, Highbridge Business Park, Oxford Road Uxbridge - Middlesex UB8 1HU -United Kingdom, first authorized in the community on 04th June 2004 via the centralized procedure. ABILIFY® (Aripiprazole) Tablets are available in strengths of 5 mg, 10 mg, 15 mg and 30 mg in EU. ABILIFY® (Aripiprazole) Orodispersible Tablets are available in strengths of 10 and 15 mg in EU.

3.1. Quality aspects

3.1.1. Introduction

The applied drug products are immediate release tablets/orodispersible tablets containing the single active substance aripiprazole; four strengths (5 mg, 10 mg, 15 mg and 30 mg) are described.

3.1.2. Active Substance

General Information

Aripiprazole is a drug substance that is described in the Ph. Eur. An ASMF with a letter of access is provided

Manufacture, characterisation and process controls

The manufacturing process is described in the confidential part of the ASMF – a redefinition of one of the starting materials has been requested.

The structure of aripiprazole was confirmed adequately. Detailed information on potential impurities (i. e. organic & inorganic impurities, organic solvents, genotoxic impurities) is provided; nevertheless, this section should be updated regarding genotoxic impurities.

Specification

The specifications of aripiprazole were set in accordance with the specific Ph. Eur. monograph as well as general requirements. The specification limits for residual solvents are also in line with Ph. Eur. limits.

Analytical methods were taken from the Ph. Eur. monograph; additional methods for control of polymorphism and residual solvents are adequately described and validated.

The batch data are considered sufficient and comply with set specifications.

Stability

Sufficient stability data of the API was provided. An in-house impurity was found in the course of these tests, for which adequate control should be explained. Moreover, a re-test period should be proposed.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The drug product Aripiprazole Mylan is an immediate release tablet/orodispersible tablet containing the active substance aripiprazole and it is available in strengths of 5 mg, 10 mg, 15 mg and 30 mg (tablets) and 10 mg and 15 mg (orodispersible tablets).

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 specification of the drug product contain adequate parameters for a tablet/an orodispersible tablet.

Stability of the product

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 12 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. A shelf-life of 24 months has been proposed for the drug product packed in HDPE bottles and cold form blister pack without any special storage condition. The proposed shelf-life is acceptable.

According to results of the in-use stability study Aripiprazole Mylan tablets are stable up to 100 days after opening the HDPE bottle pack.

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 12 months have been provided. For the drug product packed in bulk shipment pack a shelf life of 12 months is declared if stored in the original package in order to protect from moisture. A shelf-life of 24 months has been proposed for the drug product packed in cold form blister pack if stored in the original package in order to protect from moisture. The proposed shelf-life of the drug product packed in bulk shipment pack/ cold form blister pack is acceptable whereas the storage condition should be deleted in accordance to presented stability data.

Comparability exercise for Finished Medicinal Drug Product

Not applicable.

Adventitious agents

Not applicable.

3.1.4. Discussion on chemical, pharmaceutical and biological aspects

Drug Substance

Overall, the drug substance is adequately documented, but one of the proposed starting materials for the synthesis cannot be accepted and due to the requested starting material redefinition a major objection has been raised. Apart from this, a few other concerns have been raised. Regarding stability

of the API, some OOS for an impurity has been noticed and this should be explained as well as a re-test period should be set.

Drug Product

Orodispersible Tablets:

There are some other concerns identified for Aripiprazole Mylan orodispersible tablets. The maximum batch size has to be reduced in order not to exceed 10-fold of the maximum allowable production scale size and consequently the batch formula has to be revised. A process validation scheme has to be submitted with the revised maximum production scale size. Regarding the specifications the limit of the water content in the release and shelf-life specifications should be adjusted according to actual results. Some information and confirmations are missing in the sections regarding reference standards and container closure system. According to the presented stability data and based on the fact that aripiprazole is not hygroscopic the proposed storage condition is not endorsed and should be deleted in the SmPC, labelling and package leaflet.

Tablets:

There are some other concerns identified for the drug product. Clarification is awaited about the container sizes of the strengths intended to be marketed and the quantity of tablets per bottle. It is unclear which container sizes of the HDPE bottles were used during the stability study. In addition, it should be explained which container size has been used during the in-use stability study and the use of only one container size has to be justified. Regarding the specifications the limit of the water content in the release and shelf-life specifications should be adjusted according to actual results. Some information and confirmations are missing in the sections regarding reference standards and container closure system. The batch formula has to be revised in order to include all indicated production scale batch sizes. Apart from the raised other concerns the documentation of the drug product is adequate and the proposed shelf-life of 24 months without any special storage condition is acceptable.

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

A major objection has been raised for the drug substance aripiprazole and there are various other concerns regarding the drug substrance and the drug product. From the quality point of view Aripiprazole Mylan orodispersible tablets/tablets could only be recommended for approval if the major objection/ starting material redefinition will be adequately answered and if the questions regarding the applicant's part/restricted part of the ASMF and regarding the drug product can be resolved and the requested information is provided.

3.2. Non clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of aripiprazole are well known. As aripiprazole is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is thus appropriate.

The non-clinical overview is dated 11 April 2014. The report refers to 25 publications up to year 2013.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

3.2.1. Pharmacology

N/A

3.2.2. Pharmacokinetics

N/A

3.2.3. Toxicology

N/A

3.2.4. Ecotoxicity / environmental risk assessment

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

This was justified by the applicant as the introduction of Aripiprazole Mylan Tablets/Orodispersible Tablets is considered unlikely to result in any significant increase in the combined sales volumes for all aripiprazole containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

3.2.5. Conclusion on non-clinical aspects

There are no objections to approval of Aripiprazole Mylan Tablets/Orodispersible Tablets from a non-clinical point of view.

3.3. Clinical aspects

Exemption

- **Tabular overview of clinical studies**

Type of study	Study identifier	Location of study report	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	Study Status; Type of report
BA	Not Applicable								
BE	ARIP-1K-653-13	Module 5, Section 5.3.1.2	1. To evaluate the oral bioequivalence of Aripiprazole 10 mg tablets of Mylan Laboratories Limited, India and ABILIFY® (Aripiprazole) Tablets 10 mg of Otsuka Pharmaceutical Europe Ltd. Hunton House, Highbridge Business Park, Oxford Road Uxbridge - Middlesex UB8 1HU - UK (Mfd. By Bristol-Myers Sqibb S.r.l, Italy). in healthy, adult, human subjects under fasting conditions. 2. To monitor the adverse events and ensure safety of subjects.	An open-label, balanced, randomized, single-dose, two-treatment, two-period, two-sequence, two-way crossover, oral bioequivalence study in healthy, adult, human subjects under fasting conditions.	**Reference Product:** ABILIFY® (Aripiprazole) 10 mg Tablets Lot No.: 1B63270 Exp date: Aug 2013 of Otsuka Pharmaceutical Europe Ltd. Hunton House, Highbridge Business Park, Oxford Road Uxbridge - Middlesex UB8 1HU – UK (Mfd. By Bristol-Myers Sqibb S.r.l, Italy). One tablet, single dose, oral **Test Product:** Aripiprazole 10 mg Tablets Batch No. : 2001593 Mfg. date: Dec 2012 Exp date : Nov 2014 Manufactured by: Mylan Laboratories Limited, Aurangabad, India Single dose, oral	39 subjects (inclusive of 03 standbys) healthy, human adult subjects were enrolled, 33 subjects completed the study and data from 29* subjects is reported. *4 subjects were excluded from pharmacokinetic and statistical analysis as their pre-dose concentration was greater than 5% of Cmax. Criteria: 40 Years or above with a Body Mass index (BMI) range between 18.50 kg/m^2 and 30.00 kg/m^2	Healthy, adult, human male subjects	Single Dose	Complete; Abbreviated

Type of study	Study identifier	Location of study report	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	Study Status; Type of report
BA	Not Applicable								
BE	ARIP-1K-537-13	Clinical Study Report & PK report And adverse Event Listing Clinical Study **(5.3.1.2)** Literature References **(5.4)**	To evaluate the oral bioequivalence of Aripiprazole Orodispersible Tablets 10 mg of Mylan Laboratories Limited, India and ABILIFY® (Aripiprazole) Orodispersible Tablets 10 mg of Otsuka Pharmaceutical Europe Ltd. Hunton House, High bridge Business Park, Oxford Road Uxbridge – Middlesex UB8 1HU – United Kingdom in healthy, adult, human subjects under fasting conditions. To monitor the adverse events and ensure safety of subjects.	**Design:** An open-label, balanced, randomized, single-dose, two treatment, two period, two sequence, two way crossover, Oral bioequivalence study in healthy, adult, human subjects under fasting conditions. **Type of Control:** No treatment/	**Reference Product:** ABILIFY® (Aripiprazole) 10 mg Orodispersible tablets Lot No.: 1B62895 Exp date: Apr 2013 of Otsuka Pharmaceutical Europe Ltd. Hunton House High bridge Business Park. Oxford Road Uxbridge-Middlesex UB8 1HU-United Kingdom. **Test Product:** Aripiprazole Orodispersible Tablets 10 mg; Batch No.: 2001816 Manufactured date: Jan 2013 Expiry date: Dec 2014 Manufactured by: Mylan Laboratories Limited, Aurangabad, India. **Dosage Regimen:** Single oral dose **Route of Administration:** Oral	Planned: 36 Enrolled: 37 Completed: 32 Analyzed: 22 Withdrawn: Nil Range: 40 years or above	Healthy, adult, human male subjects.	Single dose	Complete abbreviated

3.3.1. Pharmacokinetics

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

Tablets:
To support the application, the applicant submitted an open-label, balanced, randomized, single-dose, two-treatment, two-period, two-sequence, two-way crossover oral bioequivalence study (ARIP–1K-653-13) of Aripiprazole 10 mg Tablets and ABILIFY® (Aripiprazole) 10 mg Tablets in healthy adult human subjects under fasting conditions.

Study No: ARIP–1K-653-13, based on Protocol Version: 01, Dated: 21 May 13 and the Informed Consent Documents (English and Vernacular languages) were reviewed and approved by Independent Ethics Committee (Chennai Ethics Committee) on 31 May 13.
Protocol Amendment no.: 01, Dated: 06 Jul 13 and additional ICD's were prepared and reviewed by CEC on 10 Jul 13.

Orodispersible Tablets:
To support the application, the applicant submitted one single-dose bioequivalence (BE) study (ARIP-1K-537-13) with Aripiprazole Orodispersible Tablets 10 mg.

3.3.1.1. Study No: ARIP–1K-653-13

Study Title
An open-label, balanced, randomized, single-dose, two-treatment, two-period, two-sequence, two-way crossover, oral bioequivalence study of Aripiprazole Tablets 10 mg of Mylan Laboratories Limited, India and ABILIFY® (Aripiprazole) Tablets 10 mg of Otsuka Pharmaceutical Europe Ltd. Hunton House, Highbridge Business Park, Oxford Road Uxbridge - Middlesex UB8 1HU – United Kingdom in healthy, adult, human subjects under fasting conditions.

Study design
The study was conducted as an open-label, balanced, randomized, single-dose, two treatment, two-period, two-sequence, two-way crossover, oral bioequivalence study in healthy, adult, human subjects under fasting conditions comparing equal doses of aripiprazole in the test and reference products. Subjects were housed in the clinical facility from at least 11.00 hours prior to dosing to at least 72.00 hours post dose in each period. Subjects were provided with a standard diet and appropriate water and posture restrictions and also continuously monitored for well-being and safety throughout the study.

STUDY CENTRES: ***Clinical Services:*** Micro Therapeutic Research Labs Private Limited, No.6, Kamarajar Salai, Selaiyur, East Tambaram,Chennai - 600 059, Tamil Nadu, India.

Date of study activities (Clinical Phase):

S. No	Study Events	Date
Clinical Phase		
01	Date of first enrollment of subjects (Check in of Period I)	15 Jul 13
02	Date of check-in of Period II	21 Aug 13
03	Date of dosing of Period I	16 Jul 13
04	Date of dosing of Period II	22 Aug 13
05	Date of check out of Period I	19 Jul 13
06	Date of check out of Period II	25 Aug 13
07	Date of post study safety sample collection	25 Aug 13 & 28 Aug 13*
08	Date of last adverse event follow-up	11 Oct 13
Bioanalytical Phase		
01	Analysis Start date	26 Sep 2013
02	Analysis End date	07 Oct 2013

Note: *- For subject no. S19, safety sample was collected on 28 Aug 13.

After an overnight fasting of at least 10.00 hours, in the morning, a single oral dose of investigational products (either T or R) was administered (as per the randomization schedule) with 240 mL of water at ambient temperature, to the subject(s) in sitting posture under supervision of the Investigator(s) and Quality Assurance auditor(s). Blood sampling were carried at pre-defined intervals up to 72.00 hours after dosing of each period.

As per study protocol, standard diet was served at around 04.00, 09.00, 13.00, 25.00, 29.00, 33.00, 37.00, 49.00, 53.00, 57.00 and 61.00 hours post-dose to all the subjects in each period.
The clinical study duration was 42 days with the washout of 37 days between the dosing days of two periods.

Collection of the blood samples
A total of 23 (06 mL each) blood samples were collected per subject in each period. The 00.00 hr blood samples was collected within 75 min before dosing and post dose samples were collected at 00.33, 00.67, 01.00, 01.50, 02.00, 02.50, 03.00, 03.50, 04.00, 04.50, 05.00, 05.50, 06.00, 07.00, 08.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and 72.00 hours after dosing . A window period of ± 02 mins from the scheduled time was allowed for all in-house post dose blood draws.

CHMP review

According to the EMA Guidance (CPMP/EWP/QWP/1401/98 Rev.1 Cor**) the design of the study is considered adequate.
The sampling period of 72 hours is sufficient to characterize the plasma concentration-time profile. Blood sampling points are appropriate to allow an accurate measurement of Tmax.

The drug administrations were separated by a washout of 37 days. It is appropriate since mean elimination half-lives (T1/2) for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately 146 hours in poor metabolisers of CYP2D6. Therefore the washout period (at least 5 times the terminal half-life) is adequate.

The study was conducted under fasting conditions. Since literature and the SmPC of the reference product ABILIFY® give no recommendation for administration of the drug in relation to food and food intake does not affect the absorption of the active substance, this is adequate.
Aripiprazole exhibits linear pharmacokinetics within the 5-30 mg and the bioequivalence study should be conducted at the highest strength. However due to serious safety concerns the highest strength cannot be administered to healthy volunteers. 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.
Therefore the dose selection (10 mg) is considered adequate.

Test and reference products
Certificates of analysis of the test and reference product have been presented by the applicant (Assay: Reference 10 mg: 101.3% and test 10 mg: 102.4%). The CHMP was of the view that the batch size of the test product was acceptable.

Population(s) studied
Healthy adult, human subjects of age 40 years or above with a Body Mass Index (BMI) range between 18.50 kg/m2 and 30.00 kg/m2 (according to the formula of BMI = weight (kg) / [height (m)]2), whose screening was performed within 29 days of check in, whose screening clinical laboratory assessments and vital sign assessments (during screening and check-in), 12-lead electrocardiogram (ECG), chest X-Ray (taken within 06 months), systolic BP more than or equal to 110 mm hg and diastolic BP more than or equal to 70 mm hg and heart rate more than 60 were within normal limits or considered by the Physician or Principal/Clinical Investigator to be of no clinical significance and who were willing to consume ova-lacto vegetarian diet were enrolled into the study.

CHMP review

In general, the study population chosen is in the line with current bioequivalence guidance. The objectives of the conducted study as listed in the protocol mention healthy subjects of either sex, but only male subjects were included. Nevertheless, this is acceptable as literature reports no gender-related differences in Aripiprazole pharmacokinetic.

It is noted, that the occurrence of dystonias appears to be rare at ages of approximately 45 years and higher (USFDA Draft Guideline, Aripiprazole; 2005). Therefore subjects younger than 45 years of age should be excluded, as well as subjects with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, since the reference product contains lactose. The applicant is asked to comment on the choice of exclusion criteria with regard to the safety/wellbeing of study subjects in line with GCP requirements and any potential influence on the outcome of the study.

Analytical methods

Sample re-assays for Aripiprazole were done on 15 samples (0.95%). All re-assays are in accordance with the presented SOP and the relevant guideline.
Incurred sample reanalysis (ISR) of Aripiprazole has been performed on 152 samples from both study periods (~10% of total samples analysed, subjects 4, 8, 12, 15, 17, 20 – 23, 25, 27, 31, 32, 35 not included); 151 out of 152 ISR samples (~99.34%) were within 20% from the mean value.

Representative chromatograms were provided for sample runs from 8 (#1-8) out of 36 subjects (above 20%).
The CHMP was of the view that the analytical method for the determination of Aripiprazole in human plasma as well as respective validations (including partial validations) were described adequately; 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, but for some validation parameters data is insufficient.

In the bioanalytical report, study-specific data for inter-batch accuracy and precision has been provided, but the LLOQ has not been considered (in the method validation report, LLOQ data is provided, but is identical with the data provided for study ARIP-1K-537-13, so considered not study-specific!); for the LLOQ, also study-specific data for inter-batch accuracy and precision should be provided according to guideline requirements.
Moreover, intra-batch accuracy and precision (at LLOQ, low QC, medium QC, high QC) has not been calculated – this should also be done.

Pharmacokinetic Variables
The pharmacokinetic parameters (Primary parameters: C_{max} and AUC_{0-72} and Secondary parameters: tmax, $t_{1/2}$ & K_{el}) were estimated in order to characterize rate and extent of absorption of the investigational drug products (Table: 2).

C_{max}	:	Maximum measured plasma concentration following each treatment.
t_{max}	:	Time of the maximum measured plasma concentration
AUC_{0-72}	:	The area under the plasma concentration versus time curve from time zero to 72.00 hrs post-dose as calculated by linear trapezoidal method
Kel (or) λz	:	First order rate constant associated with the terminal (log-linear) portion of the curve. This is estimated via linear regression of time vs. log concentration. This parameter will be calculated by linear least square regression analysis using at least last three or more non-zero plasma concentration values.
$t_{1/2}$	:	The elimination or terminal half-life will be calculated as 0.693/ Kel.

The mean (arithmetic & geometric), standard deviation (SD), coefficient of variation (CV %), minimum, median, maximum were calculated for C_{max}, AUC_{0-72}, tmax, $t_{1/2}$ & K_{el}, respectively.

The pharmacokinetic variables were considered by the CHMP to be adequate.

Statistical methods
For Aripiprazole, analysis of variance (ANOVA) was performed on the Ln-transformed data of C_{max} and AUC_{0-72} using mixed procedure of SAS® (version 9.2) software. The analysis of variance model included sequence, period, treatment and subject (sequence) as fixed effects at 5% level of the significance. For all analysis, effects were considered statistically significant if the probability (p-value) associated with 'F' was less than 0.05 and these results are tabulated in table 24. Based on comparisons of the test and reference product for L_n transformed C_{max} and AUC_{0-72} data, ratio of the least square mean, intra-subject CV %, power and 90% confidence interval was determined.
Additionally, Descriptive Statistics (arithmetic mean, standard deviation (SD), coefficient of variation (CV %), minimum, median, maximum) were calculated for Aripiprazole for all pharmacokinetic parameters C_{max}, AUC_{0-72}, t_{max}, $t_{1/2}$ and K_{el} using SAS statistical software (Version 9.2).

Criteria for Evaluation:

The 90% confidence interval of the relative mean Cmax and AUC0-72 (of Aripiprazole) of test to the reference product should be between 80.00% and 125.00% for Ln-transformed data.

CHMP review

Statistical evaluation of the PK parameters are in accordance with the bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev.1 Cor**). The statistical methods are considered adequate.

Results

Table 3: Summary of Pharmacokinetic Profile of Test product (T) of Aripiprazole (N=29)

Pharmacokinetic Parameter	Arithmetic Mean ± Standard Deviation	Coefficient of Variation	Median	Minimum	Maximum
C_{max} (ng/mL)	51.2364±11.3796	22.2101	49.4490	35.8490	82.1190
AUC_{0-72} (ng.hr/mL)	1919.9519±397.0477	20.6801	1934.2785	1085.1109	2591.6193
t_{max} (hr)	4.29±1.69	39.47	4.00	1.50	8.02
K_{el} (1/hr)	0.0091±0.0029	32.2989	0.0086	0.0041	0.0152
$t_{1/2}$ (hr)	85.2788±29.6857	34.8102	81.0625	45.7361	167.0412

Table 4: Summary of Pharmacokinetic Profile of Reference product (R) of Aripiprazole (N=29)

Pharmacokinetic Parameter	Arithmetic Mean ± Standard Deviation	Coefficient of Variation	Median	Minimum	Maximum
C_{max} (ng/mL)	47.3578±9.9024	20.9097	47.7430	24.8680	67.0180
AUC_{0-72} (ng.hr/mL)	1784.8758±391.7862	21.9503	1832.9542	960.2785	2377.6370
t_{max} (hr)	3.88±1.92	49.40	3.50	1.00	8.00
K_{el} (1/hr)	0.0094±0.0033	35.4593	0.0095	0.0035	0.0162
$t_{1/2}$ (hr)	84.5511±35.4913	41.9761	72.6175	42.8433	197.1358

Summary statistic of Test product (T) versus Reference product (R) for aripiprazole by including the subjects S04, S26, S33 and S36 were provided in below table as supportive information.

Table 5: Summary of Pharmacokinetic Profile of Test product (T) of Aripiprazole (N=33)

Pharmacokinetic Parameter	Arithmetic Mean ± Standard Deviation	Coefficient of Variation	Median	Minimum	Maximum
C_{max} (ng/mL)	51.7701±11.5110	22.2349	50.2060	35.8490	82.1190
AUC_{0-72} (ng.hr/mL)	1974.6060±437.3322	22.1478	1935.6568	1085.1109	2892.3008
t_{max} (hr)	4.12±1.68	40.73	4.00	1.50	8.02
K_{el} (1/hr)	0.0086±0.0031	36.0905	0.0083	0.0033	0.0152
$t_{1/2}$ (hr)	93.1692±38.7572	41.5987	83.7094	45.7361	209.9520

Table 6: Summary of Pharmacokinetic Profile of Reference product (R) of Aripiprazole (N=33)

Pharmacokinetic Parameter	Arithmetic Mean ± Standard Deviation	Coefficient of Variation	Median	Minimum	Maximum
C_{max} (ng/mL)	48.2674±10.8953	22.5728	47.7430	24.8680	70.3590
AUC_{0-72} (ng.hr/mL)	1848.9114±445.7878	24.1108	1850.9154	960.2785	3121.8138
t_{max} (hr)	3.82±1.84	48.21	3.50	1.00	8.00
K_{el} (1/hr)	0.0092±0.0035	38.4591	0.0093	0.0018	0.0162
$t_{1/2}$ (hr)	93.3148±62.1747	66.6290	74.4492	42.8433	383.0787

Table 7: Statistical Results of Test product (T) versus Reference product (R) for Aripiprazole (N=29)

Pharmacokinetic Parameter	Geometric Least Square Mean*		Intra Subject CV %	T/R Ratio %	90% Confidence Interval	Power %
	Test Product (T)	Reference Product (R)				
C_{max} (ng/mL)	50.2042	46.1100	17.34	108.88	100.77 - 117.64	99.41
AUC_{0-72} (ng.hr/mL)	1887.4887	1738.6992	9.68	108.56	103.94 - 113.38	100.0

*Estimate of Least square mean

Statistical Results of Test product (T) versus Reference product (R) for aripiprazole by including the subjects S04, S26, S33 and S36 were provided in below table as supportive information.

Table 8: Statistical Results of Test product (T) versusu Reference product (R) for Aripiprazole (N=33)

Pharmacokinetic Parameter	Geometric Least Square Mean*		Intra Subject CV %	T/R Ratio %	90% Confidence Interval	Power %
	Test Product (T)	Reference Product (R)				
C_{max} (ng/mL)	50.5348	47.0179	17.27	107.48	100.06 - 115.46	99.76
AUC_{0-72} (ng.hr/mL)	1922.5981	1793.5633	11.37	107.19	102.24 - 112.39	100.0

*Estimate of Least square mean

A total number of 39 subjects (inclusive of 03 standbys) were enrolled into the study. Out of these 39 enrolled subjects, 36 participated and 33 completed both the periods of the study.
Samples from 33 subjects were analyzed to determine the concentrations of aripiprazole and samples from subject nos. S10 and S18 were analyzed for safety reasons. Pharmacokinetic and statistical analysis was performed on data obtained from 29 subjects who completed the study. All concentration values below the lower limit of quantification (LLOQ) were set to "zero" for all pharmacokinetic and statistical calculations.
Note: As per section 17 point no. 03 in protocol "Subjects exhibiting pre-dose levels higher than 5% of C_{max} will be excluded from pharmacokinetic and statistical analysis"; hence subjects S04, S26, S33 and S36 were excluded from the pharmacokinetic and statistical analysis.

Table 9: Subjects excluded from pharmacokinetic and statistical analysis

Subject no.	Reason for dropout/replacement	Period	Pre-dose/ Post-dose	Date /Time	Replaced?	Replaced with
S10	Withdrawn from the study due to adverse event	II	Pre-Dose	22 Aug 13 / 08:32 Hrs	No	N/AP
S18	Withdrawn from the study due to adverse event & vomiting occurred at or before 2 times of t_{max}	II	Post-Dose	22 Aug 13 / 12:56 Hrs	No	N/AP
S19	Withdrawn from the study due to positive results of "Urine screen for drugs of abuse" test	II	Pre-Dose	21 Aug 13 / 18:05 Hrs	No	N/AP
S04	Pre-dose concentration was greater than 5% of C_{max}	II	N/AP	N/AP	N/AP	N/AP
S26	Pre-dose concentration was greater than 5% of C_{max}	I	N/AP	N/AP	N/AP	N/AP
S33	Pre-dose concentration was greater than 5% of C_{max}	I	N/AP	N/AP	N/AP	N/AP
S36	Pre-dose concentration was greater than 5% of C_{max}	I	N/AP	N/AP	N/AP	N/AP

N/AP – Not applicable

CHMP review

A total number of 39 subjects (inclusive of 3 standbys) were enrolled into the study; 36 participated and 33 completed both periods of the study. In the pharmacokinetic and statistical analysis the applicant included 29 subjects. Four subjects were excluded from the statistical analysis and their data were provided in a supportive document (inclusive pharmacokinetic evaluation including 33 subjects) since their pre-dose concentrations were higher than 5% of Cmax for the respective period (see Tab. 9 above). Formally, the applicant fulfilled the recommendations of the current guideline on bioequivalence with respect to the exclusion of study subjects. Also, the results of the pharmacokinetic and statistical analysis including 29 subjects as well as the analysis including all 33 subjects (supportive data) indicate that the reference and test product are bioequivalent.

However, the BE guideline clearly refers to the scenario of a carry-over effect and insufficient wash out period. It is considered problematic, that pre-dose concentrations greater than 5% of Cmax were found in three subjects (S26, S33 and S36) previous to administration of study drug in period I. The applicant did not comment this finding or provide an explanation.
Various reasons (e.g. mix-up of samples from different periods, mislabeling, analytical problems, false data entry into the chromatography system, violation of inclusion criteria, etc.) could be envisioned, many of them suggesting GCP non-compliance. As long as these issues are not sufficiently clarified, the validity of the entire BE-Study is questionable. A GCP inspection of the BE study is proposed (see section 1).

Conclusion: Due to the identified concern, the results of this study cannot be accepted at present and thus bioequivalence between Aripiprazole Mylan5mg, 10mg, 15mg and 30 mg tablets and Abilify® tablets cannot be concluded.

Safety data

A total of four adverse events were reported in the study, all of which were found to be “mild” in intensity. Out of the four adverse events, two events were reported during the in-house stay and were completely “resolved” without any sequelae. The other two adverse events which were recorded after the evaluation of post study laboratory assessments were deemed “lost to follow up” by the Investigator. Of these four adverse events, three were concluded as ‘related’ (possible) to the administration of investigational products and remaining one was concluded as ‘not related’ to the administration of study products. There were no deaths or Serious Adverse Events reported in the study.

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

Justification for requesting biowaiver for additional strength(s)

According to the CPMP Note for Guidance on Investigation of Bioavailability and Bioequivalence (2010) and Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1 – January. 2010), Aripiprazole 5 mg, 15 mg and 30 mg tablets satisfy the conditions for waiver of bioequivalence studies with Aripiprazole 10 mg tablets strength of the product as discussed below:

- All the strengths of Aripiprazole tablets are manufactured by the same manufacturer at the same manufacturing site using similar manufacturing process.
- The qualitative composition of all the strengths is same.
- All the four strengths are direct scale up/scale down formulations and the ratio between the amounts of each excipient to the amount of active substance is the same for all strengths.
- The *in vitro* test of dissolution characteristics demonstrates that dissolution profiles of Aripiprazole 5 mg, 15 mg, 30 mg and 10 mg tablets are similar.
- The absorption kinetics of Aripiprazole is linear within the therapeutic dose range.

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 common 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 has generated the dissolution profiles of the generic Aripiprazole tablets and EU reference product ABILIFY® tablets, in different dissolution media i.e. 0.1N Hydrochloric acid (Release media), pH 4.5 Acetate buffer and pH 6.8 Phosphate buffer.

- **0.1N Hydrochloric acid (Release media)**

More than 85% of the labeled amount of drug (aripiprazole) released within 15 minutes from both test and the reference product. Therefore, as per the provisions mentioned in CPMP guidance on the

Investigation of Bio-equivalence –CPMP/EWP/QWP/1401/98-Rev 01 – January 2010, the dissolution profiles can be considered as similar without further mathematical calculations.

- **pH 4.5 Acetate buffer**

The Applicant has calculated the similarity factor (f2 value) as given below:

- Between the EU reference product (ABILIFY® 10 mg comprimés) and the test product (Aripiprazole 10 mg tablets) used in the bio-equivalence study.
- Between the Applicant test product Aripiprazole 10 mg tablets used in the bioequivalence study and the other strengths of the test product i.e. Aripiprazole 5 mg, 15 mg and 30 mg tablets.

The similarity factor (f2) value between the test product and the EU reference product used in the bioequivalence study was found to be more than 50. Also, the similarity factor (f2 value) between the test product strength used in the bio-equivalence study and all other strengths of the test products is found to be between 50 and 100. Therefore, as per the provisions mentioned in CPMP guidance on the *Investigation of Bio-equivalence – CPMP/EWP/QWP/1401/98-Rev 01 – January 2010*, the dissolution profiles can be considered as similar without further mathematical calculations.

- **pH 6.8 Phosphate buffer**

The applicant has calculated the similarity factor (f2 value) as given below:

- Between the EU reference product (ABILIFY® 10 mg comprimés) and the test product (Aripiprazole 10 mg tablets) used in the bio-equivalence study.
- Between the applicant test product Aripiprazole 10 mg tablets used in the bioequivalence study and the other strengths of the test product i.e. Aripiprazole 5 mg, 15 mg and 30 mg tablets.

The similarity factor (f2) value between the test product and the EU reference product used in the bioequivalence study was found to be more than 50. Also, the similarity factor (f2 value) between the test product strength used in the bio-equivalence study and all other strengths of the test products is found to be more than 50. Therefore, as per the provisions mentioned in CPMP guidance on the *Investigation of Bio-equivalence –CPMP/EWP/QWP/1401/98-Rev 01 – January 2010*, the dissolution profiles can be considered as similar without further mathematical calculations.

Conclusion:

The following conclusions can be drawn based on the above discussion,

- All the strengths of the test and reference products are found to be similar (more than 85% released in 15 minutes) in 0.1N Hydrochloric acid (release dissolution media).

- The drug release profile between the test product i.e. Aripiprazole 10 mg tablets and EU reference product i.e. ABILIFY® 10 mg comprimés used in the bioequivalence study is found to be similar in the following media:

  - pH 4.5 Acetate buffer (f2 is more than 50)
  - pH 6.8 Phosphate buffer (f2 is more than 50)

- The drug release profile between the strength of test product i.e. Aripiprazole 10 mg tablets used in the bioequivalence study and other strengths of the test product Aripiprazole 5 mg, 15 mg and 30 mg tablets is found to be similar across the physiological pH range.

    - pH 4.5 Acetate buffer (f2 is more than 50)
    - pH 6.8 Phosphate buffer (f2 is more than 50)

Since, all the requirements to waive bioequivalence studies for oral solid dosage forms as mentioned in CPMP guidance on the *Investigation of Bio-equivalence –CPMP/EWP/QWP/1401/98-Rev 01 – January 2010* are fulfilled, the bio-equivalence study results of Aripiprazole 10 mg tablets can be extended to Aripiprazole 5 mg, 15 mg and 30 mg tablets.

Since the 5 mg, 15 mg and 30 mg strengths of Aripiprazole tablets fulfils all the requirements to waive bioequivalence studies for additional strengths as mentioned in *CPMP guideline on the Investigation of Bio-equivalence – CPMP/EWP/QWP/1401/98- Rev 01 – January 2010,* the bio-equivalence study results of Aripiprazole 10 mg tablets can be extended to Aripiprazole 5 mg, 15 mg and 30 mg tablets.

CHMP review

All strengths of Aripiprazole 5mg, 10 mg, 15 mg and 30mg Tablets are manufactured by the same manufacturer at the same manufacturing site using similar manufacturing process.

The unit composition for Aripiprazole 5 mg, 10mg, 15mg and 30 mg Tablets (different strengths) is the same.

Aripiprazole exhibits linear pharmacokinetics over the therapeutic dose range.

With regard to the dissolution profiles of aripiprazole tablets, 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 ARIP-1K-653-13 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 API 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).

Pharmacokinetic Conclusion

The Applicant conducted a bioequivalence study of Aripiprazole Tablets 10 mg of Mylan Laboratories Limited, India and ABILIFY® (aripiprazole) Tablets 10 mg of Otsuka Pharmaceutical Europe Ltd. Hunton House, Highbridge Business Park, Oxford Road Uxbridge - Middlesex UB8 1HU - Royaume-Uni in healthy adult subjects under fasting conditions (**Study No: ARIP–1K-653-13).**

Since aripiprazole exhibits linear pharmacokinetics within the 5-30 mg dose range it is sufficient to establish bioequivalence with only one strength. The highest strength (30 mg) cannot be administered due to potential serious safety concerns and use of the 5 mg strength would not be adequate for detecting a difference between products due to analytical challenges. Therefore, selection of a single 10 mg dose is acceptable, in line with the current BE-Guideline.

Four subjects were excluded from the statistical analysis since their pre-dose concentrations were higher than 5% of C_{max} for the respective period. Formally, the applicant fulfilled the recommendations of the current guideline on bioequivalence with respect to the exclusion of subjects from bioanalytical calculations. Also, the results of the pharmacokinetic and statistical analysis including 29 subjects (main analysis) as well as the analysis including all 33 subjects (supportive data) indicate that the reference and test product are bioequivalent.
However, the BE guideline clearly refers to the scenario of a carry-over effect and insufficient wash out period. It is considered problematic, that pre-dose concentrations greater than 5% of C_{max} were found in three subjects (S26, S33 and S36) previous to administration of study drug in period I. The applicant did not comment this finding or provide an explanation.
There are several reasons as to why pre-dose plasma samples may contain measurable drug concentrations (e.g. mix-up of samples from different periods, mislabeling, analytical problems, violation of inclusion criteria, etc.), many of them suggesting potential GCP non-compliance. As long as these issues are not sufficiently clarified, the validity of the entire BE-Study is questionable. A GCP inspection of the BE study is proposed (see section 1)

Due to the identified concern, the results of this study cannot be accepted at present and thus bioequivalence between Aripiprazole Mylan5mg, 10mg, 15mg and 30 mg tablets and Abilify® tablets cannot be concluded.

Furthermore, the biowaiver to extrapolate the bioequivalence study ARIP-1K-653-13 to the additional strengths of 15 mg and 30 mg is presently not acceptable.

3.3.1.2. Study No: ARIP-1K-537-13

Study Title
An open-label, balanced, randomized, single-dose, two-treatment, two-period, two-sequence, two-way crossover, oral bioequivalence study of Aripiprazole Orodispersible Tablets 10 mg of Mylan Laboratories Limited, India and ABILIFY® (Aripiprazole) Orodispersible Tablets 10 mg of Otsuka Pharmaceutical Europe Ltd. Hunton House, Highbridge Business Park, Oxford Road Uxbridge - Middlesex UB8 1HU - United Kingdom in healthy, adult, human subjects under fasting conditions.

Study design
The study was conducted as an open-label, balanced, randomized, single-dose, two treatment, two-period, two-sequence, two-way crossover, oral bioequivalence study in healthy, adult, human subjects under fasting conditions comparing equal doses of aripiprazole in the test and reference products. Subjects were housed in the clinical facility from at least 11.00 hours prior to dosing to at least 72.00 hours post dose in each period. Subjects were provided with a standard diet and appropriate water and posture restrictions and also continuously monitored for well-being and safety throughout the study.

STUDY CENTRES: ***Clinical Services:*** Micro Therapeutic Research Labs Private Limited, No.6, Kamarajar Salai, Selaiyur, East Tambaram,Chennai - 600 059, Tamil Nadu, India.

Date of study activities:

S.No	Study Events	Dates
	Clinical Phase	
1.	Date of first enrollment of subjects (Check in of period I)	24 Mar 13
2.	Date of Check-in of Period II	23 Apr 13
3.	Date of Dosing of Period I	25 Mar 13
4.	Date of Dosing of Period II	24 Apr 13
5.	Date of Check out of Period I	28 Mar 13
6.	Date of Check out of Period II	27 Apr 13
7.	Date of post study safety sample collection	27 Apr 13
	Bioanalytical Phase	
1.	Analysis Start date	13 June 2013
2.	Analysis End date	26 June 2013

The study protocol and annexures was prepared and IEC approval was obtained before start of the study. A total of 37 (inclusive of 01 standby subject) healthy, adult, human male subjects were enrolled into the study. The eligible subjects, who fulfilled the inclusion and exclusion criteria for the study, were enrolled and randomly assigned to one of the possible sequences of test product (T) and reference product (R) (either TR or RT) in consecutive order using SAS® (SAS Institute Inc., USA) version 9.2.
After overnight fasting of at least 10.00 hours, in the morning of each period, about 20 mL of water was given to the subjects to wet the mouth.

Study was conducted over a period of 35 days with a washout period of 30 days between each treatment.

Standard meal was provided at 04.00, 09.00, 13.00, 25.00, 29.00, 33.00, 37.00, 49.00, 53.00, 57.00 and 61.00 post-dose to all subjects. Water was restricted to 01.00 hrs pre-dose to until 01.00 post dose except for the 20 mL of water given during dosing. Postural restrictions (supine position) were maintained for at least 08.00 hours after dosing starting no longer than 15 minutes after each dose and only necessary movement were allowed during this period. Subjects were accompanied by custodians at all levels and were allowed to ambulate freely during the remaining part of the study.

Collection of the blood samples:
Totally 23 samples were collected at specified time points at 00.00 (pre-dose), 00.33, 00.67, 01.00, 01.50, 02.00, 02.50, 03.00, 03.50, 04.00, 04.50, 05.00, 05.50, 06.00, 07.00, 08.00, 10.00, 12.00, 16.00, 24.00, 36.00, 48.00 and at 72.00 hours in labeled K3EDTA – vaccutainers.

CHMP review

According to the EMA Guidance (CPMP/EWP/QWP/1401/98 Rev.1 Cor**) the design of the study is considered adequate. The orodispersible tablets (ODT) were taken without water (20 ml water was given to the subjects to wet the mouth). It is in the line with Bioequivalence Guidance since the reference medical product can be taken with or without water. The sampling period of 72 hours is sufficient to characterize the plasma concentration-time profile. Blood sampling points are appropriate to allow an accurate measurement of Tmax.
Drug administrations were separated by a washout of 30 days. The mean elimination half-lives (T1/2) for aripiprazole are approximately 75 hours in extensive metabolisers of CYP2D6 and approximately

146 hours in poor metabolisers of CYP2D. According to guideline on the investigation of bioequivalence, a wash-out period of at least 5 elimination half-lives is necessary. The washout period seems to be too short for poor metabolizer. The applicant should comment this issue.
The study was conducted under fasting conditions. Since literature and the SmPC of the reference product give no recommendation for administration of the drug in relation to food and food intake does not affect the absorption of the active substance this is adequate.
Aripiprazole exhibits linear pharmacokinetics within the 5-30 mg and the bioequivalence study should be conducted at the highest strength. However due to serious safety concerns the highest strength cannot be administered to healthy volunteers. Therefore the dose selection (10 mg) is acceptable.

Test and reference products
Certificates of analysis of the test and reference product have been presented by the applicant (Assay: Reference 10 mg: 99.2% and test 10 mg: 102.0%). The CHMP considered that the batch size of the test product was acceptable.

Population(s) studied
Healthy, adult, human subjects of age 40 years or above with a Body Mass Index (BMI) ranges between 18.50 kg/m2 to 30.00 kg/m2 (according to the formula of BMI = weight (kg) / [height (m)]2), Subjects who have no evidence of underlying disease during screening and check-in and whose screening is performed within 29 days of check-in, Subjects whose screening laboratory values are within normal limits or considered by the physician or principal/clinical investigator to be of no clinical significance, Absence of disease markers of HIV 1 & 2, hepatitis B & C virus and RPR., Systolic BP more than or equal to 110 mm hg and diastolic BP more than or equal to 70 mm hg and heart rate more than 60, Generally healthy as documented by the medical history, physical examination (including but may not be limited to an evaluation of the cardiovascular, gastrointestinal, respiratory, musculoskeletal and central nervous systems) 12-lead electrocardiogram (ECG), X-Ray, clinical laboratory assessments and vital sign assessments, Willing to give written consent and adhere to all the requirements of this protocol and Willing to take ova-lacto vegetarian diet.

CHMP review

In general, the study population chosen is in the line with current bioequivalence guidance. The objective of the conducted study listed in the protocol mentioned healthy subjects of either sex. In this study were included only male subjects. Nerveless the population chosen is acceptable as literature reports no gender-related differences in aripiprazole pharmacokinetic.

It is noted, that the occurrence of dystonias appears to be rare at ages of approximately 45 years and higher (USFDA Draft Guideline, Aripiprazole; 2005). Therefore subjects younger than 45 years of age should be excluded. Moreover according to study protocol (Section 10.1 “Screening”): “The screening interview should include specific questions to exclude subjects with a prior personal or family history of dystonic reactions to medications. Prospective study subjects should also be specifically questioned about prior neuroleptic drug exposures. Also ensure that subjects are free of illicit drugs at the time of administration of each study drug dose”. Those exclusion criteria have not been clearly described in Study Report. The Applicant is asked to comment on the choice of exclusion criteria with regard to the safety/wellbeing of study subjects in line with GCP requirements and any potential influence on the outcome of the study.

Analytical methods

Sample reassays for Aripiprazole were done on 9 samples (0.61%). All reassays are in accordance with the presented SOP and the relevant guideline.

Incurred sample reanalysis (ISR) of Aripiprazole has been performed on 152 samples from both study periods (~10% of total samples analysed, subjects 4, 8, 12, 15, 17, 20 – 23, 25, 27, 31, 32, 35 not included); 150 out of 152 ISR samples (~98.68%) were within 20% from the mean value.

Representative chromatograms were provided for sample runs from 8 (#1-8) out of 36 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) were described adequately; 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 but for some validation parameters data is insufficient.

In the bioanalytical report, study-specific data for inter-batch accuracy and precision has been provided, but the LLOQ has not been considered (in the method validation report, LLOQ data is provided, but is identical with the data provided for study ARIP-1K-653-13, so considered not study-specific!); for the LLOQ, also study-specific data for inter-batch accuracy and precision should be provided according to guideline requirements.
Moreover, intra-batch accuracy and precision (at LLOQ, low QC, medium QC, high QC) has not been calculated – this should also be done.

Long-term stability of analyte in matrix was shown over 67 days, which is insufficient with respect to the intended sample storage as the clinical phase started on March 25 2013 and analytical phase ended on June 26 2013; in the course of method validation of study ARIP-1K-653-13 (Aripiprazole tablets), an addendum to the long-term stability was provided, which gave proof of long-term stability of analyte in matrix over 115 days – this data is considered applicable also for study ARIP-1K-537-13. No further question.

Pharmacokinetic Variables

The pharmacokinetic parameters (Primary parameters: C_{max} and AUC_{0-72} and Secondary parameters: tmax, $t_{1/2}$ & K_{el}) were estimated in order to characterize rate and extent of absorption of the investigational drug products (Table: 2).

Table: 2 Pharmacokinetics variables

C_{max}	:	Maximum measured plasma concentration following each treatment.
t_{max}	:	Time of the maximum measured plasma concentration
AUC_{0-72}	:	The area under the plasma concentration versus time curve from time zero to 72.00 hrs post-dose as calculated by linear trapezoidal method
Kel (or) λz	:	First order rate constant associated with the terminal (log-linear) portion of the curve. This is estimated via linear regression of time vs. log concentration. This parameter will be calculated by linear least square regression analysis using at least last three or more non-zero plasma concentration values.
$t_{1/2}$	:	The elimination or terminal half-life will be calculated as 0.693/ Kel.

The mean (arithmetic & geometric), standard deviation (SD), coefficient of variation (CV %), minimum, median, maximum were calculated for C_{max}, AUC_{0-72}, tmax, $t_{1/2}$ & K_{el}, respectively.

The CHMP was of the view that the pharmacokinetic variables were adequate.

Statistical methods

The pharmacokinetic evaluation was carried out at Micro Therapeutic Research Labs Private Limited, Chennai, India by using WinNonlin® software (version 5.3).

For Aripiprazole, analysis of variance (ANOVA) was performed on the Ln-transformed data of Cmax and AUC0-72 using mixed procedure of SAS® (version 9.2) software. The analysis of variance model included sequence, period and treatment as fixed effect and the subjects nested within the sequence as random effect. Sequence effect was tested using subject nested within sequence as the error term at 10% level of the significance. All other main effects were tested at 5% level of the significance. For all analysis, effects (period & treatment) were considered statistically significant if the probability (p-value) associated with 'F' was less than 0.05 and sequence effect was considered statistically significant if the probability (pvalue) associated with 'F' was less than 0.1. Based on comparisons of the test and reference product for Ln-transformed Cmax and AUC0-72 data, the ratio of the least square mean was calculated, as well as the 90% confidence intervals for Ln-transformed Cmax and AUC0-72 and also the intra-subject CV % was determined.

The CHMP was of the view that the statistical evaluation of the PK parameters were in accordance with the bioequivalence guideline (CPMP/EWP/QWP/1401/98 Rev.1 Cor**). The statistical methods were considered adequate.

Results

A total number of 37 subjects (inclusive of 01 standby subject) were enrolled into the study. Of the 37 enrolled subjects, 36 subjects participated in the study. Of the 36 participated subjects, 32 subjects completed the study. Samples from 32 subjects were analyzed to determine the concentrations of Aripiprazole. Pharmacokinetic and statistical analysis was performed on data obtained from 22 subjects (as per protocol) who completed the study. All concentration values below the lower limit of quantification (LLOQ) were set to "zero" for all pharmacokinetic and statistical calculations. Subject no. S01, S02, S03, S10, S15, S24, S26, S27, S29 and S30 were excluded from the pharmacokinetic and statistical analysis (as per protocol) as their pre-dose concentration was greater than 5% of Cmax for the respective period.

Note: Subject no. S01, S02, S03, S10, S15, S24, S26, S27, S29 and S30 were included for the Pharmacokinetic and statistical analysis and are provided as a supportive document.

Table 3: Descriptive Statistics of pharmacokinetic parameters for Test product (T) of Aripiprazole (N=22)

Pharmacokinetic Parameter	Arithmetic Mean ± Standard Deviation	Coefficient of Variation	Median	Minimum	Maximum
C_{max} (ng/mL)	39.5554 ± 12.0605	30.4900	38.9605	5.4970	69.3050
AUC_{0-72}(ng.hr/mL)	1543.2168 ± 382.4676	24.7838	1640.0961	223.6948	1918.6294
t_{max} (hr)	5.55 ± 2.54	45.71	4.50	1.50	12.00
K_{el} (1/hr)	0.0100 ±0.0044	44.3347	0.0089	0.0025	0.0232
$t_{1/2}$ (hr)	85.0304 ± 49.9124	58.6995	78.5438	29.9136	278.1333

Table 4: Descriptive Statistics of pharmacokinetic parameters for Reference product (R) of Aripiprazole (N=22)

Pharmacokinetic Parameter	Arithmetic Mean ± Standard Deviation	Coefficient of Variation	Median	Minimum	Maximum
C_{max} (ng/mL)	35.6422 ± 12.5220	35.1326	35.6965	11.7680	62.2760
AUC_{0-72}(ng.hr/mL)	1385.3188 ± 329.1507	23.7599	1440.7206	600.5393	1943.2604
t_{max} (hr)	6.05 ± 4.58	75.80	4.50	1.00	24.00
K_{el} (1/hr)	0.0098 ± 0.0037	37.8905	0.0110	0.0038	0.0156
$t_{1/2}$ (hr)	85.8247 ± 43.0435	50.1528	63.0052	44.3808	182.0517

Subject no. S01, S02, S03, S10, S15, S24, S26, S27, S29and S30 were included for the Pharmacokinetic and statistical analysis and provided as a supportive document.

Table 5: Descriptive Statistics of pharmacokinetic parameters for Test product (T) of Aripiprazole (N=32)

Pharmacokinetic Parameter	Arithmetic Mean ± Standard Deviation	Coefficient of Variation	Median	Minimum	Maximum
C_{max} (ng/mL)	40.7413±10.9262	26.8186	40.3600	5.4970	69.3050
AUC_{0-72}(ng.hr/mL)	1669.5106±431.1212	25.8232	1780.2167	223.6948	2781.3436
t_{max} (hr)	5.66±2.73	48.18	4.50	1.50	12.00
K_{el} (1/hr)	0.0092±0.0042	45.7780	0.0083	0.0023	0.0232
$t_{1/2}$ (hr)	95.0273±58.0432	61.0806	83.9505	29.9136	302.6525

Table 6: Descriptive Statistics of pharmacokinetic parameters for Reference product (R) of Aripiprazole (N=32)

Pharmacokinetic Parameter	Arithmetic Mean ± Standard Deviation	Coefficient of Variation	Median	Minimum	Maximum
C_{max} (ng/mL)	37.9599±11.6974	30.8151	37.1195	11.7680	62.2760
AUC_{0-72}(ng.hr/mL)	1518.1463±388.1088	25.5647	1506.0262	600.5393	2633.2124

Table 7: Statistical Results of Test product (T) versus Reference product (R) for, Aripiprazole (N=22)

Pharmacokinetic Parameter	Geometric Least Square Mean		T/R Ratio %	90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product (T)	Reference Product (R)				
C_{max} (ng/mL)	35.6055	33.0714	107.66	93.77 to 123.62	26.58	77.53
AUC_{0-72} (ng.hr/mL)	1426.6213	1342.8328	106.24	94.85 to 118.99	21.69	89.88

Subject no. S01, S02, S03, S10, S15, S24, S26, S27, S29 and S30 were included for the statistical analysis and are provided as a supportive document.

Table 8: Statistical Results of Test product (T) versus Reference product (R) for, Aripiprazole (N=32)

Pharmacokinetic Parameter	Geometric Least Square Mean		T/R Ratio %	90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product (T)	Reference Product (R)				
C_{max} (ng/mL)	38.5102	35.8650	107.38	97.18 to 118.65	23.85	95.06
AUC_{0-72} (ng.hr/mL)	1581.3596	1463.3719	108.06	99.95 to 116.84	18.55	99.37

37 subjects (inclusive of 01 standby subject) were enrolled into the study. Of the 37 enrolled subjects, 36 subjects participated in the study. Of the 36 participated subjects, 32 subjects completed the study. Samples from 32 subjects (excluding subject no.S21, S31, S35 & S36 were not reported to the facility for Period II participation) were analyzed to determine the concentrations of aripiprazole. Pharmacokinetic and statistical analysis was performed on data obtained from 32 subjects who completed the study. The missing concentration data were presented as "M". The details of missing samples are presented in below tables:

Table 9: Missing samples details

Subject No.	Sample Time Point (hrs)	Schedule Time of collection (hh:mm)	Comments
Period II			
S21	All Time Points		Subject did not report to the facility for period II participation
S31	All Time Points		Subject did not report to the facility for period II participation
S35	All Time Points		Subject did not report to the facility for period II participation
S36	All Time Points		Subject did not report to the facility for period II participation

Table 10: Additional (supported) pharmacokinetic data for Aripiprazole in ARIP-1K-537-13

Record descriptor	Related information			
$AUC_{(0-t)}/AUC_{(0-\infty)}<0.8$	NA			
Cmax is the first point	NA			
Pre-dose sample > 5% Cmax	Period-I		Period-II	
	Test	Reference	Test	Reference
	02	03, 10	01, 10, 15, 24, 26 and 29	02, 27, 30

Note: Subject no. S01, S02, S03, S10, S15, S24, S26, S27, S29 and S30 were excluded from the Pharmacokinetic and statistical analysis as their pre-dose concentration was greater than 5% of C_{max} for the respective period.

CHMP review

Overall, 37 subjects (inclusive of 01 standby subject) were included in the study. Subject S21, S31, S35 & S36 did not report to the facility for Period II participation, therefore 32 subjects completed the study.

In the pharmacokinetic and statistical analysis the applicant included 22 subjects. Ten subjects were excluded for the statistical analysis and their data were provided as a supportive document (inclusive pharmacokinetic evaluation included 32 subjects) since their pre-dose concentrations were higher than 5% of Cmax for the respective period (see Tab. 10).

Formally, the applicant fulfilled the recommendations of the current guideline on bioequivalence with respect to the exclusion of study subjects. Also, the results of the pharmacokinetic and statistical analysis including 22 subjects as well as the analysis including all 32 subjects (supportive data) indicate that the reference and test product are bioequivalent.

However, the BE guideline clearly refers to the scenario of a carry-over effect and insufficient wash out period. It is considered problematic, that pre-dose concentrations greater than 5% of Cmax were found in three subjects (S02, S03 and S10) previous to administration of study drug in period I. The applicant did not comment this finding or provide an explanation.

Various reasons (e.g. mix-up of samples from different periods, mislabeling, analytical problems, false data entry into the chromatography system, violation of inclusion criteria, etc.) could be envisioned, many of them suggesting GCP non-compliance. As long as these issues are not sufficiently clarified, the validity of the entire BE-Study is questionable. A GCP inspection of the BE study is proposed (see Section 1)

CHMP conclusion:

Due to the identified concern, the results of this study cannot be accepted at present and thus bioequivalence between Aripiprazole Mylan 10 mg and 15 mg orodispersible tablet and Abilify orodispersible tablet cannot be concluded.

Safety data

There were 03 adverse events reported in the study, out of which 01 adverse event was considered to have possible relationship with the administration of study medication and 02 adverse events were considered unrelated to the administration of study medication. Details are listed below.

- Elevated cholesterol was reported for subject no. S12. The event was ‘Mild’ in intensity and was considered to have no relationship with the administration of study medication. Subject was found normal over examination, hence investigator advised the subject to follow diet control and visit the facility for follow-up for lipid profile test in fasting conditions after two months. The adverse event was considered as ‘ongoing’ by the investigator.
- Elevated cholesterol was reported for subject no. S18. The event was ‘Mild’ in intensity and was considered to have no relationship with the administration of study medication. Subject was found normal over examination, hence investigator advised the subject to follow diet control and visit the facility for follow-up for lipid profile test in fasting conditions after two months. The adverse event was considered as ‘ongoing’ by the investigator.
- Elevated level of SGOT & SGPT was reported for Subject no. S25. The event was ‘Mild’ in intensity and was considered to have a possible relationship with the administration of study medication. Subject was found normal over examination, hence investigator advised the subject to restrict OTC drugs and to follow a diet rich in carbohydrates and less in protein. The adverse event was considered as ‘ongoing’ by the investigator.

There were no serious adverse events in the study.

The CHMP noted that there were 3 adverse events reported in the study. Overall, the two formulations were well tolerated, with no apparent differences in safety profiles.

Justification for requesting biowaiver for additional strength(s):

According to the CPMP Guideline on the Investigation of Bioequivalence *(CPMP/EWP/QWP/1401/98 Rev. 1 – January 2010),* Aripiprazole 15 mg Orodispersible tablets satisfy the conditions for waiver of bioequivalence studies conducted on Aripiprazole 10 mg Orodispersible tablets as discussed below:

- Both the strengths of Aripiprazole Orodispersible 10 mg and 15 mg tablets are manufactured by the same manufacturer at the same manufacturing site using similar manufacturing process.
- The qualitative composition of both the strengths of Aripiprazole 10 mg and 15 mg Orodispersible tablets is the same.
- Aripiprazole 10 mg and 15 mg Orodispersible tablets are direct scale up/scale down formulations and the ratio between the amounts of each excipient to the amount of the active substance is the same.
- The *in vitro* dissolution characteristics demonstrates that dissolution profiles of Aripiprazole 10 mg and 15 mg Orodispersible tablets of Mylan Laboratories Limited' s are similar across the physiological pH range i.e. pH 1.2- pH 6.8.
- Pharmacokinetics are linear with respect to time and dose

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 15 mg tablet formulations.
The most common 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 and 15 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 has generated dissolution profiles of generic Aripiprazole 10 mg and 15 mg Orodispersible tablets and EU reference product Abilify® (Aripiprazole) 10 mg Orodispersible tablets in following media.

- pH 4.0 Acetate buffer (Release media)
- 0.1N Hydrochloric acid
- pH 4.5 Acetate buffer
- pH 6.8 Phosphate buffer

Parameter	**Conditions**
Dissolution media:	pH 4.0 Acetate buffer (Release media) 0.1N Hydrochloric acid pH 4.5 Acetate buffer pH 6.8 Phosphate buffer
Dissolution apparatus:	USP Type - II (Paddle)/EP Apparatus - II
RPM:	75
Volume:	900 ml
Temperature:	37° C ± 0.5° C
Sampling time (for profile study only) :	5, 10, 15, 20, 30, 45 and 60 minutes

pH 4.0 Acetate buffer (Release media)

The applicant has calculated the similarity factor (f2) between

- Test product (Aripiprazole 10 mg Orodispersible tablets) and EU reference product (Abilify® (aripiprazole) 10 mg Orodispersible tablets) used in bioequivalence studies
- Test product used in bioequivalence studies and test product of higher strength i.e. Aripiprazole 15 mg Orodispersible tablets

The similarity factor (f2 value) between the test product and EU reference product i.e. Abilify® (aripiprazole) 10 mg Orodispersible tablets was found to be more than 50. Therefore as per the provisions mentioned in *CPMP guidance on the Investigation of Bioequivalence – CPMP/EWP/QWP/1401/98-Rev 01 – January 2010*, the dissolution profiles can be considered as similar.

More than 85% of the labeled amount of drug (aripiprazole) released within 15 minutes from the test batch used in bioequivalence study and test product of higher strength i.e. Aripiprazole 15 mg Orodispersible tablets. Therefore, as per the provisions mentioned in CPMP guidance on the *Investigation of Bio-equivalence –CPMP/EWP/QWP/1401/98-Rev 01 – January 2010*, the dissolution profiles can be considered as similar without further mathematical calculations.

0.1N Hydrochloric acid

More than 85% of the labeled amount of drug (aripiprazole) released within 15 minutes from all the test batches (Aripiprazole 10 mg and 15 mg Orodispersible tablets) and EU reference product i.e. Abilify® (aripiprazole) 10 mg Orodispersible tablets.

Therefore, as per the provisions mentioned in CPMP guidance on the Investigation of Bioequivalence – CPMP/EWP/QWP/1401/98-Rev 01 – January 2010, the dissolution profiles can be considered as similar without further mathematical calculations.

pH 4.5 Acetate buffer

The Applicant has calculated the similarity factor (f2) between the following

- Test product (Aripiprazole 10 mg Orodispersible tablets) and EU reference product(Abilify® (Aripiprazole) 10 mg Orodispersible tablets) used in bioequivalence studies
- Test product used in bioequivalence studies (Aripiprazole 10 mg Orodispersible tablets) and test product batch of Aripiprazole 15 mg Orodispersible tablets

The results are tabulated below:

The similarity factor (f2 value) between the test product (Aripiprazole 10 mg Orodispersible tablets) and EU reference product i.e. Abilify® (aripiprazole) 10 mg Orodispersible tablets was found to be less than 50. Though the f2 value is below 50, the reference product and test product are proven to be bio-equivalent.

The similarity factor (f2 value) between the test product used in bio studies and higher strength (i.e. Aripiprazole 15 mg Orodispersible tablets was found to be more than 50. Therefore as per the provisions mentioned in CPMP guidance on the Investigation of Bio-equivalence – CPMP/EWP/QWP/1401/98-Rev 01 – January 2010, the dissolution profiles can be considered as similar.

pH 6.8 Phosphate buffer

Drug release observed in pH 6.8 phosphate buffer was significantly low (a maximum of 9% release was observed). Hence, the calculation of similarity factor does not have any significance. This insignificant release can be attributed to the fact that aripiprazole Ph. Eur. drug substance is insoluble in pH 6.8 Phosphate buffer.

CHMP review

Both strengths of Aripiprazole Orodispersible tablets 10 mg and 15 mg are manufactured by the same manufacturer at the same manufacturing site using similar manufacturing process. The unit composition for Aripiprazole 10 mg and 15 mg Orodispersible tablets (different strengths) is the same. Aripiprazole exhibits over the therapeutic dose range linear pharmacokinetics. The dissolution profiles are similar under identical conditions within the range pH 1-1.6 (pH 1.1 (0.1N) 4.0; 4.5; 6.8) for the additional strengths and the strength used in the BE-study.

Since the he similarity factor (f2 value) between the test product (Aripiprazole 10 mg Orodispersible tablets B.No: 2001816) and EU reference product i.e. Abilify® (aripiprazole) 10 mg Orodispersible tablets in pH 4.5 Acetate buffer was found to be less than 50. However the exact batches of reference product and test product were used in the BE-Study and are proven to be bio-equivalent. 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 the difference in dissolutions profiles between the 10 mg batches in not considered critical.

All the biowaiver criteria are accepted as fulfilled and thus the biowaiver claim is acceptable.

Pharmacokinetic Conclusion

The applicant conducted a bioequivalence study of Aripiprazole Orodispersible Tablets 10 mg and ABILIFY® (Aripiprazole) Orodispersible Tablets 10 mg **(No.ARIP-1K-537-13**).

Since aripiprazole exhibits linear pharmacokinetics within the 5-30 mg dose range it is sufficient to establish bioequivalence with only one strength. The highest strength cannot be administered due to potential serious safety concerns. Therefore, selection of a single 10 mg dose is acceptable, in line with the current BE-Guideline.

All of the biowaiver criteria (general requirements) are considered fulfilled and thus the biowaiver claim is acceptable.

Ten subjects were excluded from the statistical analysis since their pre-dose concentrations were higher than 5% of C_{max} for the respective period. Formally, the applicant fulfilled the recommendations of the current guideline on bioequivalence with respect to the exclusion of study subjects. Also, the results of the pharmacokinetic and statistical analysis including 22 subjects as well as the analysis

including all 32 subjects (supportive data) indicate that the reference and test product are bioequivalent.

However, the BE guideline clearly refers to the scenario of a carry-over effect and insufficient wash out period. It is considered problematic, that pre-dose concentrations greater than 5% of C_{max} were found in three subjects (S02, S03 and S10) previous to administration of study drug in period I. The applicant did not comment this finding or provide an explanation.
Various reasons (e.g. mix-up of samples from different periods, mislabeling, analytical problems, violation of inclusion criteria, etc.) could be envisioned, many of them suggesting GCP non-compliance. As long as these issues are not sufficiently clarified, the validity of the entire BE-Study is questionable. A GCP inspection of the BE study is proposed (see section 1)

Due to the identified concern, the results of this study cannot be accepted at present and thus bioequivalence between Aripiprazole Mylan 10 mg and 15 mg orodispersible tablet and Abilify orodispersible tablet cannot be concluded.

3.3.2. Pharmacodynamics

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

3.3.3. Additional data

Pack sizes:
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.

3.3.4. Post marketing experience

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

3.3.5. Discussion on clinical aspects

The applicant conducted two studies investigating bioequivalence of Aripiprazole Mylan10mg 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 10mg strength is acceptable.

Study No: ARIP–1K-653-13

Four subjects were excluded from the statistical analysis since their pre-dose concentrations were higher than 5% of C_{max} for the respective period. Formally, the applicant fulfilled the recommendations of the current guideline on bioequivalence with respect to the exclusion of subjects from bioanalytical calculations. Results of the pharmacokinetic and statistical analyses, both the main analysis including 29 subjects as well as the supportive analysis of 33 subjects indicate that the reference and test product are bioequivalent.

However, it is considered problematic, that pre-dose concentrations greater than 5% of C_{max} were found in three subjects (S26, S33 and S36) previous to administration of study drug in period I. The applicant did not comment this finding or provide an explanation.

Study No. ARIP- 1K-537- 13

Ten subjects were excluded from the statistical analysis since their pre-dose concentrations were higher than 5% of C_{max} for the respective period. Formally, the applicant fulfilled the recommendations of the current guideline on bioequivalence with respect to the exclusion of study subjects. Also, the results of the pharmacokinetic and statistical analysis including 22 subjects as well as the analysis including all 32 subjects (supportive data) indicate that the reference and test product are bioequivalent.
However, the BE guideline clearly refers to the scenario of a carry-over effect and insufficient wash out period. It is considered problematic, that pre-dose concentrations greater than 5% of C_{max} were found in three subjects (S02, S03 and S10) previous to administration of study drug in period I.

The applicant did not comment this finding or provide an explanation.

There are several reasons as to why pre dose plasma samples may contain measurable drug concentrations. According to the current guideline on bioequivalence data from these subjects should be excluded from bioequivalence calculations. However, the BE guideline clearly refers to the scenario of a carry-over effect and insufficient wash out period. The situation here is more alarming, because it remains unclear why 3 subjects had measurable drug concentrations before study drug intake in period I. This has not been addressed by the applicant and needs to be investigated properly; a thorough discussion of possible causes and of the consequences as to the credibility of study results is expected.

Two major concerns with regard to the validity of the BE studies are raised at present and a GCP inspection of the BE studies is proposed.

3.3.6. Conclusions on clinical aspects

In the presence of measurable pre- dose concentrations in period I greater than 5% of Cmax, the validity of the BE studies is questionable. Presently, due to the identified concerns, the results of these studies cannot be accepted and thus bioequivalence between Aripiprazole Mylan and Abilify® cannot be concluded.

Furthermore, the biowaiver to extrapolate the bioequivalence study ARIP-1K-653-13 to the additional strengths of 15 mg and 30 mg tablets is presently not acceptable.

3.4. Pharmacovigilance system

The applicant has submitted a Pharmacovigilance System Master File Summary (Version 5, dated 27 November 2013):

A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse

reaction suspected of occurring either in the Community or in a third country.

3.5. Risk management plan

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

The PRAC considered that the risk management plan version 1.0 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

4. Benefit/risk assessment

The application contains adequate non-clinical data; several quality issues – including a major objection regarding starting material redefinition – have to be clarified before approval could be granted.

The clinical data are presently considered inadequate. Two major concerns with regard to the validity of the BE studies and a major objection regarding the dissolution profiles of aripiprazole tablets are raised. The aspects that are inadequately demonstrated are outlined in the List of Questions.

A benefit/risk ratio comparable to the reference product can only be concluded once all outstanding issues (major objections and other concerns) raised in the list of questions are resolved.