OGYÉI
National Institute of
Pharmacy and Nutrition

H-1051 Budapest, Zrínyi u. 3.
1372 P.O. Box:450.
Tel: +36 1 88 69-300, Fax: +36 1 88 69 460
E-mail: ogyei@ogyei.gov.hu, Web: www.ogyei.gov.hu

Public Assessment Report

Name of the Product:

Asduter
10 mg, 15 mg, 30 mg tablets

(aripiprazole)

Procedure number: HU/H/0366/001-003/DC

Marketing authorisation holder: Vipharm S.A.

Date: 7 July 2015

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Asduter 10 mg, 15 mg and 30 mg tablets. The holder of the marketing authorisation is Vipharm S.A.

The active substance is aripiprazole. Each tablet contains 10 mg or 15 mg or 30 mg of aripiprazole, respectively.

The other ingredients are lactose monohydrate, maize starch, microcrystalline cellulose, hydroxypropyl cellulose, magnesium stearate, iron oxide red (E172) (for 10 mg and 30 mg) and iron oxide yellow (for 15 mg) and silica, colloidal anhydrous.

The 10 mg tablets are light red, round, flat-faced, bevelled-edge ones of 5.8 – 6.2 mm size. The 15 mg tablets are light yellow, round, flat-faced, bevelled-edge ones of 6.8 – 7.2 mm size. The 30 mg tablets are light red, round, flat-faced, bevelled-edge ones of 8.8 – 9.2 mm size.

The tablets are in OPA/Aluminium/PVC/Aluminium blisters packed in HDPE containers with push-fit tamper-evident cap equipped with dehumidifier with narrow-porous silica gel SMG.

Aripiprazole belongs to a group of medicines called antipsychotics. It is used to treat adults and adolescents aged 15 years and older who suffer from a disease characterised by symptoms such as hearing, seeing or sensing things which are not there, suspiciousness, mistaken beliefs, incoherent speech and behaviour and emotional flatness. People with this condition may also feel depressed, guilty, anxious or tense.

Asduter tablets are used to treat adults and adolescents aged 13 years and older who suffer from a condition with symptoms such as feeling "high", having excessive amounts of energy, needing much less sleep than usual, talking very quickly with racing ideas and sometimes severe irritability. In adults it also prevents this condition from returning in patients who have responded to the treatment with aripiprazole.

What patients need to know before taking Asduter?

Those who are allergic to aripiprazole or any of the other ingredients of this medicine, should not take Asduter tablets.

Warnings and precautions
Those who suffer from the following illnesses are advised to discuss their doctor before taking Asduter tablets:

- high blood sugar (characterised by symptoms such as excessive thirst, passing of large amounts of urine, increase in appetite, and feeling weak) or family history of diabetes;
- seizure;
- involuntary, irregular muscle movements, especially in the face;
- cardiovascular diseases, family history of cardiovascular disease, stroke or "mini" stroke, abnormal blood pressure;

- blood clots, or family history of blood clots, as antipsychotics have been associated with formation of blood clots;
- past experience of excessive gambling.

If patients notice they are gaining weight, develop unusual movements, experience somnolence that interferes with normal daily activities, any difficulty in swallowing or allergic symptoms, should tell it their doctor.

Elderly patients suffering from dementia (loss of memory and other mental abilities) should (or their carer/relative should) tell the doctor if they (the patient) patient have ever had a stroke or "mini" stroke.

Patients having any thoughts or feelings about hurting themselves should consult their doctor immediately. Suicidal thoughts and behaviours have been reported during aripiprazole treatment.

Patients suffering from muscle stiffness or inflexibility with high fever, sweating, altered mental status, or very rapid or irregular heart beat should consult their doctor immediately

Children and adolescents

Asduter tablets are not for use in children and adolescents under 13 years.

Other medicines and Asduter tablets

The patients should inform their doctor if they are taking, have recently taken or might take any other medicines.

Blood pressure-lowering medicines: Asduter tablets may increase the effect of medicines used to lower the blood pressure. Patients should be sure they have told their doctor if taking a medicine to keep the blood pressure under control.

Taking Asduter tablets with some other medicines may need to change the dose of Asduter tablets. It is especially important to mention the following medicines to the doctor:
- those to correct heart rhythm,
- antidepressants or any herbal remedy used to treat depression and anxiety,
- antifungal agents,
- certain medicines to treat HIV infection,
- anticonvulsants used to treat epilepsy.

Medicines that increase the level of serotonin: triptans, tramadol, tryptophan, SSRIs (such as paroxetine and fluoxetine), tricyclics (such as clomipramine, amitriptyline), pethidine, St John's Wort and venlafaxine. These medicines increase the risk of side effects. If the patient gets any unusual symptom taking any of these medicines together with Asduter tablets should see their doctor.

Asduter tablets with food, drink and alcohol

Asduter tablets can be taken regardless of meals. However, alcohol should be avoided when taking this medicine.

Pregnancy and breast-feeding

Patients who are pregnant should not take Asduter tablets unless advised by their doctor. The doctor should be informed immediately if the patient is pregnant, thinks she may be pregnant, or if she is planning to become pregnant. The following symptoms may occur in new-borns babies, of mothers that have used aripiprazole in the last trimester (last three months of their pregnancy): shaking, muscle stiffness and/or weakness, sleepiness, agitation, breathing problems, and difficulty in feeding.

If the baby develops any of these symptoms, the doctor needs to be contacted.

Breast-feeding women should consult their doctor immediately. When taking Asduter tablets, women should not breast-feed.

Driving and using machines

Patients should not drive or use any tools or machines, until knowing how Asduter tablets affect them.

Asduter tablets contain lactose

Those who have been told by their doctor that they have an intolerance to some sugars, contact their doctor before taking this medicine.

How to take Asduter tablets

The recommended dose for adults is 15 mg once a day. However, the doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day.

Use in children and adolescents above 13 years: Asduter tablets may be started at a low dose. The dose may be gradually increased to the recommended dose for adolescents of 10 mg once a day. However, the doctor may prescribe a lower or higher dose to a maximum of 30 mg once a day. As it is not possible to obtain lower doses than 5 mg with the use of Asduter tablets, the doctor may prescribe an aripiprazole-containing oral solution for this purpose.

Patients should try to take Asduter tablets at the same time each day. It does not matter whether they are taken it with or without food. However, Asduter tablets should always be taken with water and swallowed as a whole.

The patients, even if feeling better, should not alter or discontinue the daily dose of Asduter tablets without consulting the doctor.

What happens if more Asduter tablets have been taken than it should be?

If the patient realises having taken more Asduter tablets than the doctor has recommended (or if someone else has taken some of the patient's tablets), the doctor should be contacted right away. If the doctor cannot be reached, the patient should go to the nearest hospital taking the pack with him/her.

What to do if taking Asduter tablets has been forgotten?

If having one dose missed, the patient should take the missed dose as soon as realising it but two doses in one day should never be taken.

Possible side effects

Like all medicines, Asduter tablets can cause side effects, although not everybody experiences them.

Common side effects (that may affect up to 1 in 10 people): uncontrollable twitching or jerking movements, headache, tiredness, nausea, vomiting, an uncomfortable feeling in the stomach, constipation, increased production of saliva, light-headedness, trouble sleeping, restlessness, feeling anxious, sleepiness, shaking and blurred vision.

Uncommon side effects (that may affect up to 1 in 100 people): some people may feel dizzy, especially when getting up from a lying or sitting position, or may experience a fast heart rate or double vision. Some people may feel depressed.

In addition, the following side effects have been reported since the marketing of aripiprazole but their frequency is not known (it cannot be estimated from the available data):

- changes in the levels of some blood cells; unusual heart beat, sudden unexplained death, heart attack;
- allergic reactions (e.g. swelling in the mouth, tongue, face and throat, itching, rash); high blood sugar, onset or worsening of diabetes, ketoacidosis (ketones in the blood and urine) or coma,
- low sodium level in the blood; weight gain, weight loss, anorexia; nervousness, agitation, feeling anxious,
- excessive gambling; thoughts of suicide, suicide attempt and suicide; speech disorder, seizure,
- serotonin syndrome (a reaction which may cause feelings of great happiness, drowsiness, clumsiness,
- restlessness, feeling of being drunk, fever, sweating or rigid muscles), combination of fever, muscle
- stiffness, faster breathing, sweating, reduced consciousness and sudden changes in blood pressure and heart rate; fainting, high blood pressure, blood clots in the veins especially in the legs (symptoms include swelling, pain and redness in the leg), which may travel through

blood vessels to the lungs causing chest pain and difficulty in breathing (if anybody notices any of these symptoms, must seek medical advice immediately);
- spasm of the muscles around the voice box, accidental inhalation of food with risk of pneumonia, difficulty in swallowing; inflammation of the pancreas; liver failure, inflammation of the liver, yellowing of the skin and white part of eyes, reports of abnormal liver test values,
- abdominal and stomach discomfort, diarrhoea; skin rash and sensitivity to light, unusual hair loss or thinning, excessive sweating; stiffness or cramps, muscle pain, weakness;
- involuntary loss of urine, difficulty in passing urine; prolonged and/or painful erection;
- difficulty controlling core body temperature or overheating, chest pain, and swelling of hands, ankles or feet.

In elderly patients with dementia, more fatal cases have been reported while taking aripiprazole. In addition, cases of stroke or "mini" stroke have been reported.

Additional side effects in children and adolescents

Children/adolescents aged 13 years and older experienced side effects that were similar in frequency and type to those in adults except that
- sleepiness, uncontrollable twitching or jerking movements, restlessness, and tiredness were very common (greater than 1 in 10 patients) and
- upper abdominal pain, dry mouth, increased heart rate, weight gain, increased appetite, muscle twitching, uncontrolled movements of the limbs, and feeling dizzy, especially when getting up from a lying or sitting position, were common (greater than 1 in 100 patients).

How to store Asduter tablets?

Store in the original package in order to protect from moisture.

Use within 28 days after first opening of HDPE container.

Keep this medicine out of the sight and reach of children.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Asduter 10 mg, 15 mg and 30 mg tablets. The procedure was finalised at 21 April 2015. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: the Czech Republic, Poland and the Slovak Republic) concerned the generic version of aripiprazole 10 mg, 15 mg and 15 mg tablets (Asduter tablets,).

The application has been filed pursuant to Article 10(1) of Directive 2001/83/EC and therefore contained no new clinical or preclinical data, other than supporting literature where necessary.

The applicant has adequately demonstrated bioequivalence between the product and reference products. The originator (and reference) products are Abilify 10 mg, 15 mg and 30 mg tablets marketed by Otsuka Pharmaceutical Europe Ltd. approved for more than 10 years within the European Economic Area.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisations for Asduter 10 mg, 15 mg and 30 mg tablets from Vipharm S.A., Poland.

The products are indicated for the treatment of schizophrenia in adults and in adolescents aged 13 years and older, for moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in adults, and in the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics (SmPC).

II. QUALITY ASPECTS

II.1 Introduction

The chemical-pharmaceutical assessment report concerns the application for marketing authorisations via the Decentralised Procedure for products Asduter 10 mg, 15 mg and 30 mg tablets according to Article 10(1) of Directive 2001/83/EC (i.e. a generic application). The products have been developed by Vipharm S.A., Poland.

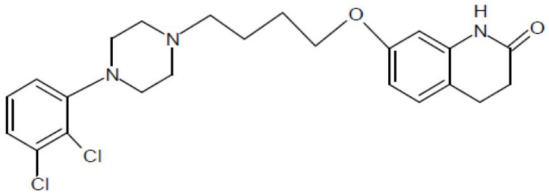
A bioequivalence study has been performed using the products Abilify® 10 mg tablets containing aripiprazole (Otsuka Pharmaceutical Europe Ltd).

II.2 Drug substance

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the Active Substance Master File (ASMF) procedure. Letter of access to the ASMF was submitted with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

International non-proprietary name (INN): aripiprazole
Chemical name: 7-[4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy]-3,4-dihydroquinolin-2(1*H*)-one.

Structure:



The active substance is white or almost white crystals or crystalline powder, which is very slightly soluble in ethanol and toluene, practically insoluble in water and n-hexane, slightly soluble in N,N-dimethylformamide, butanone and acetone. The molecule has no chiral centre, does not exhibit stereoisomerism, and it is hygroscopic. There are some known polymorphic forms of aripiprazole.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the active pharmaceutical ingredient (API) is adequate.

Evidence of structure of aripiprazole was presented and confirmed by various spectroscopic methods. It has been demonstrated that the manufacturing process consistently produces the same stable crystalline form of Aripiprazole. The impurity profile of the API containing detailed information about genotoxic impurities, residual solvents and other carryover impurities has been appropriately discussed.

The substance is specified according to the requirements of the current European Pharmacopoeia (Ph. Eur.) monograph, additional specification have only been set for residual solvents, identification (XRPD), and a certain related substance. The limits set are properly justified.

Testing methods not described in detail in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

It has been demonstrated by the presented stability and forced degradation studies that the substance is very stable, the available stability data support the proposed re-test period.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim was to develop immediate release oral tablets containing aripiprazole as active substance, which are pharmaceutically equivalent and bioequivalent to the reference Abilify® in the form of 10 mg, 15 mg and 30 mg strength tablets, with the same strengths and same qualitative composition.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.
As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies the following products were obtained:
10 mg strength: light red, round, flat-faced, bevelled-edge tablets of size of 5.8 – 6.2 mm.
15 mg strength: light yellow, round, flat-faced, bevelled-edge tablets of size 6.8 – 7.2 mm.
30 mg strength: light red, round, flat-faced, bevelled-edge tablets of size 8.8 – 9.2 mm.

The tablets are packed blister OPA/Al/PVC foil with Al foil or HDPE container with LDPE cap.

The excipients used are lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose, maize starch, yellow or red iron oxides, anhydrous colloidal silica and magnesium stearate. All excipients used comply with their respective Ph. Eur. monograph, except from the colouring

agents, iron oxide red and yellow, which are controlled in accordance with Directive 2008/128/EC.

Compliance of the products with the general monograph of the Ph. Eur. on the products with the risk of TSE has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the International Conference on Harmonisation (ICH) Q6A guideline. Appropriate control strategy was selected. The test methods have been described and adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the products is blister consisting of OPA/Al/PVC foil and aluminum foil or HDPE container with push-fit tamper-evident LDPE cap equipped with dehumidifier with narrow-porous silica gel SMG. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 24 months with the storage condition of "Store in the original package in order to protect from moisture" is approved.

The SmPC, Patient Information Leaflet (Package Leaflet, PL) and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From quality points of view the products are approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of aripirazole are well known. As aripirazole is a widely used, well-known active substance, no further non-clinical studies are required and the applicant provides none. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to the active ingredient, aripiprazole.

III.2 Pharmacology

The drug product Asduter contains the active substance aripiprazole. It is an antipsychotic drug. Its 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. 'Partial agonist' properties means that aripiprazole acts like dopamine and 5-hydroxytryptamine by activating these receptors, but less strongly than the neurotransmitters. Aripiprazole helps to normalise the activity of the brain, reducing psychotic or manic symptoms and preventing them from returning. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

The active substance is a well-known compound. No further information was provided regarding the pharmacology of aripiprazole.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the applicant.

III.4 Toxicology

Published information on toxicological studies with aripiprazole was the basis for the evaluation.

No new toxicity studies were submitted by the applicant for the product, which is acceptable for this type of application.

III.5 Ecotoxicology/environmental risk assessment (ERA)

Since Asduter 10 mg, 15 mg and 30 mg tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Abridged applications avoid the need for repetitive tests on animals and humans.

Pharmacodynamics, pharmacokinetics and toxicology of aripiprazole are well-known. As Asduter tablets are generic products, there is no need for further excessive non-clinical studies.

The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of aripiprazole is well known.

Except for establishing bioequivalence, no specific clinical studies have been performed, as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EC as amended.

The application contains an adequate review of published clinical data.

IV.2 Pharmacokinetics

IV.2.1 Literature data

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.

It 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.

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.

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

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

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

The development studies focused on obtaining a product having similar characteristics

to the reference product, i.e. dissolution profile and bioavailability.

IV.2.2 Biowaiver

The applicant claimed for biowaiver for the 15 mg and 30 mg dose strengths on the basis of general biowaiver requirements (CPMP/EWP/QWP/1401/98 Rev 1 Corr**) because results of bioequivalence study carried out with the 10 mg dose strength can be applied to the other strengths:

a) all the three strengths (10, 15 and 30 mg) of proposed pharmaceutical products are manufactured by the same manufacturer and using the same manufacturing process,
b) the qualitative composition of Aripiprazole 15 mg and 30 mg tablets is same as that of Aripiprazole 10 mg tablets,
c) the composition of all the strengths are quantitatively proportional, i.e. the ratio
d) between the amounts of each excipient to the amount of active substance is the same for all the three strengths,
e) the in-vitro dissolution profiles are similar under identical conditions for the additional strengths i.e. 15 mg and 30 mg, the strength of batch used in the bioequivalence study (i.e. 10 mg) and reference,
f) aripiprazole has linear pharmacokinetics in the therapeutic dose range (5–30 mg).

The biowaiver claim for the 15 mg and 30 mg dose-strengths is justified as general requirements for biowaiver are completely fulfilled.

IV.2.3 Bioequivalence study

The main objective of the study was to assess the bioavailability of aripiprazole from a 10 mg tablet by formulation (Aripiprazole 10 mg, Vipharm S. A.) compared with the reference tablet formulation (Abilify® 10 mg/ Otsuka Pharmaceutical Europe Ltd) following a single dose under fasting conditions in healthy subjects, and to compare safety and tolerability of these formulations.

This was a single-centre, randomized, two-way, crossover, single dose study with healthy subjects under fasting conditions.

Determination of aripiprazole in plasma was done by validated LC-MS method after liquid-liquid extraction.

Incurred sample reanalysis was performed according to the guideline on bioanalytical method validation (EMA/CHMP/EWP/192217/2009, 21 July 2011). Results of the ISR met the requirements.

Descriptive statistics were calculated for primary and other pharmacokinetic parameters of aripiprazole.

An ANOVA (analysis of variance) was performed on log-transformed values of pharmacokinetic parameters AUC_{0-72h}, C_{max} and $t_{1/2}$.

Bioequivalence was to be concluded if the 90% geometric confidence intervals of the ratio (Test/Reference, T/R) of least-squares means for ln-transformed AUC_{0-72h}, and C_{max} were within the acceptable range of 80.00% to 125.00%.

The applicant stated that the bioequivalence studies were undertaken according to GCP guidelines. No issues regarding GLP or GCP aspects have been identified during the review of this dossier.

Point estimates and 90% confidence intervals for (log-transformed) aripiprazole pharmacokinetic parameters are as follows:

Pharmacokinetic parameter	Point estimate T/R ratio (%)	90% CI (%)
C_{max}	105.18	99.35 – 111.36
AUC_{0-72h}	106.08	101.96 – 110.37

Based on the submitted bioequivalence study it can be concluded that the Aripiprazole 10 mg tablets (Vipharm S. A. Poland) and Abilify® 10 mg tablets (Otsuka Pharm. Europe Ltd., Great Britain) are bioequivalent in terms of extent and rate of absorption of aripiprazole when administered as a single dose under fasting conditions in adult healthy males and females.

IV.3 Pharmacodynamics

No clinical pharmacology studies to evaluate the pharmacodynamics of Asduter 10 mg, 15 mg, and 30 mg tablets were performed. On the basis of bioequivalence with the marketed reference product no such studies are needed.

IV.4 Clinical efficacy

No new efficacy data have been submitted and none are required. The applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy and safety profile of aripiprazole.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence studies, no new safety data were submitted and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data.

No serious adverse events were reported in this study. Both study medications were well tolerated.

IV.6 Pharmacovigilance

IV.6.1 Pharmacovigilance system

The applicant has submitted a signed and dated Summary of Pharmacovigilance System of the proposed future marketing authorisation holder Vipharm S.A., Poland. It contained all of the elements which are required According to the Article 8.3(ia) of the 2001/83/EC Directive as amended.

IV.6.2 Risk Management Plan

Summary of safety concerns	
Important identified risks	• Extrapyramidal symptoms, including tardive dyskinesia • Neuroleptic Malignant Syndrome • Seizures • Suicide-related events • Somnolence and fatigue • Pathological gambling • Weight gain • Hyperglycaemia/diabetes • Cardiovascular-related disorders (including conduction abnormalities, orthostatic hypotension, increased mortality and cerebro-vascular accident in elderly patients with dementia) • Dysphagia • Serotonin syndrome • Hepatic adverse events related with hepatic injury
Important potential risks	• Concomitant administration with potent inhibitor or inducer of CYP3A4 or CYP2D6 inhibitors and with other CNS medicinal product or alcohol
Missing information	• Safety in pregnancy and lactation • Use in paediatric patients

Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Extrapyramidal syndrome, including tardive dyskinesia	Information included in SmPC section 4.4: if signs and symptoms of other EPS appear in a patient taking Asduter, dose reduction and close clinical monitoring should be considered. Listed in SmPC section 4.8.	The marketing authorisation holder will provide healthcare professionals and patient/caregiver education at the time of product launch for the indication of Bipolar I Disorder in adolescents aged 13 years and

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
		older urging vigilance in the ongoing evaluation of extrapyramidal symptoms, weight gain, and AEs related to somnolence/fatigue.
Neuroleptic Malignant Syndrome (NMS)	Information included in SmPC section 4.3: Neuroleptic Malignant Syndrome (NMS) is a potentially fatal symptom complex associated with antipsychotic medicinal products. If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, all antipsychotic medicinal products, including Asduter, must be discontinued. Listed in SmPC section 4.8.	None
Seizures	Information included in SmPC section 4.4: aripiprazole should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures. Listed in SmPC section 4.8.	None
Suicide-related events	Information included in SmPC section 4.4: the occurrence of suicidal behaviour is inherent in psychotic illnesses and mood disorders and in some cases has been reported early after initiation or switch of antipsychotic therapy, including treatment with aripiprazole. Close supervision of high-risk patients should accompany antipsychotic therapy. Listed in SmPC section 4.8.	None
Somnolence and fatigue	Information included in SmPC sections 4.2 and 4.7. Listed in SmPC section 4.8.	The marketing authorisation holder will provide healthcare professionals and patient/caregiver education at the time of product launch for the indication of Bipolar I Disorder in adolescents aged 13 years and older urging vigilance in the ongoing

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
		evaluation of extrapyramidal symptoms, weight gain, and AEs related to somnolence/fatigue.
Pathological gambling	Information included in SmPC section 4.4. Listed in SmPC section 4.8.	None.
Weight gain	Information included in SmPC sections 4.2, 4.4 and 5.1. Listed in SmPC section 4.8.	The marketing authorisation holder will provide healthcare professionals and patient/caregiver education at the time of product launch for the indication of Bipolar I Disorder in adolescents aged 13 years and older urging vigilance in the ongoing evaluation of extrapyramidal symptoms, weight gain, and AEs related to somnolence/fatigue.
Hyperglycaemia/diabetes	Information included in SmPC section 4.4: patients treated with any antipsychotic agents, including Asduter, should be observed for signs and symptoms of hyperglycaemia (such as polydipsia, polyuria, polyphagia and weakness) and patients with diabetes mellitus or with risk factors for diabetes mellitus should be monitored regularly for worsening of glucose control. Listed in SmPC section 4.8.	None.
Serotonin syndrome	Information included in SmPC section 4.5. Listed in SmPC section 4.8.	None.
Cardiovascular-related disorders (including conduction abnormalities, orthostatic hypotension, increased mortality and cerebrovascular accident in elderly patients with dementia)	Information included in SmPC section 4.4. Listed in section 4.8.	None.
Dysphagia	Information included in SmPC section 4.4.	None.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Listed in section 4.8.	
Hepatic adverse events related with hepatic injury	Listed in SmPC section 4.8.	None.
Concomitant administration with potent inhibitor or inducer of CYP3A4 or CYP2D6 inhibitors and with other CNS medicinal product or alcohol	Information included in SmPC sections 4.2 and 4.5: when concomitant administration of potent CYP3A4 inducers with aripiprazole occurs, the aripiprazole dose should be increased. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should then be reduced to the recommended dose. Given the primary CNS effects of aripiprazole, caution should be used when aripiprazole is taken in combination with alcohol or other CNS medicinal products with overlapping adverse reactions such as sedation. Listed in SmPC section 4.8.	None.
Safety in pregnancy and lactation	Information included in SmPC section 4.6.	None.
Use in paediatric patients	Information included in SmPC sections 4.2, 4.8 and 5.1. Asduter is not recommended for use in patients below 13 years of age.	None.

In line with the reference product, the applicant's Risk Management Plan contains additional risk minimisation measures for the safety concerns 'EPS, including tardive dyskinesia', 'weight gain' and 'somnolence/fatigue'. The exact content of the education materials and necessity of the distribution of them should be clarified on national level in agreement with the National Competent Authorities in the national phase.

IV.6.2 Periodic Safety Update Reports

The Periodic Safety Update Reports (PSURs) shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the Data Lock Points and frequency of submission of the next PSUR.

IV.7 Discussion on the clinical aspects

The application concerns a generic product.

Abridged applications avoid the need for repetitive tests on animals and humans. For these application the bioequivalence studies described in section IV.2 are pivotal.

To support the application the applicant has adequately demonstrated bioequivalence between Asduter 10 mg, 15 mg, 30 mg tablets and the reference product Abilify 10 mg, 15 mg, 30 mg tablets.

There is no objection against granting the marketing authorization from a clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present applications concern Asduter 10 mg, 15 mg and 30 mg tablets. Their active substance is aripiprazole. The applicant and the future holder of authorisation is Vipharm S.A., Poland.

The products are indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older, moderate to severe manic episodes in Bipolar I Disorder and the prevention of a new manic episode in adults, and in the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.

The applicant has adequately demonstrated bioequivalence between Asduter 10 mg, 15 mg, 30 mg tablets and the reference product Abilify 10 mg, 15 mg, 30 mg tablets.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisations for Asduter 10 mg, 15 mg and 30 mg tablets.

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and user consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet was Hungarian.

The results show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached