Decentralised Procedure

Public Assessment Report

Aripiprazol Glenmark 5 / 10 / 15 / 30 mg Tabletten
Aripiprazole

DE/H/4147/001-004/DC

Applicant: Glenmark Pharmaceuticals s.r.o, Czech Republic

Reference Member State	DE

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ADMINISTRATIVE INFORMATION

Proposed name of the medicinal product(s) in the RMS	Aripiprazol Glenmark 5 / 10 / 15 / 30 mg Tabletten
Name of the drug substance (INN name):	Aripiprazole
Pharmaco-therapeutic group (ATC Code):	N05AX12
Pharmaceutical form(s) and strength(s):	Tablet 5 / 10 / 15 / 30 mg
Reference Number(s) for the Decentralised Procedure	DE/H/4147/001-004/DC
Reference Member State:	DE
Member States concerned:	LU withdrawn
Applicant (name and address)	Glenmark Pharmaceuticals s.r.o., Hvězdova 1716/2b, CZ-140 78 Praha 4, Czech Republic

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the application for *Aripiprazol Glenmark 5 / 10 / 15 / 30 mg Tabletten*, indicated

- for the treatment of schizophrenia in adults and in adolescents aged 15 years and older.
- for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment (see section 5.1).
- for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older (see section 5.1),

is approved.

II. EXECUTIVE SUMMARY

II.1 Problem statement

This decentralised application concerns a generic version of Aripiprazol, under the trade name Aripiprazol Glenmark.

The originator product is Abilify 5, 10, 15 30 mg Tabletten authorized by Otsuka Pharmaceutical Europe Ltd., United Kingdom, registered in the European Union since 4th June 2004. Period of data protection has been expired.

With Germany as the Reference Member State in this Decentralized Procedure, Glenmark is applying for the Marketing Authorisations under article 10(1) generic application for *Aripiprazol Glenmark 5 / 10 / 15 / 30 mg Tabletten* in LU. However, the applicant decided to withdraw the application in LU.

II.2 About the product

Aripiprazole, a dihydrocarbostyril (quinolinone) derivative, is a newer generation antipsychotic was first developed collaboratively by Otsuka Pharmaceutical Development & Commercialization (ODPC) and Bristol-Myers Squibb Company (BMS). It was first marketed as Abilify® and is an atypical antipsychotic (ATC Code: N05 AX12) with partial-agonist activity at dopamine D2 receptors, partial-agonist effects at serotonin 5-HT1A receptors as well as antagonistic activity at 5-HT2A receptors. It is assumed that this novel mechanism of action results in aripiprazole's favorable safety and tolerability profile.

Abilify® tablets were approved in the European Union on 4 June 2004 for the treatment of schizophrenia in adults. An orodispersible tablet and an oral solution formulation (1 mg/mL) were developed to provide alternate means of administering aripiprazole and were approved on 20 June 2005 and 28 October 2005, respectively.

Abilify is indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older.

Abilify is indicated for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment.

Abilify is indicated for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older.

II.3 General comments on the submitted dossier

With this DCP-Procedure Glenmark Pharmaceuticals s.r.o, Czech Republic is applying for the Marketing Authorisations under article 10(1) generic application for *Aripiprazol Glenmark 5 / 10 / 15 / 30 mg Tabletten* .

Active substance of *Aripiprazol Glenmark 5 / 10 / 15 / 30 mg Tabletten* is not considered as a new active substance. From a non-clinical and clinical perspective, the Modules 2.4, 2.5, 2.7, 4 and 5 are generally well structured and of good quality.

II.4 General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.
For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturers responsible for manufacture of the finished product and batch release situated in the EU.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

Aripiprazole is described in the current European Pharmacopoeia. Two sources of Aripiprazole are proposed. The drug substance data is provided in the form of an Active Substance Master File. Letters of access as well as drug substance documentation is included in the dossier for both sources of Aripiprazole. The information presented in both ASMFs is of satisfactory quality. The control tests and specifications for drug substance product are adequately drawn up. One manufacturer has provided satisfactory results of stability studies to support the proposed re-test period of 36 months and proposed storage conditions to store in original packaging below 25°C.
the other manufacturer proposes a re-test period of 60 months based on real-time data.

Drug Product

The pharmaceutical development is limited but acceptable for straightforward standard dosage form. The ingredients, the manufacturing process and the in-process controls of the drug product correspond to the current standard of pharmaceutical technology and are suitable to guarantee an appropriate product quality. The description of the analytical test methods is adequate. The validation results are plausible. All relevant quality criteria are specified in accordance with internationally acknowledged pharmacopoeias. The specified limits are in line with the requirements of the CHMP Guidelines. The stability testing data cover a time period of at least 24 months and are supported by photo stability data. Based on the provided data a shelf life up to 36 months is considered justified.

III.2 Non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of the active substance aripiprazole are well known. The Applicant has not provided additional non-clinical studies and further studies are not required. Overview based on literature review is, thus, appropriate. The non-clinical overview is adequately prepared and contains a comprehensive discussion on the impurity F/103 (aribromide).
The Applicant presented two in-vitro studies (AMES test and in-vitro chromosome aberration test) to substantiate the genotoxic potential derived from a structural alert from QSAR analysis of F/103.
Both studies have been conducted in compliance with GLP.
As a result, neither the Ames test nor the chromosome aberration test showed signs of genotoxicity.
According to EMA/CHMP/SWP/431994/2007 Rev. 3 (Questions and answers on the 'Guideline on the limits of genotoxic impurities'), "(…) a negative Ames test will overrule a structural alert and no further studies would be required providing the level remains below ICH Q3A/B limits."
Instructions regarding use of the active substance during pregnancy and lactation and information on available preclinical safety data contained in the proposed SmPC and PL, respectively, have been brought in line with the latest type II variation that was approved for the originator Abilify (EMEA/H/C/000471/II/0101; latest update of product information for Abilify EMEA/H/C/000471 - IAIN/0104).

Environmental Risk Assessment (ERA)
Since *"Aripiprazol Glenmark 5 / 10 / 15 / 30 mg Tabletten"* is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.3 Clinical aspects

Pharmacokinetics
To support this application, the applicant has submitted as report one bioequivalence study.
Submission of one bioequivalence study is justified for this hybrid application.

Study title:
Study (311/11) title: Randomized, single dose, two-period, cross-over, bioequivalence study comparing Aripiprazole 10 mg tablets with Abilify 10 mg tablets in healthy volunteers under fasting conditions.
The mean pharmacokinetic characteristics of aripiprazole after treatment with Test and Rererence products were as follows:

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

Treatment	AUC_{0-t} xg/ml/h	$AUC_{0-\infty}$ xg/ml/h	C_{max} xg/ml	t_{max} h
Test	1560.56 ± 386.57	3519.06 ± 1703.42	44.49 ± 12.29	2.5 (1-12)
Reference	1543.22 ± 420.28	3702.75 ± 2053.75	41.99 ± 12.18	3.01(1-14)
***Ratio (90% CI)**	102.04 (95.74-108.75)	96.25 (90.79 – 102.03)	107.27 (96.53-119.20)	
Within subject CV%	12.91		21.52	
	AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t. AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products **$AUC_{0-\infty}$** Area under the plasma concentration curve extrapolated to infinite time. $AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t} **C_{max}** Maximum plasma concentration **t_{max}** Time until Cmax is reached			

**ln-transformed values*

The 90% confidence intervals for the geometric mean ratios of Test to Reference formulations for AUC_{O-72} and C_{max} were within the bioequivalence acceptance range of 80 to 125%.

The bioequivalence study has been performed with aripiprazole 10 mg strengths. Extrapolation of results of Study (311/11) with 10 mg formulation to the strength 5, 15, 30 mg according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6 is considered.

Pharmacodynamics
No new pharmacodynamic studies were conducted and reference was made to literature data which is acceptable.

Clinical efficacy
The efficacy of aripiprazole in the indications demanded for approval has been well documented in literature. The applicant provided an adequate overview of recent publications. No new data were submitted.

Clinical safety
No new data were submitted. It is considered that the safety profile of *Aripiprazol Glenmark 5 / 10 / 15 / 20/ 30 mg Tabletten* will be comparable to that of the originator Abilify which is currently licensed and marketed in Europe.

User Testing

Applicant refers on the user testing of the originator product Abilify which was registered via a Centralized Procedure. The originator package leaflet was user tested, as is mentioned in the EPAR (Abilify-H-C-471-II-48 EPAR - Assessment Report). The product information proposed for Aripiprazol Glenmark 5, 10, 15, 20 and 30 mg tablets should be the same as the current SmPC, labelling and package leaflet from the originator product. The only changes made to the PL of Aripiprazol Glenmark consist of administrative data (product name and MA holder). User testing of the originator package leaflet was last accepted in 2009, as is mentioned in the EPAR (Abilify-H-C-471-II-48 EPAR - Assessment Report - Variation). Applicant has provided a bridging report in order to evaluate differences of originator and Aripiprazol Glenmark PL. It was shown that PLs are nearly identical. Regarding justification of bridging applicant has provided data which are demanded for in "CMDh questions & answers product information/information on medicinal products" (Doc. Ref.: CMDh/275/2012, Rev0 October 2012). The demands are fulfilled.

Additionally applicant has provided a user test of PL concerning an other active substance.

Synthon has previously performed a successful user test of Eplerenone 25 mg and 50 mg film-coated tablets package leaflet dated 28th April 2011. Marketing authorization holder of Eplerenone 25 mg and 50 mg film-coated tablets was Synthon BV, Nijmegen, The Netherlands. The active substance, indication and contents of all sections of the user test provided differs from that of Aripiprazol Glenmark PL but the reason to provide this user test was to show that design and lay-out of the package leaflet of Aripiprazol Glenmark (applicants house style) is acceptable to reach a positive evaluation in view of readability. The user test provided was already accepted in procedures CZ/H/0380/001-002/DC; moreover applicant confirmed that Synthon BV and Glenmark Pharmaceuticals s.r.o. are business partners and that Glenmark Pharmaceuticals s.r.o. regarding layout of PL follows the Synthon BV house style.

Summary Pharmacovigilance system

The Applicant/Proposed Future MAH has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation and as detailed in the GVP module, the RMS considers the Summary acceptable.

Risk Management Plan

Summary of safety concerns

Summary of safety concerns	
Important identified risks	1. Extrapyramidal symptoms (EPS), including tardive dyskinesia) 2. Neuroleptic malignant syndrome (NMS)
Important potential risks	1. Seizures* 2. Hyperglycemia/diabetes* 3. Suicide-related events* 4. Orthostatic hypotension* 5. Dyslipidaemia* 6. Weight gain 7. Somnolence/fatigue 8. Cardiovascular-related disorders 9. Conduction abnormalities 10. Growth 11. Low prolactin in paediatric patients 12. Dysphagia (primarily applies to schizophrenia population) 13. Lactose intolerance 14. ADHD co-morbidity 15. Drug interactions 16. Increased mortality and CVA in elderly patients with dementia 17. Pathological gambling 18. Serotonin syndrome
Missing information	1. Safety in pregnancy and lactation 2. Safety in paediatrics
*Important potential risk	

There are no additional risk minimisation measures and no additional pharmacovigilance activities.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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

Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:

- 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 DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

IV. BENEFIT RISK ASSESSMENT

The application contains an adequate review of published clinical data regarding pharmacology, efficacy and safety. In the bioequivalence study provided bioequivalence between Test and Reference product has been shown.
The bioequivalence study has been performed with aripiprazole 10 mg strengths. Extrapolation of results of Study (311/11) with 10 mg formulation to the strength 5, 15, 20, 30 mg according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6 is considered acceptable.
The application is approved.
For intermediate amendments see current product information.