

Public Assessment Report

Scientific discussion

Aripiprazol Prolepha 1 mg, 2.5 mg and 5 mg tablets (aripiprazole)

NL/H/5717/001-003/DC

Date: 2 June 2026

This module reflects the scientific discussion for the approval of Aripiprazole Prolepha 1 mg, 2.5 mg and 5 mg tablets. The procedure was finalised on 6 March 2024. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Aripiprazole Prolepha 1 mg, 2.5 mg and 5 mg tablets from Prolepha Research B.V.

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

The product 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.

The product 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.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation for Aripiprazole Prolepha 5 mg has been granted pursuant to Article 10(1) of Directive 2001/83/EC, while the marketing authorisations for Aripiprazole Prolepha 1 mg and 2.5 mg have been granted pursuant to Article 10(3) of Directive 2001/83/EC. These concern a generic (5 mg) and hybrid (1 mg and 2.5 mg) applications.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Abilify 1 mg, 2.5 mg and 5 mg, which has been registered in the EEA via a centralised procedure (EU/1/04/276/002) since 4 June 2004.

The concerned member state (CMS) involved in this procedure was Cyprus. A repeat-use procedure (NL/H/5717/001-002/E/001) was used to register the product in Germany.

II. QUALITY ASPECTS

II.1 Introduction

Aripiprazole Prolepha 1 mg is a white, round tablet. The tablet contains as active substance 1 mg of aripiprazole.

Aripiprazole Prolepha 2.5 mg is a light grey, modified rectangular tablet with a break line on one side. The tablet contains as active substance 2.5 mg of aripiprazole.

Aripiprazole Prolepha 5 mg is a blue, modified rectangular tablet, with "MC" on one side, plain on the other. The tablet contains as active substance 5 mg of aripiprazole.

The excipients are: lactose monohydrate, microcrystalline cellulose (type 101), maize starch, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, iron oxide black (E172, 2.5 mg only) and indigo carmine aluminium lake (E132, 5 mg only).

The tablets are packed in oriented polyamide/aluminium/polyvinyl chloride-aluminium (OPA/Al/PVC-Al) blisters.

II.2 Drug Substance

The active substance is aripiprazole, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Aripiprazole consists of white or almost white crystals or crystalline powder. It is practically insoluble in water, soluble in methylene chloride and very slightly soluble in ethanol 96%. Aripiprazole has no asymmetrical C-atoms; hence it has no potential isomerism. It exists in different polymorphic forms. The consistency of the physical form produced as well as the stability of the polymorphic form is sufficiently proven.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality with and meets the requirements of the monograph in the Ph.Eur., with additional tests for microbiological quality and particle size. Batch analytical data demonstrating compliance with this specification have been provided for five commercial scale batches.

Stability of drug substance

The active substance is stable for two years when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions are explained.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches of 1 mg and 5 mg and two batches of 2.5 mg in accordance with the relevant European guidelines. A commitment to perform validation for additional batches sizes is noted. As the 1 mg tablets contain less than 2% active substance the manufacturing process of this tablet is considered a non-standard process.

Control of excipients

All excipients are commonly used for oral pharmaceutical dosage forms and the qualitative composition of applied medicinal products is similar with the European reference product, with the exception of croscarmellose sodium used as disintegrant in the generic product. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity of the API and colourant, assay, average mass, uniformity of dosage units, dissolution, related substances, microbial purity and residual solvent. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data on three batches of 1 mg and 5 mg and two batches of 2.5 mg from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided from three batches of 5 mg and 1 mg and two batches of 2.5 mg stored at 25°C/60% RH (up to 24 months) and 40°C/75% RH (up to 6 months) in accordance with applicable European guidelines. Photostability study demonstrated that the product is not sensitive to light. On basis of the data submitted, a shelf life was granted of three years. No specific storage conditions needed to be included in the SmPC or on the label.

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

Scientific data and/or certificates of suitability issued by the EDQM of excipient lactose monohydrate have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Aripiprazole Prolepha has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Aripiprazole Prolepha is intended for generic (5 mg) or hybrid (1 mg and 2.5 mg) substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic (5 mg) or hybrid (1 mg and 2.5 mg) formulation of Abilify which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Aripiprazole is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the bioequivalence study ARI.5/398, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Aripiprazole 5 mg tablets (Prolepha Research B.V., Cyprus) was compared with the pharmacokinetic profile of the reference product Abilify® (aripiprazole) 5 mg tablets (Otsuka Pharmaceutical Netherlands B.V., Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition (pH 1.2, 4.0, 4.5 and 6.8). The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

The following general requirements must be met where a waiver for the additional 1 mg and 2.5 mg strengths is claimed, according to the EMA Bioequivalence guideline:

- a. the pharmaceutical products are manufactured by the same manufacturing process,
- b. the qualitative composition of the different strengths is the same,
- c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
- d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The dissolution was investigated according to the EMA Bioequivalence guideline. The calculated f_2 similarity factor values were within criteria (>50%, at pH 6.8) or aripiprazole dissolved for more than 85% in 15 min (other pH values). An f_2 value between 50 and 100% suggests that the two dissolution profiles are similar.

Bioequivalence study ARI.5/398

Design

A single-dose, randomised, two-period, two-treatment, crossover, two-way, open-label and laboratory-blind bioequivalence study was carried out under fasted conditions in 27 healthy male subjects, aged 45-54 years. Each subject received a single dose (5 mg) of one of the two aripiprazole formulations. The tablet was orally administered with 240 mL water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 42 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 2.75, 3, 3.25, 3.5, 4, 4, 5, 5.5, 6, 7, 8, 9, 10, 12, 24, 36, 48, and at 72 hours after administration of the products.

The design of the study is acceptable.

Aripiprazole may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of aripiprazole. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods

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

Results

30 subjects enrolled in the study. Three subjects were withdrawn from the study before dosing of Period II (one with ECG abnormalities and two with elevated creatine phosphokinase (CPK) levels). 27 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD, t_{max} (median, range)) of aripiprazole, 5 mg under fasted conditions.

Treatment N=27	AUC ₀₋₇₂ ($\mu\text{g}\cdot\text{h}/\text{mL}$)	AUC _{0-∞} ($\mu\text{g}\cdot\text{h}/\text{mL}$)	C _{max} (ng/mL)	t _{max} (h)
Test	631 \pm 139	1399 \pm 639	19.1 \pm 3.2	3.00 (1.00 – 7.00)
Reference	610 \pm 115	1330 \pm 791	16.8 \pm 2.6	3.25 (1.00 – 12.00)
*Ratio (90% CI)	1.03 (0.99 – 1.07)	-	1.14 (1.08 – 1.19)	-
AUC_{0-∞} Area under the plasma concentration-time curve from time zero to infinity AUC_{0-t} Area under the plasma concentration-time curve from time zero to t = 72 hours C_{max} Maximum plasma concentration t_{max} Time after administration when maximum plasma concentration occurs CI Confidence interval				

**In-transformed values*

Conclusion on bioequivalence study:

The 90% confidence intervals calculated for AUC₀₋₇₂ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Aripiprazole 5 mg is considered bioequivalent with Abilify 5 mg.

The results of study ARI.5/398 with the 5 mg formulation can be extrapolated to other strengths 2,5 mg and 1 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

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

IV.3 Risk Management Plan

The MAH has submitted a risk management plan (version 0.1, final sign off 2 October 2023), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Aripiprazole Prolepha.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	Extrapyramidal symptoms including tardive dyskinesia
Important potential risks	Orthostatic hypotension

Missing information	Use in pregnancy and lactation
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The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Abilify. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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.

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Abilify, EU/1/04/276. The bridging report submitted by the MAH has been found acceptable; bridging is justified for content.

The MAH has established a corporate PIL design and layout, which has been successfully user tested in several User Consultation tests for many approved products. This is acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Aripiprazole Prolepha 5 mg, 2.5 mg and 1 mg tablets have a proven chemical-pharmaceutical quality and are generic and hybrid forms of Abilify 1 mg, 2.5 mg and 5 mg tablets. Abilify is a well-known medicinal product with an established favourable efficacy and safety profile.

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

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Aripiprazole Prolepha with the reference product, and have therefore granted a marketing authorisation. The decentralised and mutual recognition procedure was finalised with a positive outcome on 6 March 2024.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5717/1-3/IA/001	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/intermediate used in the manufacturing process of the active substance, For an excipient <ul style="list-style-type: none"> European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph Updated certificate from an already approved manufacturer 	No	18-09-2024	Approved	N.A.
NL/H/5717/1-2/IA/002	Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier <ul style="list-style-type: none"> The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer. 	No	11-12-2024	Approved	N.A.
NL/H/5717/001-002/E/001	Repeat use – CMS Germany added	No	6-4-2025	Approved	N.A.
NL/H/5717/I B/003/G	Change in immediate packaging of the finished product <ul style="list-style-type: none"> Change in type of container or addition 	Yes	6-8-2-25	Partially approved	An evaluation of one change in

	<p>of a new container - Solid, semi-solid and non-sterile liquid pharmaceutical forms</p> <p>Change in pack size of the finished product</p> <ul style="list-style-type: none"> • Change in the number of units (e.g. tablets, ampoules, etc.) in a pack • Change outside the range of the currently approved pack sizes 	Yes			pack size is outstanding
NL/H/5717/001-003/IB/004	<p>Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products</p> <ul style="list-style-type: none"> • Other variation 	Yes	2-11-2025	Approved	N.A.
NL/H/5717/IA/005/G	<p>Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product</p> <ul style="list-style-type: none"> • Secondary packaging site <p>Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product</p> <ul style="list-style-type: none"> • Primary packaging site 	No No	23-9-2025	Approved	N.A.
NL/H/5717/1-3/IB/006	<p>Change in the (invented) name of the medicinal product</p> <ul style="list-style-type: none"> • for Nationally Authorised products 	Yes	13-11-2025	Approved	N.A.