LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Lipahar
(aripiprazole monohydrate)

SE/H/2565/01-02/DC

This module reflects the scientific discussion for the approval of Lipahar. The procedure was finalised at 2025-09-17. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have agreed to grant a marketing authorisation for Lipahar, 300 mg, 400 mg, powder and solvent for prolonged-release suspension for injection.

The active substance is aripiprazole monohydrate. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

The applied products (see above) belong to the pharmacotherapeutic group: Psycholeptics, other antipsychotics, ATC code: N05AX12.

It has been proposed that aripiprazole's efficacy in schizophrenia is mediated through a combination of partial agonism at dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonism at serotonin 5-HT_{2A} receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties of dopaminergic hypoactivity. Aripiprazole exhibits high binding affinity *in vitro* for dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors and has moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha-1 adrenergic, and histamine H_1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for cholinergic muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.

Proposed indication:
For maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole.

II.2 General comments on the submitted dossier

The applications for Lipahar et al., 300 mg, 400 mg, powder and solvent for prolonged-release suspension for injection, are Generic Art. 10(1) applications submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and concerned member states (CMS) as follows:

SE/H/2565/01-02/DC – EL
SE/H/2579/01-02/DC – AT, CZ (only 400 mg), DE, DK, EL, ES, FI, FR (only 300 mg), HU, IS, IT, NL, NO, PT
SE/H/2580/01-02/DC – AT
SE/H/2581/01-02/DC – EE, HR, LT, LV

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Abilify Maintena, 300 mg, powder and solvent for prolonged-release suspension for injection, authorised in the Union since 2013, with Otsuka Pharmaceutical Netherlands B.V. as marketing authorisation holder.

The reference product used in the bioequivalence study is Abilify Maintena, 400 mg, powder and solvent for prolonged-release suspension for injection, from Germany with Otsuka Pharmaceutical Netherlands B.V. as marketing authorisation holder.

II.3 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.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

GCP
A statement on the application of appropriate GCP standards in the submitted study has been provided.

No issues regarding GCP have been identified. The bioanalytical facility was inspected by ES authority in 2023, without any critical findings. One of the clinical facilities was inspected by AT authority in 2023. There were some critical findings, but the critical findings are not considered to affect the reliability of current study. This inspection along with other supportive documents submitted for all clinical facilities, show that there is overall no concern for the clinical facilities. No inspection of the submitted bioequivalence study is needed.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance
The structure of the drug substance has been adequately proven, and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described, and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

Drug Product
The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III.2 Non-clinical aspects

Pharmacology/Pharmacokinetics/Toxicology
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, nor does the applicant provide any. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since this is a generic product, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of these products (see above) from a non-clinical point of view.

III.3 Clinical aspects

Pharmacokinetics
To support the marketing authorisation application the applicant has conducted one bioequivalence study comparing Aripiprazole with the reference product Abilify Maintena.

Pharmacokinetic properties of the active substance
Absorption: Aripiprazole absorption into the systemic circulation is slow and prolonged following intramuscular administration due to low solubility of aripiprazole particles. The average absorption half- life of aripiprazole is 28 days. Absorption of aripiprazole from the IM depot formulation was complete relative to the IM standard (immediate-release) formulation. The dose adjusted C_{max} values for the depot formulation were approximately 5 % of C_{max} from IM standard formulation. Following a single dose administration of Aripiprazole in the deltoid and gluteal muscle, the extent of absorption (AUC) was similar for both injection sites, but the rate of absorption (C_{max}) was higher following administration to the deltoid muscle. Following multiple intramuscular doses, the plasma concentrations of aripiprazole gradually rise to a maximum plasma concentration at a median t_{max} of 7 days for the gluteal muscle and 4 days for the deltoid muscle. Steady state concentrations for the typical subject were attained by the fourth dose for both sites of administration.

Linearity: Less than dose- proportional increases in aripiprazole and dehydro- aripiprazole concentrations and AUC parameters are observed after monthly aripiprazole injections of 300 mg to 400 mg.

Elimination: After administration of multiple doses of 400 mg or 300 mg of aripiprazole, the mean aripiprazole terminal elimination half-life is respectively 46.5 and 29.9 days presumably due to absorption rate- limited kinetics.

Study C2A01319 (multiple dose study with the 400 mg strength)
Methods
This was a multiple-dose, two-way crossover study conducted in 60 patients, comparing Aripiprazole, 400 mg, prolonged-release suspension for injection with Abilify Maintena, 400 mg, prolonged-release suspension for injection.

After stabilization period (3 consecutive monthly doses) patients received six injections during period I (on days 0, 28, 56, 84, 112, 140) and six injections during period II (on days 168, 196, 224, 252, 280, 308). Blood samples for concentration analysis were collected pre-dose (Day 84, Day 112, Day 140, Day 252, Day 280 and Day 308). Blood samples were also collected frequently after 5^{th} and 6^{th} dose for each period (i.e. after day 112, 140, 280 and 308).

Plasma concentrations of aripiprazole were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for $C_{max\ ss}$, $C_{\tau\ ss}$ and $AUC_{0\text{-}\tau\ ss}$. The study was conducted between 28th February 2022 and 25th November 2023.

Results
The results from the pharmacokinetic and statistical analysis are presented in Table 1 below.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) for aripiprazole.

Treatment	$AUC_{0\text{-}\tau\ ss}$ µg*h/ml	$C_{max\ ss}$ ng/ml	$C_{\tau\ ss}$ ng/ml
Test	**210.46 n=96**	**417.21 n=100**	**265.82 n=100**
Reference	**208.22 n=96**	**412.94 n=98**	**273.66 n=97**
***Ratio (90% CI)**	**101.07 (96.84- 105.49)**	**101.03 (95.66-106.71)**	**97.14 (90.13- 104.68)**
$AUC_{0\text{-}\tau}$ area under the plasma concentration-time curve during one dosing interval C_{max} maximum plasma concentration C_{trough} plasma concentration at the end of the dosing interval t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*
*** One subject (04-05-014), concentration at 672.00 hr was missing. Hence, n=24 instead of 25 for $C_{\tau\ ss}$.*

For $C_{max\ ss}$, $C_{\tau\ ss}$ and $AUC_{0\text{-}\tau\ ss}$ the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00%.

A biowaiver was sought for the additional strength of 300 mg.

Discussion and overall conclusion
According to the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1), a single-dose study and a multiple-dose study is needed in case of accumulation. The applicant performed a multiple-dose study in patients. A study in patients is acceptable since administration of aripiprazole LAI is not considered appropriate in healthy volunteers. Waiving a single dose study is acceptable as a single dose study in patients would require the use of another antipsychotic agent, since the co-administration of oral aripiprazole would bias any comparison. In those patients, it would theoretically be possible to investigate the PK of a single dose while maintaining another oral antipsychotic but there are considerable risks and feasibility issues.

Six doses of aripiprazole LAI per period were administered without any washout period, with PK profiling taking place both after the 5th and 6th dose. According to the Guideline on the pharmacokinetic and clinical evaluation of modified dosage forms (EMA/CPMP/EWP/280/96 Corr1), in steady-state studies, the washout period of the previous treatment can overlap with the build-up of the second treatment (direct switching), provided the build-up is sufficiently long (at least 5 times terminal half-life). According to the SmPC of Abilify Maintena, the half-life was 46.5 days following an intramuscular dose of 400 mg. The SmPC also states that aripiprazole steady-state concentrations for the typical subject are attained by the 4th dose, thus it is reasonable to conclude that steady state will be achieved at the 5th dose.

The bioequivalence study (multiple dose (study C2A01319)) and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the

pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1). The study was conducted in line with the CHMP scientific advice given in 2020. The bioanalytical methods were adequately validated.

Absence of studies with the additional strength of 300 mg is acceptable. While the SmPC of Abilify Maintena states that less than dose-proportional increases in aripiprazole concentrations and AUC parameters are observed after monthly injections of 300 mg to 400 mg, the deviation from non-linearity was less than 25%. All conditions for biowaiver for additional strength, as described in the Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms (EMA/CPMP/280/96 Corr1), section 6.4.2.are fulfilled.

Pharmacodynamics/Clinical efficacy/Clinical safety
No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted. Provided that bioequivalence with the originator product is demonstrated, additional data is not necessary.

Pharmacovigilance system
Proposed MAH: Pharmathen S.A. (SE/H/2565/01-02/DC)
The Applicant 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.

Proposed MAH: Sandoz A/S and others (Sandoz group of companies) (SE/H/2579-2581/01-02/DC)

The Applicant has submitted a signed Summary of the Applicant's/Proposed Future MAH's Pharmacovigilance System together with an annex listing all relevant subsidiaries. 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
The MAH has submitted a risk management plan, 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 SE/H/2565/01-02/DC, SE/H/2579/01-02/DC, SE/H/2580/01-02/DC and SE/H/2581/01-02/DC.

Part II Safety specification
SE/H/2565/01-02/DC: The MAH has submitted the version 0.2 RMP dated 14.07.2025 and proposed the following summary of safety concerns.

SE/H/2579/01-02/DC, SE/H/2580/01-02/DC and SE/H/2581/01-02/DC: The MAH has submitted the version 1.1 RMP dated 18-July-2025 and proposed the following summary of safety concerns.

Summary of safety concerns	
Important identified risks	Extrapyramidal symptoms (EPS), including tardive dyskinesia
Important potential risks	Orthostatic hypotension
Missing information	Use in pregnancy and lactation Use in elderly patients above 65 years of age

Part III Pharmacovigilance Plan

SE/H/2565/01-02/DC: Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

SE/H/2579/01-02/DC, SE/H/2580/01-02/DC and SE/H/2581/01-02/DC: Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Part VI Summary of the RMP
The Summary of the RMP is endorsed.

Conclusion RMP assessment
SE/H/2565/01-02/DC: The submitted Risk Management Plan, version 0.2 signed 14.07.2025 is considered acceptable.

SE/H/2579/01-02/DC, SE/H/2580/01-02/DC and SE/H/2581/01-02/DC: The submitted Risk Management Plan, version 1.1 signed 18-July-2025 is considered acceptable.

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, but via different procedures.

Periodic Safety Update Report (PSUR)

Active substance is currently listed in the published EURD list

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.

- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

Common renewal date
The common renewal date will be 5 years after closure of the DCP.

IV. BENEFIT RISK ASSESSMENT

The quality of the generic products, Lipahar and others, is found adequate. There are no objections to approval of Lipahar and others from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

V. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

V.1 List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

N/A

V.2 List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

N/A

V.3 Summary of Product Characteristics (SmPC)

The approved SmPC is available in the MRI Product Index.

V.4 Package Leaflet (PL)

V.4.1 Package Leaflet

The approved PL is available in the MRI Product Index.

V.4.2 Assessment of User Testing

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 PL was English.

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.

V.5 Labelling

The approved Labelling is available in the MRI Product Index.

VI. STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-