

Public Assessment Report Scientific discussion

Safinamid ELPEN (safinamide)

SE/H/2675 /01-02/DC

This module reflects the scientific discussion for the approval of Safinamid ELPEN. The procedure was finalised at 2025-11-12. For information on changes after this date please refer to the module 'Update'.

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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 Safinamid ELPEN, 50 mg, 100 mg, Film-coated tablet.

The active substance is safinamide, safinamide mesilate. A comprehensive description of the indication and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1 About the product

Pharmacotherapeutic group: Anti-Parkinson-Drugs, monoamine oxidase -B inhibitors,
ATC code: N04BD03.

Mechanism of action

Safinamide acts through both dopaminergic and non-dopaminergic mechanisms of action. Safinamide is a highly selective and reversible MAO-B inhibitor causing an increase in extracellular levels of dopamine in the striatum. Safinamide is associated with state-dependent inhibition of voltage-gated sodium (Na⁺) channels, and modulation of stimulated release of glutamate. To what extent the non-dopaminergic effects contribute to the overall effect has not been established.

Claimed indication

For the treatment of adult patients with idiopathic Parkinson's disease (PD) as add-on therapy to a stable dose of levodopa (L-dopa) alone or in combination with other PD medicinal products in mid-to late-stage fluctuating patients.

II.2 General comments on the submitted dossier

The application for Safinamid ELPEN, 50 mg, 100 mg, film-coated tablet, is a Generic Art. 10(1) application submitted according to Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Xadago, 50 mg, film-coated tablet, authorised in the Union since 2015, with Zambon SpA as marketing authorisation holder.

The reference product used in the bioequivalence study is Xadago, 100 mg, film-coated tablet from Germany with Zambon SpA 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.

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.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

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. The applicant has provided the outcomes of recent inspections. No inspection of the submitted study is deemed necessary.

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 safinamide are well known. As safinamide 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)

An ERA document has been submitted including answers and justifications to the questions in the Phase 1 and PBT/vPvB screening decision trees in the new ERA guideline.

The default and refined PEC_{SW} values for safinamide are higher than the action limit of 0.01 µg/L, thus triggering a phase II risk assessment. Acceptable arguments have been provided supporting that the ERA of the reference product can be considered complete. Further, arguments have been provided to support the position that a risk assessment for the soil compartment is not triggered, and that an assessment of the risk for secondary poisoning is not triggered.

Safinamide is not a PBT substance.

Therefore safinamide is not expected to pose a risk to the environment.

III.3 Clinical aspects

Pharmacokinetics

To support the marketing authorisation application the applicant has conducted one single-dose bioequivalence study in the fasted state comparing Safinamide, 100 mg, film-coated tablet, with the reference product Xadago, 100 mg, film-coated tablet.

Pharmacokinetic properties of the active substance

Absorption: Safinamide has an oral bioavailability of 95 %. Following an oral dose of safinamide maximal plasma concentrations occur at approximately 1.8-2.8 hours.

There are no restrictions with respect to food in the SmPC of the originator.

Linearity: The pharmacokinetics of safinamide is linear after single and repeated doses.

Elimination: The terminal half-life is 20-30 hours.

Study 2861 - Fasted

Methods

This was a single-dose, two-way crossover study conducted in 24 healthy volunteers, comparing Safinamide, 100 mg, film-coated tablet, with Xadago, 100 mg, film-coated tablet, under fasting conditions. Blood samples for concentration analysis were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of safinamide were determined with an LC-MS/MS method. Analysis of variance (ANOVA) was performed on the ln-transformed data for AUC_{0-72} and C_{max} . The study was conducted between 2024-02-26 and 2024-04-11.

Results

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

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, $t_{\max}$ median, range) for safinamide, n=24.

Treatment	AUC₀₋₇₂ ng*h/ml	C_{max} ng/ml	t_{max} h
Test	18761.50 ± 2845.49	711.70 ± 121.70	1.67 (1.00 – 6.00)
Reference	18373.44 ± 3226.87	690.38 ± 168.60	1.33 (1.00 – 6.00)
*Ratio (90% CI)	102.49 (100.72 - 104.29)	104.55 (99.33 - 110.05)	-
AUC ₀₋₇₂ area under the plasma concentration-time curve from time zero to 72 hours C _{max} maximum plasma concentration t _{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

For AUC₀₋₇₂ and C_{max} 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 50 mg.

Discussion and overall conclusion

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence study (2861), Safinamide, 100 mg, film-coated tablet, can be considered bioequivalent with Xadago, 100 mg, film-coated tablet.

From a pharmacokinetic point of view, absence of studies with the additional strength of 50 mg is acceptable, as all conditions for biowaiver for additional strength, as described in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr) are fulfilled and since the pharmacokinetics of safinamide is linear.

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: ELPEN Pharmaceutical Co. Inc.

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.

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/2675/01-02/DC.

Part II Safety specification

The MAH has submitted the version 0.4 RMP dated 29/10/2025 for SE/H/2675/01-02/DC and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	• Dyskinesia • Teratogenicity
Important potential risks	• Retinal degeneration in patients with Parkinson disease treated with safinamide • Use in severe hepatic impairment • Impulse control disorders (ICDs) • Concomitant use of MAOIs, serotonergic drugs, and/or pethidine
Missing information	• Use in patients with history and/or presence of retinal disease • Use of safinamide in patients aged <30 years • Long term use >3 years • Whether specific inhibitors of the amidases involved in the metabolism of safinamide to NW-1153, may increase the exposure of safinamide

The Summary of safety concerns is in line with the safety concerns listed for the originator Xadago and is considered appropriate.

Part III Pharmacovigilance Plan

Routine pharmacovigilance is suggested and in accordance with the originator the applicant has proposed follow-up questionnaires concerning risk of retinal degeneration in PD patients treated with safinamide, which is acknowledged. 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

The submitted Risk Management Plan, version 0.4 signed 29/10/2025 and 0.2 signed 03/06/2025 respectively 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

Quality of the generic product, Safinamid ELPEN, is found adequate. There are no objections to approval of Safinamid ELPEN, 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

Post approval commitments

N/A

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

- **Additional risk minimisation measures (including educational material)**

N/A

- **Obligation to conduct post-authorisation measures in accordance with Article 21a of Directive 2001/83/EC**

N/A

- **Specific obligation to complete post-authorisation measures for the marketing authorisation under Exceptional circumstances in accordance with 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

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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.

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
-	-	-	-	-	-