LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Lanthanum Orifarm
(lanthanum, lanthanum (III) carbonate octahydrate)

SE/H/2395/01-03/DC

This module reflects the scientific discussion for the approval of Lanthanum Orifarm. The procedure was finalised on 2025-03-03. 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, a marketing authorisation has been granted for Lanthanum Orifarm, 500 mg, 750 mg, 1000 mg, Chewable tablet.

The active substance is lanthanum, lanthanum (III) carbonate octahydrate. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Lanthanum Orifarm, 500 mg, 750 mg, 1000 mg, chewable tablet, is a hybrid application submitted according to Article 10(3) of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK and NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Fosrenol, 500 mg, chewable tablet, authorised in Sweden since 2004, with Takeda Pharmaceuticals International AG Ireland Branch as marketing authorisation holder.

Potential similarity with orphan medicinal products
N/A

II. QUALITY ASPECTS

II.1 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.

II.2 Medicinal 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. NON-CLINICAL ASPECTS

Pharmacology/Pharmacokinetics/Toxicology
Pharmacodynamic, pharmacokinetic and toxicological properties of lanthanum carbonate octahydrate are well known. As lanthanum carbonate octahydrate 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 Lanthanum Orifarm is a natural substance, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

Conclusions on studies: The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, lanthanum carbonate octahydrate is not expected to pose a risk to the environment.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has submitted *in vitro* tests and phosphate binding studies (equilibrium binding study and kinetic binding study) comparing Lanthanum Orifarm with the reference product Fosrenol.

Pharmacokinetic properties of the active substance
Lanthanum is present in the environment. Measurement of background levels in non-lanthanum-treated chronic renal failure patients during Phase III clinical trials revealed concentrations of <0.05 to 0.90 ng/mL in plasma, and <0.006 to 1.0 µg/g in bone biopsy samples.

Absorption
Lanthanum has low aqueous solubility (<0.01 mg/mL at pH 7.5) and is minimally absorbed following oral administration. Absolute oral bioavailability is estimated to be <0.002% in humans.

In healthy subjects, plasma AUC and C_{max} increased as a function of dose, but in a less than proportional manner, after single oral doses of 250 to 1000 mg lanthanum, consistent with dissolution-limited absorption. The apparent plasma elimination half-life in healthy subjects was 36 hours.

In renal dialysis patients dosed for 10 days with 1000 mg lanthanum 3 times daily, the mean (± sd) peak plasma concentration was 1.06 (± 1.04) ng/mL, and mean AUC_{last} was 31.1 (± 40.5) ng·h/mL. Regular blood level monitoring in 1707 renal dialysis patients taking lanthanum for up to 2 years showed no increase in plasma lanthanum concentrations over this time period.

Discussion and overall conclusion
To support the marketing authorisation application, the applicant has submitted *in vitro* tests and phosphate binding studies (equilibrium binding study and kinetic binding study).

In certain cases a PK bioequivalence study in humans may be indicative of therapeutic equivalence (e.g. drugs that are mainly absorbed from the sites of action).

In those cases where some degree of drug absorption and systemic bioavailability is observed, a bioequivalence study is required in order to address systemic safety, unless otherwise justified. Lanthanum is minimally absorbed following oral administration. The absence of PK bioequivalence study is acceptable provided that *in vitro* equivalence is demonstrated.

Equivalence with the reference product has been demonstrated *in vitro*. The *in vitro* tests and phosphate binding studies are assessed in the quality assessment report.

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

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 Lanthanum Orifarm.

Part II Safety specification
Part II Module SVIII has been updated in line with the PSUSA/00003175/202103. The additions are underlined.

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Gastrointestinal obstruction, Ileus, Subileus, Gastrointestinal perforation • Lanthanum deposition in the gastrointestinal tract
Important potential risks	• Lanthanum deposition (e.g. bone, liver) • Systemic allergic reactions • Medication error associated with incompletely chewed/unchewed tablet
Missing information	• Effects of lanthanum deposition on long term use

Part III Pharmacovigilance Plan
Routine pharmacovigilance is suggested, and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Part V Risk minimisation measures
Part V risk minimisation tables has been updated in line with the PSUSA/00003175/202103.

Part VI Summary of the RMP
The Summary of the RMP has been updated in line with the RMP updates specified above.

Conclusion RMP assessment
The MAH has satisfactorily responded to the questions raised and updated the RMP accordingly.

The submitted Risk Management Plan, version 2.0 signed 11.12.2024 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.

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PL) has been performed on the basis of a bridging report making reference to Fosrenol, SE/H/0481/001-004/E/001 regarding content and Kaliumklorid Orifarm, DK/H/2347/001 regarding design/layout and format.

The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Lanthanum Orifarm, is found adequate. There are no objections to approval of Lanthanum Orifarm, from a non-clinical and clinical point of view. The absence of bioequivalence studies is acceptable. Equivalence with the reference product has been demonstrated *in vitro*, which is acceptable given the local site of action. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Lanthanum Orifarm, 500 mg, 750 mg, 1000 mg, Chewable tablet was positively finalised on 2025-03-03.

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Public Assessment Report – Update

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

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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