LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report

Scientific discussion

Natriumoxibat Reig Jofre (sodium oxybate)

SE/H/1742/01/DC 2017-1326

This module reflects the scientific discussion for the approval of Natriumoxibat Reig Jofre. The procedure was finalised on 2018-11-21. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Natriumoxibat Reig Jofre, 500 mg/ml, oral solution, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Laboratorio Reig Jofre, S.A. applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DK, ES, FI and FR as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Xyrem, 500 mg/ml, oral solution authorised in the Community since 2005, with UCB Pharma Ltd as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

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

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

III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

Natriumoxibat Reig Jofre is an oral solution containing the same active substance in the same amount as the originator. Both the test and the reference product are simple formulations only containing active substance, pH adjuster and water. In accordance with the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1), waiving the bioequivalence study is acceptable.

IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

IV.3 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, characterize, prevent or minimize risks relating to Natriumoxibat Reig Jofre.

Safety specification
The MAH has submitted an updated version of the RMP, version 0.2 dated 18/05/2018, and proposed the following summary safety concerns:

Important identified risks	Overdose
	Respiratory depression
	CNS depression
	Depression/suicidality
	Convulsions
	Misuse/Abuse
	Dependence/withdrawal

	Diversion/criminal use
	Alcohol interaction
	Psychosis
Important potential risks	Aggravation of cardiac failure due to additional sodium load
	Fluid retention in patients with compromised renal function due to additional sodium load
Missing Information	Use in pregnancy/lactation
	Use in children/adolescents
	Use in elderly
	Use in patients with BMI ≥40 kg/m^2

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

Risk minimisation measures
Distribution, send list and the final wordings of the educational material is a matter of decision on national level. However, educational material is considered as a condition, defined as bullet points below (section VI.3).

Summary of the RMP
The submitted Risk Management Plan, version 0.2, signed 18/05/018 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 Xyrem 500 mg/mL oral

solution (EMEA/H/C/000593) and Pantoprazole 40 mg powder for solution for injection (UK/H/2757/01/DC). 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, Natriumoxibat Reig Jofre, is found adequate. There are no objections to approval of Natriumoxibat Reig Jofre, from a non-clinical and clinical point of view. The product information is acceptable.
The application is therefore recommended for approval.

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

N/A

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

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

The Marketing Authorisation Holder (MAH) shall develop an educational programme for Natriumoxibat Reig Jofre to ensure that physicians who intend to prescribe Natriumoxibat Reig Jofre are aware about the posology of Natriumoxibat Reig Jofre and about the important risks. The four components of this comprehensive program are:

- Healthcare Professional Checklist (i.e. treatment initiation forms): to remind physicians to check the contraindications, warnings, and precautions in the SmPC and specifically highlighting that Natriumoxibat Reig Jofre can cause CNS and respiratory depression, that alcohol may result in the potentiation of CNS depression and that Natriumoxibat Reig Jofre has an abuse potential.
- Frequently Asked Questions (FAQ) Patient Information Sheet (to be given to the patient): to provide patients with responses to some questions they might have about taking Natriumoxibat Reig Jofre.
- How to Take Natriumoxibat Reig Jofre brochure (to be given to the patient): to provide patients with information related to the use of Natriumoxibat Reig Jofre.
- Patient Alert Card (to be given to the patient): to remind patients, physicians and/or pharmacists of the important safety information related to the use of Natriumoxibat Reig Jofre.

VII. APPROVAL

The Decentralised procedure for Natriumoxibat Reig Jofre, 500 mg/ml, oral solution was positively finalised on 2018-11-21.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected	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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