COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Arixobat 500 mg/ml, oral solution

(sodium oxybate)

NL/H/4915/001/DC

Date: 21 December 2020

This module reflects the scientific discussion for the approval of Arixobat 500 mg/ml, oral solution. The procedure was finalised at 16 September 2020. 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
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
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 Arixobat 500 mg/ml, oral solution, from Aristo Pharma GmbH.

The product is indicated for the treatment of narcolepsy with cataplexy in adult patients.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Xyrem 500 mg/ml oral solution which has been registered in EEA by UCB Pharma S.A. since 13 October 2005 via a centralised procedure (EU/1/05/312).

The concerned member states (CMS) involved in this procedure were Denmark, Norway and Sweden.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Arixobat is a clear oral solution. Each ml of solution contains 500 mg of sodium oxybate.

The oral solution is packed in a 200 mL amber PET (polyethylene terephthalate) bottle containing 180 mL of oral solution and closed with an external white, inner transparent child-resistant plastic screw cap composed of HDPE/polypropylene with a white sealing disk made of expanded polyethylene. Each carton contains one bottle, a graduated measuring device (transparent polypropylene syringe with white PE piston) 4.5 g capacity with 0.25 g graduations, a transparent LDPE adaptor of the syringe, two orange polypropylene dosing cups of 90 ml capacity and two white HDPE screw closures. A comma is used as decimal separator on the syringe graduation.

The excipients are: malic acid (for pH adjustment), sodium hydroxide (for pH adjustment) and purified water.

II.2 Drug Substance

The active substance is sodium oxybate (gamma hydroxy butyric acid sodium salt), an established active substance, however not described in the European Pharmacopoeia

(Ph.Eur.). The drug substance is a fine, almost white and odourless powder, which is freely soluble in water, practically insoluble in ethanol and in methylene chloride. As the molecule does not contain a chiral centre, optical isomerism does not apply. No polymorphism in sodium gamma hydroxy butyrate has been observed or reported in the literature.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process comprises of one chemical stage, as well as a final purification step. The starting materials, solvents and reagents have been adequately described and are acceptable. Overall, the manufacturing process is sufficiently described in the ASMF procedure.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. The proposed limits for impurities are in accordance with the relevant ICH guideline. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance

Stability data on the active substance have been provided for five batches stored at 25°C/60% RH (up to 60 months) and three batches stored at 40°C/75% RH (6 months). The batches were stored in accordance with applicable the ICH guideline. Based on the data submitted, a retest period could be granted of 60 months when stored under the stated conditions.

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. No bioequivalence studies have been provided. Given the proposed product is an aqueous solution for oral use which is essentially similar, in terms of composition and physico-chemical characteristics to the reference product Xyrem 500 mg/ml oral solution, this is acceptable.

Manufacturing process
The manufacturing process consist of preparation of solution, filtration, filling and closure and has been validated according to relevant European guidelines. It is considered a standard process. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients
All excipients are controlled conform Ph.Eur. 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, identification, assay, related substances, pH, density, fill volume, uniformity of mass of delivered doses from multidose containers, microbial quality, and water loss. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches 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 for three batches stored at 25°C/60% RH (24 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). One batch is also stored in inverted position at long-term conditions. No general differences between upright and inverted position can be observed. The product is photo stable upon direct exposure. Based on the provided stability data the proposed shelf-life of 3 years is regarded acceptable. No specific storage conditions are necessary. An in-use shelf-life after opening of 45 days, and an in-use shelf-life after dilution of 24 hours are acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Arixobat has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. The following post-approval commitment was made:

- The MAH commits to perform additional in use-studies when the final products are close to the end of their shelf life.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Arixobat is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Xyrem which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is 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

Arixobat is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

According to the current Guideline on Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** '*If the test product is an aqueous oral solution at time of administration and contains an active substance in the same concentration as an approved oral solution, bioequivalence studies may be waived*'.
The MAH states that according to the SmPC of Xyrem 500 mg/ml oral solution, the active substances and excipients are qualitatively and quantitatively the same in the test product and the reference product; thus, both medicinal products are bioequivalent. Therefore, an abridged application under Article 10(1) of Directive 2001/83/EC as amended is justified.

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, characterise, prevent or minimise risks relating to Arixobat.

Table 1. Summary table of safety concerns as approved in RMP

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 comprised 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

The Marketing Authorisation Holder (MAH) shall develop an educational programme for sodium oxybate to ensure that physicians who intend to prescribe are aware about the posology of sodium oxybate 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 sodium oxybate can cause CNS and respiratory depression, that alcohol may result in the potentiation of CNS depression and that sodium oxybate 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 sodium oxybate.
- How to take sodium oxybate brochure (to be given to the patient): to provide patients with information related to the use of sodium oxybate and reminder to instruct the patient that they should only use the syringe provided in the package.
- 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 sodium oxybate and containing a warning to always use the syringe supplied with the pack.

The MAH will established a controlled distribution program that enhances existing controls for sodium oxybate to allow reaching the intended population of narcolepsy patients while minimising the risk of sodium oxybate being diverted by those seeking to misuse it.

As part of the key elements of the additional risk minimisation measures above the MAH indicates that all important identified risks are addressed in each educational material. The

statement includes that the actual content of educational materials (HCP checklist, FAQ Patient Information Sheet, Patient Brochure and Patient Alert Card) and distribution plan in individual countries will be agreed with National Competent Authority before product launch.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Xyrem. No new clinical studies were conducted. 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. The test consisted of: a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL 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. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Arixobat 500 mg/ml, oral solution has a proven chemical-pharmaceutical quality and is a generic form of Xyrem 500 mg/ml oral solution. Xyrem is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product contain the same active substance and the dose administered is the same, no bioequivalence study is deemed necessary. A biowaiver has been granted.

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 Arixobat with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 16 September 2020.

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