COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Lorazepam Prolepha 0.5 mg, tablets

(lorazepam)

NL License RVG: 123766

Date: 25 March 2020

This module reflects the scientific discussion for the approval of Lorazepam Prolepha 0.5 mg, tablets. The procedure was finalised on 20 November 2019. 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 Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Lorazepam Prolepha 0.5 mg, tablets, from Prolepha Research B.V.

The product is indicated for:

- Short-term symptomatic treatment of anxiety and insomnia caused by anxiety, where the anxiety is severe, disabling or subjecting the individual to extreme distress
- Premedication before general anaesthesia or before minor surgical procedures, investigations or operative dentistry.

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

This application is claiming to be a hybrid medicinal product of the UK reference products Lorazepam 1 and 2.5 mg Tablets, which were first granted licences to John Wyeth and Brother Limited in 1985. The EU originator product is Temesta 2.5 mg tablets (Laboratoires Biodim, France), which was granted in June 1973. No 0.5 mg tablet strength is available for this product.

This national procedure concerns a line extension to the existing marketing authorisations of Lorazepam GenRx 1 mg and 2.5 mg tablets, which are approved for marketing in the Netherlands in 1997 (NL License RVG 19695 and 19696) in a national procedure and on 23 September 2012 in procedure (NL/H/3485/001-002/DC). The current application adds a new strength, 0.5 mg, to the marketing authorisation of Lorazepam GenRx.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application as a 0.5 mg strength innovator product is not available. For the clinical data of lorazepam, reference is made to Lorazepam GenRx 1 mg and 2.5 mg tablets.

II. QUALITY ASPECTS

II.1 Introduction

Lorazepam Prolepha 0.5 mg is a white, round, flat, beveled, scored tablet and contains 0.5 mg lorazepam.

The tablets are packed in opaque Alu/Alu blisters.

The excipients are: lactose monohydrate, povidone (K 30), crospovidone Type A, maize starch, microcrystalline cellulose (E460), sodium starch glycolate, polacrilin potassium and magnesium stearate (E572)

II.2 Drug Substance

The active substance is lorazepam, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Lorazepam is a white or almost white crystalline powder and practically insoluble in water, sparingly soluble in ethanol (96%), sparingly soluble or slightly soluble in methylene chloride. Lorazepam exhibits polymorphism, but since lorazepam is solubilised in the drug product, the polymorphism is not considered important.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for one batch.

Stability of drug substance

The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

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 explained. The intention was to make an additional strength for the previously approved 1 mg and 2.5 mg strengths.

Reference has been made to the bioequivalence study performed with the 2.5 mg strength. This study already has been evaluated for a previous application (NL/H/ NL/H/3485/001-002/DC) concerning the 1 mg and 2.5 tablet strengths. For the 0.5 mg strength a biowaiver has been requested making reference to the above mentioned bioequivalence study.

Dissolution studies have been provided and the results show that the 0.5 mg strength exhibit rapid release of the active substance as more than 85% dissolved within 15 minutes in all three dissolution media studied. Overall, the pharmaceutical development has been adequately performed.

Manufacturing process

The manufacturing process consists of weighing, mixing, drying, sieving and tabletting and has been validated according to relevant European guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients

The specifications of the excipients comply with the corresponding (Ph. Eur.) monographs. 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 general description, disintegration, hardness, average weight, lorazepam identification, lorazepam assay, related substances, uniformity of dosage units, dissolution, microbial contamination and impurities. 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 (15 months in PVC/PE/PVDC-aluminium blisters and 30 months in Alu/Alu blisters), 30°C/65% RH (12 months) and 40°C/75% RH (6 months). Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. A photostability study showed that the product is sensitive to light. On basis of the data submitted, a shelf life was granted of 15 months when stored in the PVC/PE/PVDC-Aluminium blisters and 30 months when stored in the Aluminium-Aluminium blisters. The labelled storage conditions are “Store below 25°C. Store in original package to protect from light” and considered acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

With the exception of lactose monohydrate, no excipients are sourced from animal or human origin. The suppliers of lactose monohydrate have confirmed that the lactose is sourced from healthy animals under the same conditions as milk for human consumption. No genetically modified organisms (GMO) have been used in the preparation of these products.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that for Lorazepam Prolepha 0.5 mg, tablets has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since for Lorazepam Prolepha 0.5 mg, tablets is intended for hybrid 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 hybrid formulation of Lorazepam 1 and 2.5 mg Tablets 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 MEB agrees that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Lorazepam 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 MEB agrees that no further clinical studies are required.

For this line extension, the bioequivalence study with the higher 2.5 mg strength that was used for the initial procedure (NL/H/3485/001-002/DC) has been submitted and a biowaiver has been requested for the additional 0.5 mg strength. The bioequivalence study and the biowaiver will be discussed below.

IV.2 Pharmacokinetics

Biowaiver

A biowaiver has been requested to extrapolate the results of the bioequivalence study performed with the 2.5 mg strength to the 0.5 mg strength.

The MAH provided a publication of a study from Morrison *et al*. (1984)[1] as scientific justification for the linearity in pharmacokinetics of lorazepam. The guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) states that: *Assessment of linearity will consider whether differences in dose-adjusted AUC meet a criterion of ± 25%*. Although this assessment has not been performed in the publication, linearity has been observed between 1.5 mg and 3.0 mg doses. A biowaiver for the 0.5 mg can therefore be accepted as no difference in pharmacokinetics is expected for the 0.5 mg dose. Furthermore, the applicant provided dissolution studies comparing the 0.5 mg tablet with the 2.5 mg tablet (the strength evaluated in the bioequivalence study). Both strengths demonstrate more than 85% dissolution within 5 min. Therefore, the biowaiver is acceptable.

Bioequivalence study

A two-period, two-sequence, two-way, open-label, crossover, randomised study, comparing the pharmacokinetics of the proposed test product 2.5 mg strength tablets versus the reference product Temesta 2.5 mg tablets (Laboratoires Biodim, France) in fasted subjects.

Volunteers were dosed with either treatment after an overnight fast of at least 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 72 hours post dose. The two treatment arms were separated by a 6-day washout period.

The pharmacokinetic results (presented as geometric least-squares means, ratios and 90% confidence intervals) for serum lorazepam are presented below:

Parameters (Units)	**In-transformed Data**			**90% Confidence Interval (Parametric**
	Geometric Least Squares Mean			
	Test Product-B	**Reference Product-A**	**Ratio (B/A)%**	
Cmax (ng/mL)	29.233	29.133	100.087	93.889-106.694
AUC0-t (ng.h/mL)	490.126	478.266	101.663	97.705-105.781
AUC0-∞ (ng.h/mL)	521.872	507.587	101.782	98.172-105.525

AUC0-∞ area under the plasma concentration-time curve from time zero to infinity
AUC0-t area under the plasma concentration-time curve from time zero to t hours
Cmax maximum plasma concentration

[1] Morrison G. Chiang ST. Koepke HH. Walker BR. Effect of renal impairment and hemodialysis on lorazepam kinetics. Clinical Pharmacology & Therapeutics. 1984; 35(5):646- 52

The 90% confidence intervals for Cmax and AUC for test versus reference products are within predefined acceptance criteria specified in the "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 rev 1/, Corr**). The data support the claim that the 2.5 mg test product is bioequivalent to the 2.5 mg reference product.

As the 1 and 2.5 mg strengths of the product meet the criteria specified in the "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 rev 1/, Corr**), the extrapolation of results and conclusions from the bioequivalence study on the 2.5 mg strength to the 1 mg strength 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 Lorazepam Prolepha.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Abuse, misuse and dependence
Important potential risks	None
Missing information	- Use in pregnant women

The MEB agrees that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Lorazepam 1 and 2.5 mg Tablets. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study and a biowaiver that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Lorazepam GenRx 1 mg and 2.5 mg tablets, NL/H/3485/001-002/DC. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Lorazepam Prolepha has a proven chemical-pharmaceutical quality and is a hybrid form of Temesta tablets. Temesta is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that efficacy and safety has been shown, and has therefore granted a marketing authorisation. Lorazepam Prolepha 0.5 mg, tablets was authorised in the Netherlands on 20 November 2019.

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
- Type IB: A.z; - Type IA: A.7 (3x); - Type IA: B.II.b.3 a; - Type IA: B.II.d.1 d; - Type IB: B.II.d.1 d(2x); - Type II: B.II.d.1 e - Type IA; B.II.d.2.b - Type IAin: B.II.e.5 a 1; - Type IA: B.III.1.a 2	- Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products. - Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Article 45 or 46 of Regulation (EC) No 1901/2006; implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH	yes	29-11-2019	Approved	-
Type IB: B.II.f.1.b.1	Change in the shelf-life or storage conditions of the finished product; extension of the shelf life of the finished product as packaged for sale (supported by real time data)	yes	06-01-2020	Approved	-
- Type IB: C.I.z - Type IA(IN): C.I.3a	- Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products. - Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Article 45 or 46 of Regulation (EC) No 1901/2006; implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH	yes	27-02-2020	Approved	-