COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Lorazepam Medochemie Bohemia 0.5 mg, 1 mg and 2.5 mg tablets

(lorazepam)

NL/H/4647/001-003/DC

Date: 1 April 2020

This module reflects the scientific discussion for the approval of Lorazepam Medochemie Bohemia 0.5 mg, 1 mg and 2.5 mg tablets. The procedure was finalised at 30 January 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 Lorazepam Medochemie Bohemia 0.5 mg, 1 mg and 2.5 mg tablets, from Medochemie Bohemia, spol. s r.o..

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.
The product may also be used as premedication before diagnostic procedures, or before surgical interventions.

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

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Temesta 2.5 mg tablets which has been registered in France by Laboratoires Biodim since June 1973.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application as an additional indication compared to the reference product (i.e., premedication before diagnostic procedures, or before surgical interventions) is proposed. The German originator products Tavor 1 and 2.5 mg tablets also have this indication. This indication has also been approved in UK/H/4683/001-002/DC (now NL/H/3485/001-002/DC) and DE/H/5247-8/001-002/DC. Furthermore, the application for the 0.5 mg tablets is made under Article 10(3), a hybrid application of Directive 2001/83/EC as amended, because the reference product is not available in the strength 0.5 mg.

The concerned member states (CMS) involved in this procedure were Belgium, Germany and Italy.

II. QUALITY ASPECTS

II.1 Introduction

Lorazepam Medochemie Bohemia 0.5 mg is a white, round, rounded edge tablet and contains 0.5 mg lorazepam.
Lorazepam Medochemie Bohemia 1 mg is a white, round, flat, bevelled, scored tablets, with the inscription “1.0” on one side. The tablet contains 1 mg lorazepam and can be divided into equal halves.
Lorazepam Medochemie Bohemia 2.5 mg is a white, round, flat, bevelled, scored tablet. The tablet contains 2.5 mg lorazepam and can be divided into equal halves.

The tablets are packed in blisters of OPA/Aluminium/PVC/Aluminium.

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

The three tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is lorazepam, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white or almost white crystalline powder. It is practically insoluble in water, sparingly soluble in alcohol, sparingly soluble or slightly soluble in methylene chloride. Lorazepam exhibits polymorphism and the form used by for the development and manufacture is Form I. It has been confirmed that the active substance manufacturer is able to consistently produce the same crystalline form.

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 Ph.Eur.

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. The specification includes testing as per Ph. Eur. monograph for lorazepam and additional testing specified in the CEP. The MAH also controls the particle size and polymorphic form. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

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 function explained. To support the application, one bioequivalence study has been performed using the 2.5 mg strength of the finished product, and for the other strengths a biowaiver has been requested. Comparative dissolution profiles from two batches for each strength sourced from different suppliers are presented. In pH 1.2, 4.5 and 6.8, more than 85% of the active is released within 15 minutes for the 2.5 mg biobatch strength and the additional strength of the test product. All results show dissolution above 85% in 15 min hence the profiles are all comparable without further statistical analysis. Tablet breakability of the 1 mg and 2.5 mg strengths was tested and results achieved complied with the specifications given in the Ph. Eur. for subdivision of tablets. Overall, the pharmaceutical development has been adequately performed.

Manufacturing process

The manufacturing process involves blending, wet granulation, drying, final blending and tabletting and has been validated according to relevant European guidelines. Process validation data on the product have been presented for three commercial scale batches per strength in accordance with the relevant European guidelines.

Control of excipients

The excipients comply with the specifications of the monographs of the Ph. Eur. or United States Pharmacopeia/National Formulary. 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, identity, disintegration, tablet hardness, average weight, assay, related substances, an impurity, uniformity of dosage units (content uniformity), dissolution and microbial purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The proposed specifications comply in general with the requirements of the Ph. Eur. and applicable ICH guidelines. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three production scaled batches for each strength 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 of each strength stored at 25°C/60% RH (27-30 months), 30°C/65% RH (12 months), 40°C/75% RH (6 months). The batches were stored in accordance with applicable European guidelines. A photostability study has been performed and the results showed that the product is sensitive to light. On basis of the data submitted, a shelf life was granted of 30 months for the 0.5 mg strength

and 27 months for the 1 mg and 2.5 mg strengths. The labelled storage conditions are: 'Store below 25°C. Store in the original blister in order to protect from light.'
Holding time of 6 months is being requested for the bulk product. Holding time studies at warehouse conditions for the tablets in bulk packaging show that all results are within specification limits and no specific trends have been observed following batches of each strength stored for 6 months at warehouse storage conditions. Based on holding time data, the proposed holding time of 6 months in the bulk packaging for Lorazepam 0.5mg, 1mg and 2.5mg tablets is acceptable. Unless otherwise justified, the bulk product holding storage conditions are 15°C - 25°C. Considering the in-house simulation study and bulk stability studies of 6 months at warehouse conditions, the manufacturer concluded that transportation under controlled storage conditions between the manufacturing and packaging site will not have any impact on the drug product. This is acceptable.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
A TSE statement for lactose confirming compliance with Note for Guidance EMA/410/01, current version is provided. The MAH confirms that the lactose is produced from milk obtained from healthy animals in the same conditions as those used to collect milk for human consumption.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Lorazepam Medochemie Bohemia 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 Lorazepam Medochemie Bohemia 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 Temesta 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

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 member states agreed that no further clinical studies are required.

For this hybrid application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Lorazepam Medochemie Bohemia 2.5 mg tablets (Medochemie Bohemia, spol. s r.o., Czech Republic) is compared with the pharmacokinetic profile of the reference product Temesta 2.5 mg tablets (Laboratoire Biodim, France).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A biowaiver has been requested for the 0.5 mg and 1 mg strengths and could be granted as the following criteria have been fulfilled:

- The pharmaceutical products are manufactured by the same manufacturing process
- The qualitative composition of the different strengths is the same
- The bioequivalence study has been conducted with the highest strength
- The compositions are dose proportional
- The MAH has adequately demonstrated dissolution studies comparing the 0.5 mg tablet and 1 mg tablet with the 2.5 mg tablet (the strength evaluated in the bioequivalence study). All strengths demonstrate more than 85% dissolution within 5 minutes.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 26 healthy subjects with a mean age of 37.8 (SD ±6.5). Each subject received a single dose (2.5 mg) of one of the 2 lorazepam formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were 2 dosing periods, separated by a washout period of 5 days.

Blood samples were collected at pre-dose and at 0.33, 0.66, 1.0, 1.33, 1.66, 2.0, 2.33, 2.66, 3.0, 3.33, 3.66, 4.0, 5.0, 6.0, 7.0, 9.0, 12.0, 24.0, 36.0, 48.0 and 72 hours after administration of the products.

The design of the study is acceptable. Lorazepam may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of lorazepam. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
One subject withdrew from the study due to personal reasons and one subject was with drawn due to a positive alcohol test. Therefore, 24 subject completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of lorazepam under fasted conditions.

Treatment N=24	**AUC_{0-t}** (ng.h/ml)	**$AUC_{0-\infty}$** (ng.h/ml)	**C_{max}** (ng/ml)	**t_{max}** (h)
Test	490126 (± 153.921)	521872 (± 177.765)	29.233 (± 6.172)	1.403 (±0.874)
Reference	478266 (± 134.317)	507587 (± 152.145)	29.133 (± 6.781)	1.653 (±1.018)
***Ratio (90% CI)**	1.02 (0.98 – 1.06)	1.02 (0.98 – 1.06)	1.00 (0.94 – 1.07)	--
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity **AUC_{0-t}** area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration				

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Lorazepam Medochemie Bohemia is considered bioequivalent with Temesta.

The results of study with the 2.5 mg formulation can be extrapolated to other strengths 0.5 mg and 1 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

The application for Lorazepam 0.5mg tablets is made under Article 10.3, hybrid application of Directive 2001 / 83 / EC as amended, as the designated reference product is not available in the strength 0.5 mg. In The Netherlands, only 1 mg scored tablets are available on the market to fulfil the 0.5 dose. The extension with the 0.5 mg tablet is supported. The 0.5 mg strength fits well within the current posology, which includes a starting dose of 0.5 mg. Moreover, the strength facilitates gradual down-tapering at treatment discontinuation, as recommended in the SmPC. The additional 0.5 mg tablet is considered convenient for the patient as they do not have to split the 1 mg tablets.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 Medochemie Bohemia.

Table 2. 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 woman

The member states agreed 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 Temesta. Risk management is adequately addressed. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this 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-containing product of Medochemie Ltd, approved in the procedure DE/H/5247-48/DC. The bridging

report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Lorazepam Medochemie Bohemia 0.5 mg, 1 mg and 2.5 mg tablets has a proven chemical-pharmaceutical quality and are hybrid forms of Temesta 2.5 mg 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.

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 Lorazepam Medochemie Bohemia with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 30 January 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