COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Lorazepam Medochemie Bohemia 4 mg/ml, solution for injection

(lorazepam)

NL/H/5225/001/DC

Date: 29 March 2022

This module reflects the scientific discussion for the approval of Lorazepam Medochemie Bohemia. The procedure was finalised at 1 December 2021. 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 4 mg/ml, solution for injection, from Medochemie Bohemia, spol. s.r.o.

The product is indicated in adults and adolescents above 12 years of age:

- As premedication, before surgical procedures or prior to diagnostic procedures.
- For symptomatic treatment of acute anxiety states and agitation in patients who, for some reason, are unable to take oral medication.

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 European reference product (ERP) Temesta 4 mg/ml, solution for inejction (NL RVG 08192) which has been registered in The Netherlands by Pfizer B.V. since 1976 (original product).

The concerned member state (CMS) involved in this procedure was France.

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

II. QUALITY ASPECTS

II.1 Introduction

Lorazepam Medochemie Bohemia is a clear, colourless or almost colourless hypertonic solution, free from visible particles.

The product contains as active substance 4 mg/ml of lorazepam per ampoule.

The solution is packed in clear, glass ampoules and boxes.

The excipients are macrogol 400, benzyl alcohol and propylene glycol (E1520).

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, practically insoluble in water, sparingly soluble in ethanol (96%), sparingly soluble or slightly soluble in methylene chloride. Lorazepam exhibits polymorphism, but since lorazepam is solubilized 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 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 and meets the requirements of the monographs in the Ph.Eur. The analytical procedures for appearance, solubility, identification, related substances, loss on drying, sulphated ash, assay and bacterial endotoxins have been described. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance
The active substance is stable for five years when stored in double polyethylene bags in a polyethylene container. 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 drug product was developed to be identical to the reference product Temesta solution for injection 4 mg/ml marketed by Pfizer and authorized in the Netherlands. Since the drug product is of the same pharmaceutical form, is to be administered via the same route and contains the same quantity of lorazepam as the reference product, the applicant is not required to demonstrate bioequivalence. Sufficient details are provided for drug formulation development, including a

comparisons between the drug product and reference product. The manufacturing process development is considered sufficiently described.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three full-scale batches in accordance with the relevant European guidelines. The process is a preparation of sterile solution for injection and is considered a non-standard manufacturing process. Some details should be added to the description of the manufacturing process. Relevant process parameters are indicated. Information and justification on the maximum processing time has been provided. In addition to in-process controls the following additional tests were conducted; environmental monitoring, chemical and microbiological stability of the product during solution preparation and ampule filling, depyrogenation/sterilization of ampules, filter compatibility, viability and bacterial retention, filter extractables and process media fill. All parameters and attributes were found to be within acceptable ranges and according to acceptance criteria. The evaluation reports provided illustrate that the proposed drug product can be manufactured according to the proposals in the dossier.

Control of excipients

All the excipients used in the manufacturing of the drug product are commonly used in medicinal products and comply with their respective monographs in the 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 description, visible particles, clarity and color of solution, extractable volume, identification, related substances, assay, assay of benzyl alcohol, particle matter: sub-visible particles, sterility and bacterial endotoxins. 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. The established limits of quantitation for the specified and unspecified impurities for related substances are below the ICH Q3B reporting threshold of 0.1%. This is acceptable. Forced degradation studies were performed for assay, related substances and benzyl alcohol content. Peak purity was investigated and mass balance is demonstrated. The methods are considered as stability indicating.

Batch analytical data from three batches of each batch size from the proposed production site have been provided, demonstrating compliance with the specification. All parameters are within the specified limits. Impurities are well controlled. A risk assessment on elemental impurities has been provided. The risk evaluation on nitrosamines is acceptable; all potential sources of nitrosamines have been addressed and no risks of nitrosamine formation have been identified. Therefore, further control strategies are not required.

Stability of drug product

Stability data on the product have been provided for three batches up to 21 months under long term (5 °C) stability and six months under accelerated conditions (25 °C) in accordance with applicable European guidelines demonstrating the stability of the product for 18 months On basis of the data submitted, a shelf life was granted of 18 months with the special storage condition "Store and transport refrigerated. Keep in the original package in order to protect from light", and an in-use shelf-life of 1 hour at 2-8°C. The proposed shelf-life is acceptable as sufficient data is provided. The in-use shelf-life was established using a product near to or at the end of shelf-life and set at 1 hour. Freeze/thaw stability study are performed, showing no influence.

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 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 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 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 generic application, the MAH has submitted no bioequivalence studies, the reason for this is discussed below.

IV.2 Pharmacokinetics

Lorazepam Medochemie Bohemia 4 mg/ml, solution for injection is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Lorazepam Medochemie Bohemia 4 mg/ml is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

Biowaiver

The proposed product can be administered intravenously or intramuscularly, has the same qualitative and similar quantitative composition and the same type of solution as that of the reference product Temesta. Hence, the absence of a bioequivalence study is agreed in line with the BE guideline.

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 1. Summary table of safety concerns as approved in RMP

Important identified risks	• None

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. 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. Risk management is adequately addressed. This generic 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 Temesta 4 mg/ml solution for injection (RVG 08192) for key safety messages and Bysimin 20 mg/ml solution for injection (SE/H/1611/01/DC) for design and lay-out. 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 4 mg/ml, solution for injection has a proven chemical-pharmaceutical quality and is a generic forms of Temesta. Temesta is a well-known medicinal product with an established favourable efficacy and safety profile.

Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes. 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 concerned 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 1 December 2021.

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