COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Temelor 4 mg/ml solution for injection

# (lorazepam)

# NL/H/4352/001/DC

# Date: 23 August 2019

**This module reflects the scientific discussion for the approval of Temelor 4 mg/ml solution for injection. The procedure was finalised at 23 May 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

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| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| CMD(h) | Coordination group for Mutual recognition and Decentralised procedure for human medicinal products |
| CMS | Concerned Member State |
| 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 Temelor 4 mg/ml solution for injection from Medochemie Iberia, S.A.

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 pathological anxiety and tension 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 innovator product Temesta 4 mg/ml solution for injection (NL Licence RVG 08192) which has been centrally registered in the EEA by Pfizer B.V. since 24 November 1976.

The concerned member states (CMS) involved in this procedure were Bulgaria, Cyprus, Czech Republic, Estonia, Croatia, Lithuania, Latvia, Malta, and Romania.

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

# II. QUALITY ASPECTS

## II.1 Introduction

Temelor is a clear, colourless or almost colourless hypertonic solution, free from visible particles, for injection.

The solution is packed in type I, clear glass ampoule of 2 ml filling capacity. Each ampoule contains 4 mg/ml lorazepam (4 mg per 1 ml ampoule). The ampoules are placed in moulded polyvinyl chloride trays, which are then sealed by a protective PE transparent foil.

The excipients are macrogol, benzyl alcohol, and propylene glycol.

## 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. Batch analytical data demonstrating compliance with this specification have been provided for sufficient batches.

Stability of drug substance
The active substance is stable for five 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. Sufficient details are provided for drug formulation development, including a comparison between the drug product and reference product. The manufacturing process development is considered sufficiently described.

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, it is not required to submit bioequivalence studies.

Manufacturing process
The process is a preparation of sterile solution for injection and is considered a non-standard manufacturing process. It is described in sufficient details. Relevant process parameters are indicated. Information and justification on the maximum processing time have been provided.

The in-process controls are sufficient for a sterile solution for injection and the manufacturing process has been validated with three full scale batches. 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.

Control of excipients

All the excipients used in the manufacturing are commonly used in medicinal products and comply with their respective monographs in the Ph.Eur. Additionally, since nitrogen is intended for use in a parenteral preparation, in-house analytical procedures for assay and microbiological quality are described and validated. 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. Batch analytical data from three batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Three batches were included in the stability study. The MAH submitted stability data up to 21 months under long term stability and six months under accelerated conditions. At accelerated conditions out of specification (OoS) is observed for assay and related substances at three and six months. At long-term storage conditions no OoS results are observed. The results from the photostability study indicate that the drug substance and drug product are photolabile, and the drug product should therefore be kept in its secondary packaging.

On the basis of the data submitted, a shelf life was granted of 18 months with the storage condition “Store and transport refrigerated. Keep in the original package in order to protect from light”, and an in-use shelf-life of one hour at 2-8°C. The in-use shelf-life was established using a product near to or at the end of shelf-life and set at one hour. Freeze/thaw stability study have been performed, showing no influence. The special storage conditions are accepted.

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 Temelor 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 Temelor 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.

### IV.2 Pharmacokinetics

Biowaiver

Temelor 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 Temesta 4 mg/ml solution for injection 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.

### 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 Temelor.

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 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. 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

Temelor 4 mg/ml solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Temesta 4 mg/ml solution for injection. 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 member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Temelor with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 23 May 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 |
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