CBG MEB

Public Assessment Report

Scientific discussion

Lorazepam GenRx 1 mg and 2.5 mg tablets

(lorazepam)

NL/H/3485/001-002/DC

Date: 13 March 2015

This module reflects the scientific discussion for the approval of Lorazepam GenRx 1 mg and 2.5 mg tablets. The initial decentralised procedure was finalised on 23 September 2012. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Lorazepam GenRx 1 mg and 2.5 mg tablets from GenRx B.V.

These are prescription-only medicines 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.

Lorazepam is a benzodiazepine drug with a short to medium duration of action. It has all the well-known intrinsic benzodiazepine effects, such as anxiolytic, sedative/hypnotic, anticonvulsant, and muscle relaxing properties. It is a powerful anxiolytic. It is a unique benzodiazepine insofar as it has also found use as an adjunct antiemetic in chemotherapy.

These were applications submitted according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products 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.

The initial RMS for this product was the UK, the current RMS is the Netherlands. The concerned member states (CMS) involved in this procedure are Estonia, Greece and Lithuania.

No new non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

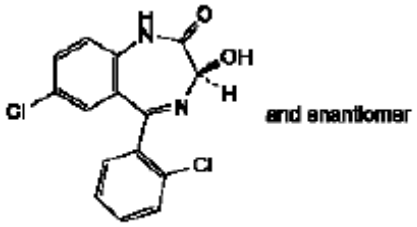
In support of these applications, the applicant has submitted a two-period, two-sequence, two-way, open-label, crossover, randomised study, comparing the pharmacokinetics of the proposed 2.5 mg strength tablets versus Temesta 2.5 mg tablets (Laboratoire Biodim, France). The bioequivalence study was conducted in accordance with Good Clinical Practice (GCP).

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of originator products that have been licensed for over 10 years.

II. QUALITY ASPECTS

II.1 Drug Substance

rINN:	Lorazepam
Chemical name:	(3*RS*)-7-Chloro-5-(2-chlorophenyl)-3-hydroxy-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 2*H*-1,4-benzdiazepine-2-one,7-chloro-5-(2-chlorophenyl)-1,3-dihydro-3-hydroxy-(±) (±)-7-Chloro-5(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2*H*-1,4-benzodiazepine-2-one
Structure:	



Molecular formula:	$C_{15}H_{10}Cl_2N_2O_2$
Molecular weight:	321.2
Appearance:	White or almost white crystalline powder
Solubility:	Practically insoluble in water, sparingly soluble in ethanol (96%), sparingly soluble or slightly soluble in methylene chloride.

With the exception of the container-closure system and stability, all aspects of the manufacture and control of the active ingredient are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.2 Medicinal Product

Excipients
Other ingredients consist of the pharmaceutical excipients lactose monohydrate, povidone (K30), crospovidone (Type A), maize starch, microcrystalline cellulose (E460), sodium starch glycolate, polacrilin potassium and magnesium stearate (E572). With the exception of polacrilin potassium, all excipients are controlled to their respective European Pharmacopoeia monograph. Polacrilin potassium is controlled to a suitable United States Pharmacopoeia/National Formulary specification.

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.

Pharmaceutical Development
The objective of the development programme was to formulate globally acceptable, stable and bioequivalent products that could be considered generic medicinal products of the originator products Lorazepam 1 and 2.5 mg Tablets, which were first granted licences to John Wyeth and Brother Limited in 1985.
A satisfactory account of the pharmaceutical development has been provided. Comparative *in vitro* assay and impurity profiles have been provided for the proposed products versus the originator products.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the finished products. The manufacturing process has been validated using commercial and pilot-scale batches and has shown satisfactory results.

A commitment has been provided to perform validation studies on the first three commercial-scale batches when they are manufactured.

Finished Product Specifications
The finished product specifications proposed are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container-Closure System
The finished products are packaged in opaque polyvinylchloride/polyethylene/polyvinylidene chloride/aluminium blisters in pack sizes of 10, 14, 15, 20, 28, 30, 50, 60, 90, 100 and 500 tablets. Not all pack sizes may be marketed. However, the marketing authorisation holder has committed to submitting mock-ups to the relevant authorities before marketing any pack size.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 15 months, with the storage conditions “Store below 25°C. Store in original package to protect from light.”

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Suitable justification has been provided for the non-submission of an environmental risk assessment. As these products are intended for generic substitution with products that are currently marketed, no increase in environmental burden is expected.

III.2 Discussion on the non-clinical aspects

As the pharmacodynamic, pharmacokinetic and toxicological properties of lorazepam are well-known, no further non-clinical studies are required and none have been provided.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the products’ pharmacology and toxicology.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

With the exception of the bioequivalence study, no new clinical pharmacology data have been submitted and none are required for applications of this type.

The below bioequivalence study was submitted to support these applications, in accordance with the *Guideline on the Investigation of Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). The bioequivalence study was conducted in accordance with Good Clinical Practice (GCP).

Bioequivalence study
A two-period, two-sequence, two-way, open-label, crossover, randomized study, comparing the pharmacokinetics of the proposed test product 2.5 mg strength tablets versus the reference product Temesta 2.5 mg tablets (Laboratoire 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)%	
C_{max} (ng/mL)	29.233	29.133	100.087	93.889-106.694
AUC_{0-t} (ng.h/mL)	490.126	478.266	101.663	97.705-105.781
$AUC_{0-\infty}$ (ng.h/mL)	521.872	507.587	101.782	98.172-105.525

$AUC_{0-\infty}$ 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

The 90% confidence intervals for C_{max} 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.2 Pharmacovigilance System and Risk Management Plan

The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a risk management plan for these products. A RMP was not required at the time of dossier submission.

IV.3 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. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A package leaflet has been submitted along with results of consultations with target patient groups ('user testing'), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Lorazepam GenRx 1 mg and 2.5 mg tablets have a proven chemical-pharmaceutical quality and are a generic forms 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.

No new or unexpected safety concerns arose from these applications. The SmPCs, PLs and labelling are satisfactory and consistent with those for the reference products.

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 GenRx 1 mg and 2.5 mg tablets with the reference product, and have therefore granted a marketing authorisation.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached