COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Clobazam Sandoz 10 mg, tablets (clobazam)

NL/H/5284/001/DC

Date: 28 February 2022

This module reflects the scientific discussion for the approval of Clobazam Sandoz 10 mg, tablets. The procedure was finalised on 22 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 Clobazam Sandoz 10 mg, tablets, from Sandoz B.V.

The product is indicated for:

- Short-term symptomatic treatment of anxiety

  Benzodiazepines should only be used if the condition is severe, disabling, or if the patient is in extreme suffering as a result of the disorder.

- As an adjuvant therapy in epileptic seizures, when the patient takes other anti-epileptic medicines but cannot be stabilised completely with these medicines

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 Frisium, tablets 10 mg (NL RVG 09600) which has been registered in the Netherlands by Genzyme Europe B.V. since 9 February 1982 via a national procedure.

The concerned member states (CMS) involved in the current procedure were Norway and Sweden.

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

II. QUALITY ASPECTS

II.1 Introduction

Clobazam Sandoz is a white to off-white round tablet with break line and debossed with 'C' and '1' on one side and plain on other side. The tablet can be divided into equal doses. Each tablet contains 10 mg of clobazam.

The tablets are packed in PVC//Aluminium blisters.

The excipients are: lactose monohydrate, microcrystalline cellulose, maize starch, pregelatinized starch, colloidal anhydrous silica and magnesium stearate.

II.2 Drug Substance

The active substance is clobazam, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a crystalline powder and is insoluble in water.

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 monograph in the Ph.Eur. and the CEP. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches from the drug substance manufacturer, and on two batches from the drug product manufacturer.

Stability of drug substance

The active substance is stable for five years when stored in double polyethylene bags placed in polyethylene drums. Assessment thereof was part of granting the CEP and has been granted by the EDQM. The drug product manufacturer assigned a shorter (12 month) retest period.

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 main development studies performed were the characterisation of the reference product, dissolution method development, formulation and manufacturing process optimisation studies. The functionality of the proposed break line on the tablet has been adequately demonstrated. Results on an apple sauce study indicate no issues in quality of the drug product crushed and mixed with apple sauce.

The dissolution method development has been adequately described. Comparative dissolution at 3 pHs has been studied in support of bioequivalence and the biowaiver of strengths. The choice for the finalised dissolution method for routine control has been justified. A bioequivalence study was performed with a batch of a 20 mg product strength versus a batch of the corresponding reference product strength. A biowaiver of strength was requested for the 10 mg strength product. Both will be discussed in section IV on clinical aspects.

Manufacturing process

The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product have been presented for three batches of the minimum production scale. A commitment has been provided to perform a hold time study on a second batch of the bulk stage (compressed tablets). The product is manufactured using conventional manufacturing techniques.

Control of excipients

The excipients comply with Ph.Eur. requirements. 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 tests for description, identity, average weight of tablets, loss on drying, dissolution, assay, subdivision of tablets, uniformity of dosage units, related substances, microbial limit test and residual solvents. The release and shelf-life limits are identical for all parameters, except for loss on drying. 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 the proposed production site have been provided on three full scale production batches, demonstrating compliance with the release specification. A sufficient risk evaluation on the presence of nitrosamine impurities in the drug product has been provided.

Stability of drug product

Stability data on the product have been provided on three production scaled batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Alu/PVC blisters. Except for a slight increase for loss on drying at both storage conditions, no clear trends or changes were observed in any of the tested parameters at both storage conditions in any of the batches. The impurities were not detected. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. The claimed shelf-life of 24 months is supported by the available 24 months data and is acceptable with the storage condition: “This medicinal product does not require any special storage conditions”.

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

Scientific data and/or certificates of suitability issued by the EDQM have been provided for lactose monohydrate and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Clobazam Sandoz 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 Clobazam Sandoz 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 Frisium 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

Clobazam 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 one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Clobazam Sandoz 20 mg, tablets was compared with the pharmacokinetic profile of the reference product Frisium, tablets 20 mg (Sanofi-Aventis Deutschland GmbH). A justification for biowaiving the lower strength (10 mg) was submitted. The MAH only requested marketing authorisation for the 10 mg product strength.

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

One single dose bioequivalence study with the highest strength under fasting conditions is sufficient to support this application of a product with immediate release. Because pharmacokinetics of clobazam are dose linear in at least the dose range of 10-20 mg (Tolbert et al., J Clin Pharmacol. 2019), a study at the highest strength is justified. The drug can be taken regardless of food intake, which justifies a study under fasting conditions.

In addition, the SmPC of the test product states: “The tablets can be ground and mixed in apple sauce” and “The administration of clobazam tablets with food or ground in apple sauce slows down the absorption rate by about 1 hour, but does not affect the total absorption rate.” Since the SmPC of the test product states the same as the SmPC of the reference product (Frisium) on this specific subject, the MAH was not required to perform an additional bioequivalence study in which the tablets are ground and mixed in apple sauce. The submitted justification by the MAH is considered as supportive. The compatibility of the test product with apple sauce is discussed in section II on quality aspects.

<u>Biowaiver</u>
For the 10 mg product strength a biowaiver was requested. The different product strengths comply with the following biowaiver criteria from CPMP/EWP/QWP/1401/98 Rev.1/Corr **:

- The different product strengths are manufactured by the same manufacturing process;
- The products have the same qualitative composition;
- The products are quantitatively proportional;
- Appropriate *in vitro* dissolution data have confirmed the adequacy of waiving additional *in vivo* bioequivalence testing. The used dissolution method is acceptable in view of the recommendations for dissolution methods for biowaivers of additional strengths.

Therefore, similarity can be accepted and a biowaiver for the 10 mg product strength has been granted.

Bioequivalence study

Design

An open-label, single-dose, randomised, two-period, two-treatment, crossover bioequivalence study was carried out under fasted conditions in 36 healthy subjects, aged 19-41 years. Each subject received a single dose (20 mg) of one of the two clobazam formulations. The tablet was orally administered with 240 ml water after an overnight fasting period of at least 11 hours. The participants were allowed to drink water (apart from the mentioned 240 mL) until 1 hour before dosing, and from 1 hour after dosing. There were two dosing periods, separated by a washout period of 28 days. Blood samples were collected pre-dose and at 0.083, 0.167, 0.250, 0.333, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 12.00, 16.00, 24.00, 36.00, 48.00, 60.00, and 72.00 hours after administration of the products. The design of the study is acceptable.

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

Three subjects were withdrawn from the study, due to an emergency at home (one subject), refusing to continue (one subject), and a positive drugs of abuse screening (one subject). 33 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=33	AUC_{0-72h} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	11169 ± 2713	473 ± 124	1.25 (0.25 – 4.00)
Reference	11129 ± 2469	441 ± 109	1.75 (0.33 – 4.00)
Ratio (90% CI)	1.0003 (0.9787 – 1.0223)	1.0702 (0.9970 – 1.1489)	Not applicable

AUC_{0-72h} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

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, the 20 mg clobazam test product is considered bioequivalent with the respective product strength of Frisium.

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 Clobazam Sandoz.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• None
Important potential risks	• None
Missing information	• None

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 Frisium. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the 20 mg test product is similar to the pharmacokinetic profile of the 20 mg reference product strength. A biowaiver has been granted for the 10 mg product strength, for which authorization was requested. 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 Clobazam TioFarma 10 mg and 20 mg, tablets (RVG 105491 and 105492) for key messages, and to Alendronate/Colecalciferol 70 milligrams/140 micrograms tablets (NL/H/3578/001/DC and NL/H/3587/001/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

Clobazam Sandoz 10 mg, tablets has a proven chemical-pharmaceutical quality and is a generic form of Frisium, tablets 10 mg. Frisium 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 Clobazam Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 22 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