CBG MEB

Public Assessment Report

Scientific discussion

Zonisamide Warren 25 mg, 50 mg and 100 mg, hard capsules

(zonisamide)

NL/H/3450/001-003/DC

Date: 2 November 2017

This module reflects the scientific discussion for the approval of Zonisamide Warren 25 mg, 50 mg and 100 mg, hard capsules. The procedure was finalised on 28 September 2016. 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
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
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
USP	United States Pharmacopoeia

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Zonisamide Warren 25 mg, 50 mg and 100 mg, hard capsules from Warren Generics s.r.o.

The product is indicated for:
- monotherapy in the treatment of partial seizures, with or without secondary generalization, in adults with newly diagnosed epilepsy
- adjunctive therapy in the treatment of partial seizures, with or without secondary generalization, in adults, adolescents, and children aged 6 years and above

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 Zonegran 25 mg, 50 mg and 100 mg, capsules hard (NL License RVG 72869, 72139 and 72140) which has been registered by a centralised procedure (EU/1/04/307/002-004) by Eisai Ltd. since 10 March 2003.

The concerned member states (CMS) involved in this procedure were Germany, Spain, Portugal and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Zonisamide Warren is a hard capsule containing white to off-white powder:
- Zonisamide Warren 25 mg is a white-white opaque coloured hard gelatin capsule of size “4” imprinted with “I” on the cap and “22” on the body with black ink. The capsule contains 25 mg of zonisamide.
- Zonisamide Warren 50 mg is a grey-white opaque coloured hard gelatin capsule of size “3” imprinted with “I” on the cap and “21” on the body with black ink. The capsule contains 50 mg of zonisamide.
- Zonisamide Warren 100 mg is a red-white opaque coloured hard gelatin capsule of size “1” imprinted with “I” on the cap and “20” on the body with black ink. The capsule contains 100 mg of zonisamide.

The hard capsules are packed in clear PVC/PVdC/Aluminum blister packs.

The excipients are:
Capsule content - microcrystalline cellulose, hydrogenated vegetable oil, sodium laurilsulfate and silica colloidal anhydrous
Capsule shell – gelatin, water and titanium dioxide (E171)
The 50 mg capsules additionally contain iron oxide black (E172) and the 100 mg capsules sunset yellow (E110) and allura red (E129).

The three capsule strengths are dose proportional.

II.2 Drug Substance

The active substance is zonisamide, an established active substance described in the United States Pharmacopoeia (USP). Zonisamide is a white to off-white powder which is highly soluble in water, freely soluble in dimethylformamide and sparingly soluble in methanol and ethyl acetate. Zonisamide

exhibits no potential isomerism. The crystalline form of the product is manufactured and no polymorphisms exist.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process of zonisamide follows a three step process. A narrow description is provided. The route of synthesis is adequately described and the proposed starting material is acceptable. Specifications and certificates of analysis on the starting material and solvents and reagents have been provided. Sufficiently qualified limits are included in the specifications for toluene and methylene dichloride.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. It has been established in-house, with requirements for appearance, solubility, identification, water content, melting range, sulphated ash, heavy metals, related substances, assay, residual solvents, chloride content and microbial limit test. Batch analytical data demonstrating compliance with this specification have been provided for three commercial scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three exhibit batches stored at 40°C/75% RH (6 months) and 25°C/60% RH (60 months) and one scale-up batch 25°C/60% RH (48 months). No significant changes in data observed or any out of specification data obtained and the proposed retest period of 48 months at 25˚C is acceptable based on the data provided.

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 choices of the packaging and manufacturing process are justified. The pharmaceutical development of the product has been adequately performed.

One bioequivalence study was performed with the 100 mg strength. Dissolution results and additional statistical analysis of the results in order to support the bioequivalence study have been provided. Although the profiles are not similar under all conditions tested, the justification on the discrepancy of the dissolution study and the bioequivalence study is sufficient. For the other strengths, a biowaiver was proposed. Dissolution data was provided with the 100 mg strength capsules of the batch used in the study and the two lower strengths in three requested media (pH 1.2, 4.5 and 6.8). Zonisamide dissolved for more than 85% within 15 minutes in all cases.

Manufacturing process
The manufacturing process involves blending, lubricating and capsule filling. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for the lubricated blend and three consecutive exhibit scale batches of each strength of zonisamide capsules. The product is manufactured using conventional manufacturing techniques. Process validation for full scaled batches will be performed post authorisation.

Control of excipients
All the excipients (except opaque capsules) are in compliance with their respective monograph of the current edition of the in European Pharmacopoeia (Ph.Eur.). Opaque capsules are tested according to an in-house specification. The qualitative requirements of the individual components of the capsule

shell and qualitative composition of the printing ink is provided, the information is sufficient. 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, identification, colourants, dissolution, water content, assay, related substances, microbial enumeration and uniformity of dosage units. The release limits and shelf life limits are identical for all tests, except for water content. 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 exhibit scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided for three exhibit batches of Zonisamide Warren 25 mg, 50 mg and 100 mg capsules for 6 months under accelerated conditions (40°C/75% RH) and 36 months at long-term conditions (25°C/60% RH). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. All tests and parameters were found to be within the specification limits. Results of a photostability study show that the drug product is photostable. Based on the currently available stability data a maximum shelf life of 36 months can be granted, the proposed storage condition ('This medicinal product does not require any special storage conditions.') is considered justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The excipient gelatin is of animal origin. Scientific data and/or certificates of suitability issued by the EDQM have been provided 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 Zonisamide Warren 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 Zonisamide Warren 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 Zonegran 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

Zonisamide 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

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Zonisamide Warren (Warren Generics s.r.o., Czech Republic) is compared with the pharmacokinetic profile of the reference product Zonegran (Eisai Ltd, UK).

The choice of the reference product
The choice of the reference product in the bioequivalence studies is accepted, as Zonegran has been registered through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
Biowaiving for the 25 and 50 mg capsules based on the bioequivalence study with the highest strength of 100 mg can be granted as:

- the strengths have been manufactured by the same process and manufacturer
- the pharmacokinetics can be considered linear
- the compositions are qualitatively similar and dose proportional
- the dissolution is very rapid for all strengths at pH 1.2, 4.5 and 6.8 (>85% within 15 minutes)

Design
A single-dose, open-label, randomised, two-treatment, two-period cross-over bioequivalence study was carried out under fasted conditions in 24 healthy male (n=22) and female (n=2) subjects, aged 19-42 years. Each subject received a single dose (100 mg) of one of the 2 zonisamide 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 26 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.33, 1.66, 2, 2.33, 2.66, 3, 3.33, 3.66, 4, 4.33, 4.66, 5, 5.5, 6, 8, 10, 12, 24, 48 and 72 hours after administration of the products.

The design of the study is acceptable. Zonisamide may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of zonisamide. 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. The half-life of zonisamide is about 60 hours. Therefore plasma levels should be measured over a period of at least 72 hours. The wash-out period of 26 days is adequate.

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 (male) subjects withdrew just before start of the second period for personal reasons. Therefore 21 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=21	AUC_{0-t} µg.h/ml	C_{max} ng/ml	t_{max} h
Test	61.82 ± 12.61	1254 ± 250	4.35 ± 2.49
Reference	58.98 ± 12.73	1254 ± 248	3.35 ± 1.52
***Ratio (90% CI)**	1.05 (1.03 - 1.07)	1.00 (0.95 - 1.04)	--

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} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Zonisamide Warren is considered bioequivalent with Zonegran.

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 Zonisamide Warren.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Hypersensitivity • Skin eruptions • Haematological events • Kidney stones • Disordered body temperature and dehydration • Pancreatitis and elevated amylase and lipase • Muscle disorders • Weight loss • Metabolic acidosis and its potential for osteopenia • Suicide/suicidal thoughts
Important potential risks	• Seizures following sudden withdrawal • Effects on ability to drive and use machines • Use in patients with renal impairment • Use in pregnancy • Use in elderly • Developmental and maturational impairment in children and adolescents
Missing information	• Use in impaired liver function • Use in children below 6 years

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 Zonegran. 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

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of two rounds with 10 participants and 12 questions each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Zonisamide Warren 25 mg, 50 mg and 100 mg, hard capsules have a proven chemical-pharmaceutical quality and are generic forms of Zonegran 25 mg, 50 mg and 100 mg hard capsules. Zonegran 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 Zonisamide Warren with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 28 September 2016.

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
NL/H/3450/001/IA/001	Update of PI	PI	28-4-2017	Approval	