COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ethosuximide Strides 250 mg capsules, soft

(ethosuximide)

NL/H/4514/001/DC

Date: 9 September 2019

This module reflects the scientific discussion for the approval of Ethosuximide Strides 250 mg capsules, soft. The procedure was finalised on 12 June 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

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
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 Ethosuximide Strides 250 mg capsules, soft from Strides Pharma (Cyprus) Limited.

The product is indicated for:

- Pyknoleptic absences as well as complex and atypical absences.
- Myoclonic-astatic petit mal and myoclonic fits of adolescents (impulsive petit mal), if other medicinal products are not effective and/or are not tolerated.

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 Ethymal 250 mg soft capsules (NL Licence RVG 02982) which has been registered in the Netherlands by Apotex Europe B.V. since 15 December 1967.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Ethosuximide Strides 250 mg is a red coloured, oblong shaped soft gelatin capsule containing colourless to red colour viscous liquid. Each capsule contains 250 mg ethosuximide.

The capsules are packed in a bottle pack consisting of high density polyethylene container with outer white opaque polypropylene child resistant closure.

The excipients are:
Capsule contents – macrogol
Capsule shell – gelatin, glycerol (E 422), liquid sorbitol (non-crystallising), FD& C Red #3 (E 127), purified water.

II.2 Drug Substance

The active substance is ethosuximide, an established active substance described in the European Pharmacopoeia. The active substance is a white waxy solid powder and is freely soluble in water, and very soluble in dichloromethane, ethanol (96%), methanol, toluene and

ether. Ethosuximide shows polymorphism. However this is not seen as critical for the proposed drug product, since the drug product concerns a solution in the final capsules The synthetic route followed gives racemic ethosuximide.

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 in line with the Ph. Eur. and established in-house. The specification is considered acceptable. Method verification reports have been provided for the assay, related substances and residual solvents analytical methods.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches.

Stability of drug substance

Stability data on the active substance has been provided for three batches stored at 25°C/60% RH for up to 5 years. Based on the results, a re-test period of 5 years, stored below 25°C is granted.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The MAH has discussed the chirality of the drug substance and the particle size in relation to the drug product.
An *in-vivo* bioequivalence study was done using reference product Ethymal 250 mg capsules and test product Ethosuximide Strides 250 mg capsules. Dissolution studies were carried out on test and reference product at pH 0.1N/4.5/6.8. The results of the comparative studies show comparative dissolution between test and reference product.

Manufacturing process

The manufacturing process involves the following steps: gelatin paste preparation, fill preparation, encapsulation, drying, capsule sorting, wiping of capsules, lubrication, inspection and metal detection and packaging. The manufacturing process is described in detail, including the in-process controls and hold times for intermediates and bulk capsules.

The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches.

Control of excipients

The excipients comply with the Ph. Eur. requirement, except for erythrosine (FD & C Red 3). Acceptable in-house specifications have been provided for erythrosine (FD & C Red 3). All specifications are acceptable.

Quality control of drug product

The product specification includes tests for description, identification of ethosuximide and erythrosine, uniformity of dosage units, assay, dissolution, related substances, moisture content and microbial limits. The analytical methods have been adequately validated. Batch analytical data have been provided on three full-scale batches, demonstrating compliance with the release specification, except for the dissolution limit which was amended during the course of the marketing authorisation application; stability results show compliance with the amended dissolution limit.

Stability of drug product

Stability data on the product has been provided for three full-scale batches stored at accelerated (40°C/75% RH± 5°C) and long term (25°C/60% RH ± 5°C) storage conditions. The conditions used in the stability studies are according to the ICH stability guideline. Stability data up to 15 months has been provided, including dissolution data at 15 months time point. Based on these data, the claimed shelf life of 24 months, stored below 25°C has been granted.

The batches were stored in the proposed packaging material (HDPE container). Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. An in-use stability of 60 days has been granted.

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

Gelatine is the only material of animal origin used. Valid CEPs from the suppliers have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ethosuximide Strides 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 Ethosuximide Strides 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 Ethymal, 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

Ethosuximide 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 a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Ethosuximide Strides 250 mg (Strides Pharma (Cyprus) Limited, Cyprus) is compared with the pharmacokinetic profile of the reference product Ethymal 250 mg soft capsules (Apotex Europe B.V., the Netherlands).

The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 42 (+ 2 stand-by) healthy subjects (38 males/4 females) aged 18-42 years. Each subject received a single dose (250 mg) of one of the 2 ethosuximide formulations. The tablet was orally administered with 240 ml water after an overnight fast of 10 hours. There were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. The procedures followed for a fasting study are according to the bioequivalence guideline. The sampling time period until 72 hours post-dose is sufficient to determine the t_{max} and provide a reliable estimate of the extent of exposure for this immediate-release product, as the absorption phase is covered. The wash-out period of 21 days is sufficient to prevent carry-over effects considering that this was more than 5X the half-life of ethosuximide (i.e. 30 – 60 hours).

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

One subject terminated from the study prior to dosing of period I, due to an adverse event, and was replaced by a stand-by subject. Forty-two subjects were dosed in Period-I. Three subjects did not did not report to the clinical facility for check-in of period II due to personal reasons and dropped-out from the study. Hence, 39 subjects completed the study and were included for pharmacokinetic and statistical analysis.

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

Treatment N=39	**AUC_{0-72} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**	**$t_{1/2}$ (h)**
Test	301.06 ± 51	--	9.86 ± 2.40	0.50 (0.17– 6.00)	--
Reference	292.78 ± 50	--	9.78 ± 2.32	0.50 (0.17– 6.00)	--
***Ratio (90% CI)**	1.3 (1.01–1.05)	--	1.01 (0.95 – 1.07)	--	--
CV (%)	--	--	--	--	--

$AUC_{0-\infty}$	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
t_{max}	time for maximum concentration
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

Conclusion on bioequivalence study

One subject had reach t_{max} at the first sampling time point post-dose for both test and reference product. Statistical analyses including or excluding this particular subject did not affect the conclusion on bioequivalence.

The 90% confidence intervals calculated for AUC_{0-72} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Ethosuximide Strides 250 mg is considered bioequivalent with Ethymal 250 mg soft capsules.

Safety

Three adverse events (AEs) were reported during post-study safety assessment. These were mild in nature and judged as not related to study drug. During study, two AEs (4.88 %) were related to test product treated subjects and one AE (2.50 %) was related to a reference product treated subject. The remaining AEs not attributed to any treatment as they were reported prior to dosing of period I. The adverse events observed between the test and reference product are comparable.

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 Ethosuximide Strides.

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

Important identified risks	• Dyskinesia • Bone marrow injury
Important potential risks	• Suicidal ideation and behaviour • Congenital malformation with use in pregnancy
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 Ethymal. 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: a pilot test, followed by two rounds with 10 participants 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 package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ethosuximide Strides 250 mg capsules, soft has a proven chemical-pharmaceutical quality and is a generic form of Ethymal 250 mg soft capsules. Ethymal 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 Ethosuximide Strides with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 June 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