COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Oxcarbazepine ADOH 150 mg, 300 mg and 600 mg, film-coated tablets (oxcarbazepine)

NL/H/5347/001-003/DC

9 May 2022

This module reflects the scientific discussion for the approval of Oxcarbazepine ADOH. The procedure was finalised at 9 February 2022. 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 Oxcarbazepine ADOH 150 mg, 300 mg and 600 mg, film-coated tablets, from ADOH B.V.

The product is indicated for the treatment of partial seizures with or without secondarily generalised tonic-clonic seizures.

Oxcarbazepine ADOH is suitable for use as monotherapy as well as for use in combination with other anti-epileptics in adults and children from 6 years of age 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 European reference product Trileptal 150 mg, 300 mg, 600 mg film-coated tablets (RVG 24750-24752) which has been registered in the Netherlands by Novartis Pharma B.V. since February 2000 (original product).

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

Oxcarbazepine ADOH 150 mg film-coated tablets
Light pink, ovaloid slightly biconvex tablets, scored on both sides.

Oxcarbazepine ADOH 300 mg film-coated tablets
Grey, ovaloid slightly biconvex tablets, scored on both sides.

Oxcarbazepine ADOH 600 mg film-coated tablets
Yellow, ovaloid slightly biconvex tablets scored on both sides.

And contains as active substance 150 mg, 300 mg and 600 mg oxcarbazepine.

The film-coated tablets are packed in blisters made of polyvinyl chloride/polyvinylidene chloride film and aluminum foil in boxes.

The excipients are:

All strengths:
Tablet core – cellulose – microcrystalline 102 (E460), hypromellose 2910 (E464), crospovidone (type A) (E1202), silica – colloidal anhydrous (E551) and magnesium stearate (E470b).

150 mg strength:
Tablet coating – hypromellose 2910 (E464), talc (E553b), titanium dioxide (E171), macrogol/PEG 8000 (E1521), iron oxide red (E172) and black iron oxide (E172).

300 mg strength:
Tablet coating – hypromellose 2910 (E464), talc (E553b), titanium dioxide (E171), macrogol/PEG 8000 (E1521), iron oxide red (E172), black iron oxide (E172) and iron oxide yellow (E172).

600 mg strength:
Tablet coating – hypromellose 2910 (E464), talc (E553b), titanium dioxide (E171), macrogol/PEG 8000 (E1521) and iron oxide yellow (E172).

The three tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is oxcarbazepine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Oxcarbazepine is a white or faintly orange, crystalline powder with limited aqueous solubility and slight hygroscopicity. Oxcarbazepine exhibits polymorphism, the polymorphic form A is consistently produced by the manufacturer.

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. The analytical procedures for microbial limits and particle size distribution have been adequately validated. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for 24 months/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.

The quantitative composition for each strength of the reference product has been provided. The development of the product has been described, the choice of excipients is justified and their functions explained. The choices of the packaging and manufacturing process are justified in relation to the innovator.

Since the dissolution conditions used are different for the three available strengths, the applicant has adequately demonstrated the discriminatory power of each dissolution method.

The MAH has proposed a biowaiver for the 150 mg and 300 mg strengths. All conditions for this biowaiver have been met as per the requirements on the Guideline on the Investigation of Bioequivalence. The MAH has submitted dissolution data between the test and reference product and between different doses of the test product at the different buffers and comparative dissolution data without the use of surfactant.

Manufacturing process
The manufacturing process consists of mixing, granulation, milling, drying, blending, compression, coating and packaging. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches for the 150 mg and 300 mg strengths in accordance with the relevant European guidelines. The MAH has stated that the process for 600 mg strength will be validated in the commercial batches and the protocol used has been provided.

Control of excipients
The excipients comply with Ph.Eur. except for the coating agent Opadry. 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, size, identification, related substances, dissolution, uniformity of dosage units by mass variation, assay and microbial limits. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The risk assessment with regards to elemental impurities and nitrosamines are acceptable.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from three batches for each tablet strength from the proposed production site has been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three batches per tablet strength for 24 months at long term (30°C/75%RH & 25°C/60%RH) and six months at accelerated (40°C/75%RH) conditions in accordance with applicable European guidelines demonstrating the stability of the product for 24 months. On basis of the data submitted, a shelf life was granted of 24 months with no special storage conditions.

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 Oxcarbazepine ADOH 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 Oxcarbazepine ADOH 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 Trileptal 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

Oxcarbazepine 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 Oxcarbazepine 600 mg Film-Coated Tablet (ADOH B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Trileptal 600 mg Film-Coated Tablet (Novartis Pharma B.V., Netherlands).

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

Biowaiver

A bioequivalence study on the highest strength (600 mg strength) has been carried out. Pharmacokinetics are linear in the therapeutic dose range. A biowaiver is requested for the 150 and 300 mg strength as all the following criteria are fulfilled:

a) the pharmaceutical products are manufactured by the same manufacturing process;
b) the qualitative composition of the different strengths is the same;
c) the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths;
d) in vitro dissolution data between the 150 mg, 300 mg and 600 mg (biobatch) showing comparable dissolution have been submitted.

Bioequivalence studies

Design

A randomized, open-Label, two-way crossover bioequivalence study was carried out under fasted conditions in 44 healthy subjects, aged 24-36 years. Each subject received a single dose (600 mg) of one of the two oxcarbazepine formulations in each period. The tablet was orally administered with 240 ml water after an overnight fast. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected at pre-dose and 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 9, 12, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

Oxcarbazepine may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of oxcarbazepine. 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.

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
Out of a total of 44, 41 subjects were eligible for pharmacokinetic analysis. One subject did not show up for check in. Two subjects had non-zero baseline concentrations and were withdrawn as well.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of oxcarbazepine (600 mg) under fasted conditions.

Treatment N=41	**AUC_{0-t} (ng.h/ml)**	**$AUC_{0-\infty}$ (ng.h/ml)**	**C_{max} (ng/ml)**
Test (GM)	7637.01	7975.60	2364.32
Reference (GM)	7952.43	8301.70	2425.74
***Ratio (90% CI) (GM)**	96.03 (91.89 – 100.36)	96.07 (92.11 – 100.21)	97.47 (87.54 – 108.52)
CV (%)	11.8	11.3	28.8
Power (%)	>99	>99	92.7

$AUC_{0-\infty}$ 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
CV coefficient of variation
CI confidence interval
GM geometric mean

**ln-transformed values*

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 Oxcarbazepine ADOH is considered bioequivalent with Trileptal.

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 Oxcarbazepine ADOH.

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

Important identified risks	• Hypersensitivity • Severe cutaneous reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis and erythema multiforme • Bone marrow depression • Hyponatraemia
Important potential risks	• Suicidal ideation and behaviour • Teratogenic potential • Rhabdomyolysis • Interaction with valproate • Interaction with SSRI and amphetamine • Interactions with anticoagulants • Arthralgia • Dysarthria • Chest pain • Eye disorders after vaccine exposure
Missing information	• Exposure during pregnancy

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 Trileptal. 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 language used for the purpose of user testing the PL was English. The test consisted of two rounds of user testing with ten 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

Oxcarbazepine ADOH 150 mg, 300 mg and 600 mg, film-coated tablets have proven chemical-pharmaceutical quality and are generic forms of Trileptal 150 mg, 300 mg, 600 mg film-coated tablets. Trileptal 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 concerned member state, on the basis of the data submitted, considered that essential similarity has been demonstrated for Oxcarbazepine ADOH with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 9 February 2022.

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