COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Carbamazepine Umedica 100 mg, 200 mg and 400 mg, tablets

(carbamazepine)

NL/H/4941/001-003/DC

Date: 12 November 2021

This module reflects the scientific discussion for the approval of Carbamazepine Umedica 100 mg, 200 mg and 400 mg, tablets. The procedure was finalised at 12 April 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
QC	Quality Control
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 Carbamazepine Umedica 100 mg, 200 mg and 400 mg, tablets, from Umedica Netherlands B.V.

The product is indicated for:

- Epilepsy - generalised tonic-clonic and partial seizures.
  Note: Carbamazepine tablet is not usually effective in absences (petit mal) and myoclonic seizures. Carbamazepine Umedica can be used both as monotherapy and in combination with other anti-epileptic treatment.
- The paroxysmal pain of trigeminal neuralgia.
- For the prophylaxis of manic-depressive psychosis in patients unresponsive to lithium therapy.

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 Tegretol 100 mg, 200 mg and 400 mg tablets (NL RVG 11401 and 03899) which have been registered in The Netherlands since 6 June 1986 (100 mg, tablets), 18 April 1973 (200 mg), and in Spain on 1 August 1983 (400 mg) by Novartis Pharma B.V.

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

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

II. QUALITY ASPECTS

II.1 Introduction

- Carbamazepine 100 mg is a pink coloured, round shaped, flat bevelled edge, uncoated, single scored tablet debossed with ‘CAR’ and ‘100’ on the scored side and plain on the other side. Each tablet contains 100 mg carbamazepine.
- Carbamazepine 200 mg is a pink coloured, capsule shaped, biconvex, uncoated tablet, debossed ‘CAR’ on one side and ‘200’ on the partially scored side. Each tablet contains 200 mg carbamazepine.
- Carbamazepine 400 mg is a pink coloured, capsule shaped, biconvex, uncoated tablet, debossed ‘CAR 400’ on one side and a score line on both sides. Each tablet contains 400 mg carbamazepine.

The tablets can be divided into equal doses.
The tablets are packed in transparent Aluminium/PVDC coated rigid PVC/PE laminate blisters.

The excipients are - pregelatinised starch, colloidal anhydrous silica, croscarmellose sodium (E486) , FD & C red 40/Allura red AC AL (E129) and magnesium stearate (E572).

II.2 Drug Substance

The active substance is carbamazepine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to off-white powder. The active substance is very slightly soluble in water, freely soluble in methylene chloride, sparingly soluble in acetone and in ethanol (96 percent). Carbamazepine exhibits polymorphism between three forms: form I, II and III. The last one is the most stable one. Therefore, the MAH has selected polymorphic Form III of carbamazepine for development purposes. The MAH has shown that this Form III is retained in the final drug product.

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 with additional tests for residual solvents, X-ray diffraction and sieving. Batch analytical data demonstrating compliance with this specification have been provided for five full scaled batches.

Stability of drug substance
The active substance is stable for five years when stored in an air tight container. 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 choice of excipients is justified and their functions explained. The choices of packaging and manufacturing process are justified in relation to the innovator. The manufacture and composition of the bio-batch used in bioequivalence studies is similar to the marketed product. A split tablets stability study was performed to show compliance with the drug product specification after splitting. All results were found within the proposed limits. Comparative dissolution profiles at three pH values without surfactants have been included, together with the proposed quality control (QC) dissolution method. The discriminating power of the QC dissolution method has been demonstrated. The proposed QC dissolution method is acceptable and the *in vitro* dissolution studies support the observed *in vivo* bioequivalence. The dissolution equivalence at three pH in support of the biowaiver of strength has been demonstrated for the 100 mg and 200 mg strengths. Additional information regarding the suitability of the drug product for paediatric patients has been included. In 2009 the European Food Safety Authority has re-assessed the safety of azo dyes and has come to the conclusion that it is unlikely that oral consumption of the food colours under consideration, either individually or in combination, would trigger severe adverse reactions in human subjects at the current levels of use. As a consequence, the 2012 Guideline on the pharmaceutical development of medicines for paediatric use does not preclude the use of azo dyes in medicines for children but rather considers that azo dyes can be considered as any other colouring agent i.e. it overrules the limitation to the use of azo dyes as stipulated in the 2006 Excipients Guideline. In conclusion, the use of azo dyes at the current concentration is considered acceptable.

Manufacturing process

The manufacturing process consist of wet granulation followed by blending, lubrication and compression. The product is manufactured using conventional manufacturing techniques. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three pilot scaled batches in accordance with the relevant European guidelines. A commitment to perform the process validation on the first three commercial batches has been included by the MAH. The proposed bulk holding time of not more than 30 days for the core tablets can be granted as it is in line with EMA Guideline on Manufacture of the finished dosage form.

Control of excipients

The excipients comply with Ph.Eur. requirements. Appropriate tests and limits for the functionality related characteristics described in the Ph.Eur. monograph of certain excipients have been included in the excipient's specifications, when relevant. 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, water content,

uniformity of dosage units by mass variation, dissolution, assay, impurities, microbiological quality and residual solvents. The release and shelf-life requirements for dissolution have been tightened in line with the EMA guidelines on dissolution specification. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. A risk evaluation concerning the presence of nitrosamine impurities in the product and applying the principles outlined in the notice "Information on nitrosamines for marketing authorisation holders (EMA/189634/2019)" has been provided and is acceptable. Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three pilot scaled batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three pilot scaled batches per strength stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months) for product packed in PVDC coated rigid PVC/PE laminate and Aluminium lid foil blisters in accordance with the ICH stability guideline. Photostability studies were performed for one pilot batch per strength in accordance with ICH recommendations and showed that the product is stable when exposed to light. On basis of the data submitted, a shelf life was granted of 24 months. No specific storage conditions are required.

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 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 Carbamazepine Umedica has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:

- The MAH hereby commits to complete the ongoing stability study till the proposed shelf life. First three commercial batches of drug product will be charged for long term stability study. Then, one batch will be charged annually for long term study for all strengths.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Carbamazepine Umedica 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 Tegretol 400 mg tablets 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

Carbamazepine 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 Carbamazepine Umedica 400 mg, tablets (Umedica Netherlands B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Tegretol 400 mg tablets (Novartis Pharma B.V., The Netherlands).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products (if applicable) in different member states. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

A waiver for the additional 100 and 200 mg tablet strengths is granted. The following justification was provided by the MAH:

- It is an immediate release drug product.
- The drug products are manufactured by the same manufacturing process.
- The qualitative composition of the of all strengths of Carbamazepine Umedica 100 mg, 200 mg and 400 mg, tablets strengths are same.
- The composition of the strengths 100 mg, 200 mg and 400 mg tablets is quantitatively proportional.
- Appropriate *in vitro* dissolution data provided for confirming the adequacy of waiving additional *in vivo* bioequivalence testing.
- In general, the requirements for a waiver for additional strengths stated in the bioequivalence guideline were met, except for the in-vitro dissolution similarity. New comparative dissolution testing between the test biobatch 400 mg and the lower strengths (i.e. 200 and 100 mg) was done using paddle apparatus with a rotation speed of 50 rpm at pH 1.2, 4.5 and 6.8. According to the MAH, all f2 values are ≥50. This is not agreed for pH 6.8 in the 100 mg strength. The MAH has performed comparative dissolution testing at pH 6.8 using the same dose (i.e. 4 tablets 100 vs 1 tablet 400 mg), of the bioequivalence batch (400 mg strength) against the lower strength - 100 mg, using 50 rpm rotation speed. Similarity is demonstrated as the f2 value between the 400 and 100 mg tablets is above 50. The biowaiver for the 100 mg and 200 mg strengths are granted as all requirements are now fulfilled.

Bioequivalence studies

Design

An open-label, randomised, single dose, two-treatment, two-sequence, two-period, truncated, crossover, bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 18 - 42 years. Each subject received a single dose (400 mg) of one of the two carbamazepine formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 27 days.

Blood samples were collected pre-dose and at 0.5, 1, 2, 3, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 11, 12, 14, 16, 18, 20, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. A single dose study is considered appropriate to support the application for the proposed immediate-release product. The conduct of the study under fasting conditions is appropriate as food does not affect the absorption of carbamazepine.

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
All 48 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=48	AUC_{0-72} (ng.h/ml)	C_{max} (ng/ml)	t_{max} (h)
Test	266539 ± 36949	5438 ± 936	11.00 (1.00-24.02)
Reference	260874 ± 34720	5292 ± 930	16.00 (4.00-36.00)
***Ratio (90% CI)**	1.02 (0.99-1.05)	1.03 (0.99-1.07)	-

AUC_{0-72} area under the plasma concentration-time curve from time zero to 72 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_{0-72} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Carbamazepine Umedica is considered bioequivalent with Tegretol.

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 Carbamazepine Umedica.

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 Tegretol. 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: a pilot test with five participants, 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

Carbamazepine Umedica 400 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Tegretol 400 mg tablets. Tegretol 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 Carbamazepine Umedica with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 April 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