IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Carbamazepine 200 mg Tablets
Carbamazepine
PA22871/010/002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Carbamazepine 100 mg, 200 mg and 400 mg Tablets on 30th October 2020 for the treatment of epilepsy, paroxysmal pain of trigeminal neuralgia and prophylaxis of manic depressive psychosis in patients unresponsive to lithium therapy.
This application for a marketing authorisation was submitted in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as a generic application. To support the application, the applicant has submitted a bioequivalence study, performed on Carbamazepine 400 mg Tablets and the reference product Tegretol 400 mg.
The United Kingdom (UK) were the RMS at the start of the decentralised procedure with Ireland (IE) as CMS. Due to Brexit, after assessment of day 180 responses IE became the RMS for the DCP procedure.

The product is a prescription only medicine which may be renewed.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie.

Name of the product	Carbamazepine 100 mg Tablets, Carbamazepine 200 mg Tablets, Carbamazepine 400 mg Tablets
Name(s) of the active substance(s) (INN)	Carbamazepine
Pharmacotherapeutic classification (ATC Code)	N03AF01
Pharmaceutical form and strength(s)	100.00, mg, 200.00 mg, 400.00 mg Tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA22871/010/001, PA22871/010/002, PA22871/010/003
Marketing Authorisation Holder	Azure Pharmaceuticals Ltd 12 Hamilton Drive The Rock Road Blackrock Co. Louth A91 T997 Ireland
MRP/DCP No.	IE/H/1119/001-003/DC
Reference Member State	Ireland

II. QUALITY ASPECTS

II.1. Introduction

This application is for Carbamazepine 100 mg, 200 mg & 400 mg tablets

II.2 Drug substance

The active substance is Carbamazepine, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Composition of the medicinal product

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with the Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Carbamazepine 100mg, 200mg & 400mg Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Tegretol on the European market. No new preclinical data have been submitted.

The pharmacodynamic, pharmacokinetic and toxicological properties of carbamazepine are well known. As carbamazepine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on literature review is, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment

Since Carbamazepine 100 mg 200 mg & 400 mg Tablets are 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.3 Discussion on the non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate. As carbamazepine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

Carbamazepine is a well known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product marketed by MAH.

For this generic application, the applicant has submitted one bioequivalence study for the 400mg dose in which the pharmacokinetic profile of the test product Carbamazepine 400mg Tablets is compared with the pharmacokinetic profile of the reference product Tegretol® 400 mg immediate release tablets by Novartis Pharmaceuticals UK Limited, Trading as Geigy Pharmaceuticals, Surrey, GU16 7SR, UK, (RP).

The reference medicinal products cited for these applications are Tegretol 100mg Tablets (PL 00101/0461), Tegretol 200mg Tablets (PL 00101/0462) and Tegretol 400mg Tablets (PL 00101/0463), authorised to Novartis Pharmaceuticals UK Limited;

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Based on the pharmacokinetic parameters of active substance, the reference table and test tablet are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The pharmacokinetics of the active substance are linear in the range 50-600mg.
The results of the bioequivalence study performed with the 400mg Tablets therefore apply to the other strengths.

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 100 mg, 200 mg and 400 mg Tablets.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Tegretol 100mg Tablets (PL 00101/0461), Tegretol 200mg Tablets (PL 00101/0462) and Tegretol 400mg Tablets (PL 00101/0463), authorised to Novartis Pharmaceuticals UK Limited. The Applicant has committed to keeping the product information updated in line with the reference product.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Absorption

Carbamazepine is absorbed almost completely but relatively slowly from the tablets. The conventional tablets yield mean peak plasma concentrations of the unchanged substance within 12 hours (chewable tablets 6 hours; syrup 2 hours) following single oral doses. With respect to the amount of active substance absorbed, there is no clinically relevant difference between the oral dosage forms. After a single oral dose of 400mg carbamazepine (tablets) the mean peak concentration of unchanged carbamazepine in the plasma is approx 4.5µg/ml.

The bioavailability of carbamazepine in various oral formulations has been shown to lie between 85-100%.

Ingestion of food has no significant influence on the rate and extent of absorption, regardless of the dosage form of carbamazepine.

Steady-state plasma concentrations of carbamazepine are attained within about 1-2 weeks, depending individually upon auto-induction by carbamazepine and hetero-induction by other enzyme-inducing drugs, as well as on pre-treatment status, dosage, and duration of treatment.

Different preparations of carbamazepine may vary in bioavailability; to avoid reduced effect or risk of breakthrough seizures or excessive side effects, it may be prudent to avoid changing the formulation.

Distribution

Carbamazepine is bound to serum proteins to the extent of 70-80%. The concentration of unchanged substance in cerebrospinal fluid and saliva reflects the non-protein bound portion in plasma **(**20-30%**).** Concentrations in breast milk were found to be equivalent to 25-60% of the corresponding plasma levels.

Carbamazepine crosses the placental barrier. Assuming complete absorption of carbamazepine, the apparent volume of distribution ranges from 0.8 to 1.9 L/kg.

Biotransformation

Carbamazepine is metabolised in the liver, where the epoxide pathway of biotransformation is the most important one, yielding the 10, 11-transdiol derivative and its glucuronide as the main metabolites.

Cytochrome P450 3A4 has been identified as the major isoform responsible for the formation of carbamazepine 10, 11-epoxide from carbamazepine. Human microsomal epoxide hydrolase has been identified as the enzyme responsible for the formation of the 10,11-transdiol derivative from carbamazepine-10,11 epoxide. 9-Hydroxy-methyl-10-carbamoyl acridan is a minor metabolite related to this pathway. After a single oral dose of carbamazepine about 30% appears in the urine as end-products of the epoxide pathway.

Other important biotransformation pathways for carbamazepine lead to various monohydroxylated compounds, as well as to the N-glucuronide of carbamazepine produced by UGT2B7.

Elimination

The elimination half-life of unchanged carbamazepine averages approx. 36 hours following a single oral dose, whereas after repeated administration it averages only 16-24 hours **(**auto-induction of the hepatic mono-oxygenase system**)**, depending on the duration of the medication. In patients receiving concomitant treatment with other enzyme-inducing drugs (e.g. phenytoin, phenobarbitone), half-life values averaging 9-10 hours have been found.

The mean elimination half-life of the 10, 11-epoxide metabolite in the plasma is about 6 hours following single oral doses of the epoxide itself.

After administration of a single oral dose of 400mg carbamazepine, 72% is excreted in the urine and 28% in the faeces. In the urine, about 2% of the dose is recovered as unchanged drug and about 1% as the pharmacologically active 10, 11-epoxide metabolite.

Characteristics in patients

The steady-state plasma concentrations of carbamazepine considered as "therapeutic range" vary considerably inter-individually; for the majority of patients a range between 4-12µg/ml corresponding to 17-50µmol/l has been reported. Concentrations of carbamazepine 10, 11-epoxide (pharmacologically active metabolite): about 30% of carbamazepine levels.

Owing to enhanced carbamazepine elimination, children may require higher doses of carbamazepine (in mg/kg) than adults to maintain therapeutic concentrations.

There is no indication of altered pharmacokinetics of carbamazepine in elderly patients as compared with young adults.

No data are available on the pharmacokinetics of carbamazepine in patients with impaired hepatic or renal function.

IV.3 Pharmacodynamics

Pharmacotherapeutic group: Anti-epileptic, neurotropic and psychotropic agent; (ATC Code: N03 AF01). Dibenzazepine derivative.

As an antiepileptic agent its spectrum of activity embraces: partial seizures (simple and complex) with and without secondary generalisation; generalised tonic-clonic seizures, as well as combinations of these types of seizures.

The mechanism of action of carbamazepine, the active substance of Carbamazepine, has only been partially elucidated. Carbamazepine stabilises hyperexcited nerve membranes, inhibits repetitive neuronal discharges, and reduces synaptic propagation of excitatory impulses. It is conceivable that prevention of repetitive firing of sodium-dependent action potentials in depolarised neurons via use- and voltage-dependent blockade of sodium channels may be its main mechanism of action.

Whereas reduction of glutamate release and stabilisation of neuronal membranes may account for the antiepileptic effects, the depressant effect on dopamine and noradrenaline turnover could be responsible for the antimanic properties of carbamazepine.

IV.4 Clinical Efficacy
N/A

IV.5 Clinical Safety
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 100 mg, 200 mg and 400 mg Tablets.

The approved summary of safety concerns is outlined in the table below:

Important identified risks	• Serious Haematological Disorders (Agranulocytosis, aplastic anaemia, leucopenia and bone marrow depression) • Severe hepatic reactions • Suicidal ideation and behaviour • Serious cutaneous and dermatological reactions [Toxic Epidermal Necrolysis (TEN)/ Lyell's syndrome, Stevens-Johnson Syndrome (SJS), Drug rash with eosinophilia (DRESS), or less severe Acute generalized exanthematous pustulosis (AGEP)] • Use in patients with atrioventricular block, a history of bone marrow depression or a history of hepatic porphyrias • Concomitant use with Monoamine Oxidase Inhibitors (MAOIs) • Hyponatremia • Lithium enhanced neurotoxicity (following concomitant use with Lithium) • Neonatal toxicity • Congenital anomalies • Risk of thrombosis with concomitant Direct Oral Anticoagulants (DOAC's) use
Important potential risks	• Impaired male fertility and/or abnormal spermatogenesis • Effects when Breast-feeding
Important missing information	• None

Routine risk minimisation measures and routine pharmacovigilance activities are in place to address the safety concerns outlined above.

Periodic Safety Update Reports (PSURs) should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

IV.6 Discussion on the clinical aspects

This is a generic medicinal product, therefore new efficacy or safety clinical trials were not conducted. A bioequivalence study was carried out to demonstrate bioequivalence to an authorised reference medicinal product which is on the European market.

V. OVERALL CONCLUSIONS

Carbamazepine 100mg 200mg and 400mg Tablets are a generic form of name of reference product Tegretol 100mg Tablets (PL 00101/0461), Tegretol 200mg Tablets (PL 00101/0462) and Tegretol 400mg Tablets (PL 00101/0463), authorised to Novartis Pharmaceuticals UK Limited; the MAs were granted on 04/07/1997.

Tegretol 100mg Tablets (PL 00101/0461), Tegretol 200mg Tablets (PL 00101/0462) and Tegretol 400mg Tablets (PL 00101/0463), authorised to Novartis Pharmaceuticals UK Limited is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that *Carbamazepine 100mg 200mg and 400mg Tablets* demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

VII. UPDATES