Medicines Evaluation Board

Public Assessment Report
Scientific discussion

Carbamazepine Retard 200 mg and 400 mg Focus Care, prolonged-release tablets (carbamazepine)

NL License RVG: 128678 & 128680

Date: 20 July 2026

This module reflects the scientific discussion for the approval of Carbamazepine Retard 200 mg and 400 mg Focus Care, prolonged-release tablets. The procedure was finalised on 17 February 2023 for the 400 mg strength and on 22 June 2023 for the 200 mg strength. For information on changes after this date, please refer to section 'steps taken after finalisation' at the end of this PAR.

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List of abbreviations

AE	Adverse Event
AI	Acceptable Intake
ANOVA	Analysis of Variance
BCS	Biopharmaceutics Classification System (-based biowaiver)
BE	Bioequivalence
CBG /MEB	College ter Beoordeling van Geneesmiddelen / The Medicines Evaluation Board
CHMP	Committee for Medicinal Products for Human Use
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
ERP	European Reference Product
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation (of Technical Requirements for Pharmaceuticals for Human Use)
LALA	Locally applied, locally acting products
MAH	Marketing Authorisation Holder
PAR	Public Assessment Report
PD	Pharmacodynamics
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PL	Package Leaflet
PSURs	Periodic safety update reports
QC	Quality control
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
USP/NF	United States Pharmacopoeia/National Formulary

Note: *Not all abbreviations may apply for this PAR.*

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Carbamazepine Retard 200 mg and 400 mg Focus Care, prolonged-release tablets, from Focus Care Pharmaceuticals B.V.

The product is indicated for:

Epilepsy
- Complex or simple partial seizures, with or without secondary generalisation.
- Generalised tonic-clonic seizures (grand mal).

Carbamazepine Retard Focus Care can be used as either monotherapy or combination therapy.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

II. EXECUTIVE SUMMARY

II.1. Rationale for the product

The marketing authorisation has been granted pursuant to Article 10(1) Generic medicinal product application of Directive 2001/83/EC, which concerns a generic application.

To demonstrate bioequivalence with the reference medicinal product, the MAH has submitted data on bioequivalence studies and has requested a biowaiver for the lower, 200 mg strength. See Section V. Clinical aspects.

In this national procedure the reference medicinal product is the centrally authorised Tegretol CR 200 mg and 400 mg prolonged release tablets, which has been authorised in The Netherlands (NL License number RVG 11874 and 11875) since 12 April 1988.

This application has been assessed with The Netherlands as Reference Member State (RMS).

II.2. About the product

Pharmaco-therapeutic group (ATC Code): N03AF01
Dispensing status: Prescription only.

II.3. General comments on the application

N.A.

II.4. General comments on compliance with GMP, GLP, GCP and agreed ethical principles.

The MEB has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the MEB has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the MEB has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

GMP active substance
Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the medicinal product and batch release situated in the EU.

GCP
Based on the data and documents submitted, the MEB has been assured that the studies were conducted and reported in compliance with GCP: a GCP statement and audit certificate(s) were provided; monitoring report(s) and recent inspection(s) by competent authorities identified no concerns relevant to the study; and, where conducted outside the EU, compliance with the ethical requirements of EU legislation (Directive 2001/20/EC or Regulation EU No. 536/2014, as relevant) was confirmed.

III. QUALITY ASPECTS

III.1. Introduction

Carbamazepine Retard are prolonged-release tablets. Each tablet contains 200 mg or 400 mg of carbamazepine as active substance. The tablets of the different strengths can be distinguished by their colour and size and are as follows:

<u>200 mg strength</u>
The tablet is yellow-orange, oval and biconvex, with a score line on both sides. The tablet measures 12.20 x 5.60 mm. The tablet can be divided into equal doses.

<u>400 mg strength</u>
The tablet is brownish-orange, oval and biconvex, with a score line on both sides. The tablet measures 16.80 x 6.70 mm. The tablet can be divided into equal doses.

The excipients are:
Tablet core - povidone (K-30), colloidal anhydrous silica, polyacrylate dispersion 30 per cent, ethyl cellulose, microcrystalline cellulose (E460), croscarmellose sodium (E468), talc (E553b) and magnesium stearate (E470b).

Tablet coating - hypromellose (HPMC E-5), macrogolglycerol hydroxy stearate 40, titanium dioxide (E171), talc (E553b), red iron oxide (E172) and yellow iron oxide (E172).

The two tablet strengths are dose proportional.

The prolonged-release tablets are packed in blisters made of aluminium/ polyvinyl chloride/ polyvinylidene chloride (Alu/PVC/PVDC) or in high-density polyethylene (HDPE) containers.

III.2. Active Substance

The structure of the active substance has been adequately proven and its physico-chemical properties are sufficiently described. The active substance is carbamazepine, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Carbamazepine is a white or almost white crystalline powder. It is very slightly soluble in water, freely soluble in methylene chloride, and sparingly soluble in acetone and ethanol (96 per cent).
Carbamazepine shows polymorphism, polymorphic form III is consistently produced.

Manufacturing process
The manufacture of the active substance has been adequately described. The used starting materials, solvents and reagents are considered acceptable. Adequate tests and acceptable specifications have been adopted for these.

Quality control of the active substance
The active substance specification includes relevant tests and the limits for impurities and degradation products have been justified in accordance with the applicable ICH Guidelines for impurities in new Drug Substances. The analytical methods applied are suitably described and non-compendial methods have adequately been validated. The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur and in-house requirements, with additional limits for the particle size. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of the active substance
The active substance is stable for five years when stored under the stated conditions.

III.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 the excipients is justified, and their functions are explained. The same excipients are used as in the reference product, with the addition of povidone K30. The use of this excipient is justified in the formulation trials. The MAH has thoroughly described the formulation development. The MAH has also presented information about the selected QC dissolution method. This proposed dissolution method is adequately justified. Compliance with the test for subdivision of tablets in the Ph. Eur. monograph on Tablets has been demonstrated at release and end of shelf life of the drug product batches representative of the commercial process. Subsequently, supportive *in vitro* dissolution data have been provided demonstrating that these equal halves show dissolution profiles similar to those of the undivided tablets.
The comparative dissolution studies to support the results obtained in the BE-study, and the studies in support of the biowaiver of strength have been performed in accordance with the appropriate guidance. The presented dissolution data at pH 1.2, 4.5 and 6.8 (without

surfactant) are adequate to support the BE-study results and the biowaiver of strength for the 200 mg tablets.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process consists of the following steps: wet granulation, blending, coating (twice), mixing and finally, compression and coating of the tablets. The manufacturing process has been sufficiently described and critical steps have been identified. The manufacturing process has been validated according to relevant European/ICH guidelines.

Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the current version of the Ph.Eur. monograph where possible. The remaining excipients comply with the United States Pharmacopeia–National Formulary. These specifications are acceptable.

Quality control of the medicinal product
The medicinal product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification of carbamazepine and colouring agents, average mass, dissolution, uniformity of dosage units, related substances, assay, microbial enumeration tests, loss on drying, and residual solvents. The release and shelf-life tests and limits are identical for all test parameters with the exception of loss on drying. Limits in the specification have been justified and are considered appropriate for the adequate quality control of the product.

An adequate risk evaluation report on nitrosamines has been submitted. No risk for the presence of nitrosamines in the medicinal product was identified. This justifies the absence of any further testing for nitrosamine impurity in the active substance and medicinal product.

Satisfactory validation data for the non-compendial analytical methods have been provided. Batch analytical data for three scale batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of the medicinal product
Stability data on the product have been provided for three batches of both strengths stored at 25°C/ 60% RH (24 months) and 40°C/75% RH (6 months). The stability was tested in accordance with applicable European guidelines. The batches were stored in blister and HDPE bottle. Photostability studies were performed in accordance with ICH recommendations. The results showed that the product is stable when exposed to light. Based on the data submitted, a shelf life of three years was granted. The labelled storage conditions are: “There are no special storage conditions for this medicinal product”. This also applies for the HDPE container.

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.

III.4. Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the Member State considers that Carbamazepine Retard has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and medicinal product.

IV. NON-CLINICAL ASPECTS

IV.1. Introduction

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

IV.2. Ecotoxicity/environmental risk assessment (ERA)

At the time of the approval of this application, before 1 September 2024, the revised ERA guideline (EMEA/CHMP/SWP/4447/00 Rev. 1- Corr.*) was not yet applicable. At that point of time the conclusion for this medicinal product was: since Carbamazepine Retard is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

IV.3. Discussion on the non-clinical aspects

This product is a generic formulation of Tegretol CR which is available on the European market. Reference was made to the preclinical data obtained with the reference medicinal product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 State agreed that no further non-clinical studies are required.

V. CLINICAL ASPECTS

V.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 Member State agreed that no further clinical studies are required, besides the three bioequivalence studies discussed below. Bioequivalence has been investigated in line with the EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**).

V.2. Pharmacokinetics

To support the application, the MAH has submitted three bioequivalence studies comparing the pharmacokinetic profiles of the test product Carbamazepine Retard 400 mg Focus Care, prolonged-release tablets, from Focus Care Pharmaceuticals B.V., the Netherlands and the reference medicinal product Tegretol 400 mg prolonged release tablets, Novartis Pharmaceuticals UK, Ltd, United Kingdom. A biowaiver was requested for the lower 200 mg strength. The formula and manufacturing process of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

According to the EMA bioequivalence guideline, the following general requirements must be met where a waiver for additional strength is claimed:

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 (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

The requirements a - d are met.

Regarding the comparative dissolution profiles, the calculated f_2 similarity factor values were within criteria (>50) at pH 4.5 and 6.8. An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar. For the results at pH 1.2, bootstrapping was applied. See also section VIII of this report (Overall conclusion).

As the conditions for the biowaiver criteria are met, a biowaiver for the 200 mg strength has been granted

Bioequivalence studies

BE Study No: 486-15, pivotal fasting study

Design

A single-dose, randomised, open label, two-treatment, two-period, two-sequence, two way crossover bioequivalence study was carried out under fasted conditions in 60 healthy (45 male / 15 female) subjects, aged 18-43 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 a fasting period of at least 10 hours. There were two dosing periods, separated by a washout period of 28 days.

The plasma concentration time curve was used to assess the rate and extent of absorption. Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 48, 72, 120, 168 and 240 hours after administration of the products.

The SmPC recommends administering the product with liquid, either whole or - if half-tablets have been prescribed - as half-tablets, without chewing, during or after a meal. Due to the controlled release of carbamazepine, a twice-daily dosage is generally possible.

The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** Note for Guidance on the investigation of bioavailability and bioequivalence.

Bioanalytical/statistical methods
The bioanalytical method has been adequately validated according to current guidelines (ICH M10 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 the dosed 60 subjects, 48 subjects completed the clinical phase of the study successfully. One subject was withdrawn from the study on medical grounds in Period-I. Four subjects were withdrawn from the study due to emesis in Period-I. One subject discontinued from the study on his own accord in Period-II. Two subjects were withdrawn from the study on medical grounds in Period-II. Finally, four subjects were withdrawn from the study due to protocol non-compliance in Period-II. A total of 48 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of carbamazepine, 400 mg under fasted conditions.

Treatment N=48	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	330799 ± 100190	349067 ± 111231	3949 ± 834	26.00 (5.00 – 36.00)
Reference	321191 ± 97801	342435 ± 108706	3851 ± 922	24.00 (5.00 – 48.00)
***Ratio (90% CI)**	103.3 (98.92 – 107.77	102.2 (97.86 – 106.76)	103.2 (99.19 – 107.43)	--

$AUC_{0-\infty}$	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 = 240 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval
*****	Back-transformed from ln-transformed least-squares mean values

BE Study No: 515-15, fed conditions
Design
A single-dose, randomised, open label, two-treatment, two-period, two-sequence, two-way crossover bioequivalence study was carried out under fed conditions in 44 healthy male subjects, aged 20-44 years. Each subject received a single dose (400 mg) of one of the carbamazepine formulations. The tablet was orally administered with 240 mL water after a fasting period of at least 10 hours followed by a standardised high-fat and high calorie breakfast. There were two dosing periods, separated by a washout period of 28 days.

The plasma concentration time curve was used to assess the rate and extent of absorption. Blood samples were collected pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 48, 72, 120, 168 and 240 hours after administration of the products.

The SmPC recommends administering the product with liquid, either whole or - if half-tablets have been prescribed - as half-tablets, without chewing, during or after a meal. Due to the controlled release of carbamazepine, a twice-daily dosage is generally possible.

The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** Note for Guidance on the investigation of bioavailability and bioequivalence.

The bioequivalence study under fed conditions is in accordance with the CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** Note for Guidance on the investigation of bioavailability and bioequivalence.

Bioanalytical/statistical methods
The bioanalytical method has been adequately validated according to current guidelines (ICH M10 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
44 Subjects enrolled in the study. Six subjects were withdrawn, all in Period II: two subjects discontinued on their own accord, two subjects were withdrawn on medical grounds, one was withdrawn due to vomiting and one due to non-compliance. A total of 38 subjects were eligible for pharmacokinetic analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of carbamazepine, 400 mg under fed conditions.

Treatment N=38	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	t_{max} (h)
Test	392710 ± 75209	415376 ± 87517	4745 ± 614	13.51 (8.00 – 28.00)
Reference	391236 ± 77667	414266 ± 91613	4509 ± 588	24.00 (11.00 – 30.00)
***Ratio (90% CI)**	100.3 (97.28 – 103.49)	100.3 (97.23 – 103.48)	105.2 (102.23 – 108.21)	--

$AUC_{0-\infty}$	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 = 240 hours
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval
*	Back-transformed from ln-transformed least-squares mean values

BE Study No: BA19636346, multiple dose study (fasting)
Design
A multiple dose steady state oral bioequivalence study was carried out under fasted conditions in 54 healthy male subjects, aged 20-43 years. Each subject received multiple doses (of 400 mg each) of one of the carbamazepine formulations. The tablet was orally administered with 240 mL water at every 12 hours interval after a fasting period of at least 9 hours for all morning doses and at least 4 hours for all evening doses. There were two dosing periods. The interval between the last dosing on Day 10 of period I to first dosing on Day 01 of period II was 12 days.

The plasma concentration time curve was used to assess the rate and extent of absorption. Blood samples were collected pre-dose (at several time points) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours after each administration of the products.

The SmPC recommends administering the product with liquid, either whole or - if half-tablets have been prescribed - as half-tablets, without chewing, during or after a meal. Due to the controlled release of carbamazepine, a twice-daily dosage is generally possible.

The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** Note for Guidance on the investigation of bioavailability and bioequivalence.

Bioanalytical/statistical methods
The bioanalytical method has been adequately validated according to current guidelines (ICH M10 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
56 Subjects enrolled in the study. One subject withdrew consent on his own record, and one on medical grounds. A total of 54 subjects completed the clinical part of the study in its entirety, all 54 were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of carbamazepine, 400 mg under fasted conditions.

Treatment N=54	$AUC_{tau,ss}$ (µg.h/mL)	$C_{max,ss}$ (µg/mL)	$C_{tau,ss}$ (µg/mL)	$t_{max,ss}$ (h)
Test	114.485 ± 21.403	10.367 ± 1.956	8.849 ± 1.900	5.00 (1.00 - 11.00)
Reference	114.088 ± 21.271	10.318 ± 1.968	8.812 ± 1.692	5.00 (2.00 - 9.00)
***Ratio (90% CI)**	100.38 (97.74 - 103.09)	100.54 (97.89 - 103.26)	99.99 (96.66 - 103.44)	--

$AUC_{tau,ss}$ Area under the concentration-time curve over a dosing interval at steady-state
$C_{max,ss}$ Maximum plasma concentration at steady state
$C_{tau,ss}$ Drug concentration at the end of a dosing interval at steady-state
$t_{max,ss}$ Time after administration when maximum plasma concentration occurs at steady-state
CI Confidence interval (geometric mean)
* Back-transformed from ln-transformed least-squares mean values

Conclusion on bioequivalence studies:
The 90% confidence intervals calculated for AUC_{0-t}, and C_{max} are within the conventional bioequivalence acceptance range of 80% – 125%. In addition, the 90% confidence intervals for $C_{max,ss}$, $C_{tau,ss}$ and $AUC_{tau,ss}$ are within 90% - 111%. Based on the submitted bioequivalence studies Carbamazepine Retard Focus Care 400 mg is considered bioequivalent with Tegretol CR 400 mg under fasted and fed conditions.

As a biowaiver has been granted, the results of studies 486-15, 515-15 and BA19636346 with the 400 mg formulation can be extrapolated to the lower 200 mg strength, in accordance with the conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **.

V.3. Summary Pharmacovigilance system

The MAH has submitted a signed summary of the MAH's and/or Proposed Future MAH's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the legal requirements as set out in the Commission implementing regulation and as detailed in the GVP module, the MEB considers the summary acceptable.

V.4. 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 Retard Focus Care. At the time of approval, the accepted version of the RMP was version 1.1 with sign-off date 1 June 2022.

Table 4. Summary table of safety concerns as approved in the RMP

Important identified risks	• Congenital malformations and neurodevelopmental disorders
Important potential risks	• Suicidal ideation and behaviour
Missing information	None

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

V.5. Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the reference medicinal product Tegretol CR. The MAH demonstrated through three bioequivalence studies that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference medicinal product. A biowaiver is granted for the lower strength. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference medicinal product.

VI. 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.

A user consultation with target patient groups on the package leaflet (PL) has been performed based on a bridging report making reference to Meizine 200 mg and 400 mg prolonged release tablets and to Carbamazepine 100 mg, 200 mg and 400 mg Focus Care tablets (NL license RVG 129005 and RVG 129006). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VII. POST-APPROVAL COMMITMENTS (PAC's)

Post-approval commitments: not applicable.

VIII. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Carbamazepine Retard 200 mg and 400 mg Focus Care has a proven chemical-pharmaceutical quality and is a generic form of Tegretol CR 200 mg and 400 mg prolonged release tablets. Tegretol CR is a well-known medicinal product with an established favourable efficacy and safety profile. Bioequivalence has been shown between the test and reference medicinal products, in line with the requirements of European guidance documents.

This procedure was discussed in the Board meeting 1018 held on 22 December 2022. The following was discussed:

Three major objections were still unresolved in the second round, regarding the functionality of the tablet score line, the proposed specification limits for finished-product dissolution tests, and the dissolution profiles for the biowaiver of strength for the 200 mg strength.
The two major objections concerning the functionality of the score line and the specification limits for dissolution tests have since been resolved. The third major objection, regarding the dissolution profiles for the biowaiver of strength for the 200 mg strength, remained unresolved, meaning this strength could not be approved. On this basis, a previously issued notice of intent to refuse was being converted into a final refusal.

The MEB, based on the data submitted, considered that essential similarity has been demonstrated for the Carbamazepine Retard Focus Care 400 mg strength with the reference medicinal product, and have therefore granted a marketing authorisation on 17 February 2023. For the 200 mg strength, the national procedure was finalised with a negative outcome on 23 December 2022.

The MAH lodged an objection against the negative decision for the 200 mg strength on 7 February 2023. The MAH stated that the dissolution conditions stated in the previous round were due to a typographical error and has provided new data of dissolution profiles performed in the requested conditions (900 ml medium without surfactant, paddle 50 rpm, media pH 1.2, 4.5 and 6.8) comparing one tablet of the 400 mg biobatch against 2 tablets of one batch of the 200 mg strength. For the results at pH 1.2, bootstrapping was applied because of too high per cent relative standard deviation at the initial time points for the 200 mg strength. The results give a lower 90% confidence interval far above 50. Furthermore, according to the requirements of the Guideline on Investigation of bioequivalence, the direct f_2 calculation can be applied including the timepoints 180, 360, 540 and 720 minutes. The MEB has calculated f_2 this way, resulting in f_2= 95.6. For the results at pH 4.5 and 6.8, direct calculation of f_2 was possible and resulted in both cases in values well above 50.
Based on above, the similarity of the dissolution profiles of the 400 mg biobatch against 2x 200 mg tablets is adequately confirmed in the conditions required in the guideline on BE.
Concluding, the requested biowaiver of strength for Carbamazepine Retard Focus Care 200 mg is approvable from a quality point of view.

The negative outcome for the 200 mg strength has been revoked and converted into a positive outcome on 22 June 2023.

IX. RECOMMENDATIONS AND CONDITIONS FOR MARKETING AUTHORISATION AND PRODUCT INFORMATION

IX.1. List of recommendations not falling under Article 21a/22 of Directive 2001/83/EC

N.A.

IX.2. List of conditions pursuant to Article 21a or specific obligations pursuant to Article 22 of Directive 2001/83/EC

N.A

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
N.A.	N.A.	N.A.	N.A.	N.A.	N.A.