30 April 2020
EMA/352448/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 29(4) of Directive 2001/83/EC

Invented name and associated names: Carbamazepin Tillomed 200 mg and 400 mg prolonged-release tablets

INN: carbamazepin

Applicant: Laboratorios Tillomed Spain S.L.U.

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Table of contents

1. Information on the procedure

An application was submitted under the decentralised procedure for Carbamazepin Tillomed and associated names, 200 mg and 400 mg prolonged-release tablets on 29 October 2018.

The legal basis under which the application was submitted: under Article 10(1) of Directive 2001/83/EC.

The application was submitted to the reference Member State (RMS) Germany and the concerned Member States (CMS) Croatia, Italy, Netherlands, Poland, Sweden and United Kingdom.

The decentralised procedure DE/H/5881/001-002/DC started on 02 January 2019.

On day 210, major issues on bioequivalence, raised by the United Kingdom, remained unresolved; hence the procedure was referred to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), under Article 29, paragraph 1 of Directive 2001/83/EC, by Germany on 20 December 2019. The CMDh 60-day procedure was initiated on 06 January 2020.

Day 60 of the CMDh procedure was on 05 March 2020 and as no agreement could be reached the procedure was referred to the CHMP.

On 06 March 2020 the RMS Germany therefore triggered a referral under Article 29(4) of Directive 2001/83/EC. The United Kingdom raised objections on the acceptance range of AUC and C_{max} of carbamazepine for the investigation of bioequivalence, that were considered to be a potential serious risk to public health.

2. Scientific discussion

2.1. Introduction

Carbamazepine, a sodium channel blocker, is an anticonvulsant medication.

The applicant has submitted an application under article 10(1) of Directive 2001/83/EC for Carbamazepin Tillomed 200 mg and 400 mg prolonged release tablets. The reference medicinal product is Tegretol Prolonged Release 200 mg and 400 mg Tablets by Novartis Pharmaceuticals UK Limited.

The proposed indications include epilepsy (generalised tonic-clonic and partial seizures) in newly diagnosed patients with epilepsy and in those patients, who are uncontrolled or unable to tolerate their current anti-convulsant therapy, paroxysmal pain of trigeminal neuralgia and prophylaxis of manic-depressive psychoses in patients unresponsive to lithium therapy.

In order to demonstrate bioequivalence, the applicant has submitted three bioequivalence studies performed with the highest strength (400 mg) of Carbamazepine prolonged release tablets against the reference product Tegretol 400 mg; a single dose fasting study (P 670/15), a single dose fed study (LBS-004-18) and a multiple dose fed study (LBS-005-18). In addition, a single-dose fed study with a replicative design was presented (752/16).

Within the study protocols the applicant prospectively specified that the 90% CI of the test/reference (T/R) ratio of the geometric LSM of the C_{max} of carbamazepine had to be within the acceptance interval of 80.00-125.00 % and the AUC_{0-t} had to be within the acceptance interval 90.00-111.11% when rounded off to two decimals. The obtained results are in accordance with these conditions.

According to the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) *"In specific cases of products with a narrow therapeutic index, the acceptance interval for AUC should be*

tightened to 90.00-111.11%. Where C_{max} is of particular importance for safety, efficacy or drug level monitoring the 90.00-111.11 % acceptance interval should also be applied for this parameter."

During the CMDh procedure, one CMS, the UK, raised concerns with regards to the range for the bioequivalence acceptance criteria for C_{max} of carbamazepine extended release (ER) formulation. UK considered that, in line with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1), the acceptance range for the investigation of bioequivalence for carbamazepine should be tighten to 90 - 111.11% for both AUC and C_{max} based on the grounds that carbamazepine is an antiepileptic drug with narrow therapeutic index (NTI) and complex pharmacokinetic (PK) profile. In this context, the UK was of the opinion that bioequivalence has not been demonstrated between the test and the reference medicinal product (Tegretol 200 mg and 400 mg Prolonged Release tablets) since all the fed studies (LBS-004-18, LBS-005-18 and 752/16) are considered failed studies for C_{max}.

Moreover, as a consequence of the above concerns, the UK considered that patients receiving carbamazepine are carefully titrated to an optimum dose, and if any change is needed, this should be done among bioequivalent products. Therefore, it was argued that it is essential to have tighter acceptance limits for both C_{max} and AUC. Therefore, the UK was of the opinion that the application was considered not approvable.

Overall, during the CMDh procedure an agreement could not be reached with regards to whether the conventional (80 -125%) or the tighter (90 - 111.11%) bioequivalence acceptance criteria should be used for the C_{max} of the ER formulations of carbamazepine, hence the issue was referred to the CHMP.

2.2. Assessment of the issues raised as a potential serious risk to public health

In support to this application, three open label, randomized bioequivalence studies have been performed with the highest strength (400 mg) of Carbamazepine prolonged release tablets. A single dose fasting study (P 670/15), a single dose fed study (LBS-004-18) and a multiple dose fed study (LBS-005-18).

The prespecified acceptance ranges for bioequivalence in the study protocols were 90% confidence interval (CI) of the ratio [Test/Reference] of the geometric LSM of the C_{max} of carbamazepine had to be within the acceptance interval of 80.00-125.00 % and for $LnAUC_{0-t}$ had to be within the acceptance interval 90.00-111.11% when rounded off to two decimals.

The **Single dose fasting study (670/15)** was an open label, balanced, randomised, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study in healthy, adult, human subjects under fasting conditions. 90 % CI of the T/R ratio of the LSM of primary target parameters were 102.33% [98.10-106.75%] for C_{max}, 104.96% [100.33-109.81%] for AUC_{0-t} and 105.70% [101.22-110.37%] for AUC_{0-inf}. Bioequivalence between the products was concluded based on the pre-specified criteria.

The **Single dose fed study (LBS-004-18)** was an open-label, randomised, single-dose two-treatment, two-period, two-sequence, two-way crossover bioequivalence study with at least 28 days washout period between each administration in healthy, adult, male subjects under fed conditions. The study showed bioequivalence between the products based on the results that are within the range of the pre-specified criteria; 90% CI of the T/R ratio of the LSM of primary target parameters were 108.02% [103.88-112.33%] for $C_{max,}$ 105.67% [101.43-110.09%] for AUC_{0-t} and 105.71% [101.28-110.32%] for AUC_{0-inf}.

The **Multiple dose fed study (LBS-005-18)** which was an open-label, randomized, multiple-dose, two-treatment, two-period, two-sequence, two way crossover bioequivalence study in healthy, adult, male subjects under fed condition showed also bioequivalence based on the results of the 90% CI of T/R ratio of the LSM of primary target parameters which are within the range of the pre-specified criteria: 107.25% [102.98-111.70%] for C_{max}, 106.72% [102.63-110.97%] for AUC_{ss0-12} and 108.21% [103.60-113.03%] for $C_{0-\tau,ss,0-12}$.

Plasma concentrations were slightly above the therapeutical range (about 13-14 µg/ml), but this was observed for both the test and reference product. There is no significant difference between peak-to-trough fluctuation of test and reference formulation (p=0.390).

In addition to these three studies, the applicant conducted also **a single-dose fed study (752/16)** with a replicative design. This was an open label, balanced, randomized, two-treatment, four-period, two-sequence, single dose, crossover, replicate, oral bioequivalence study in healthy, adult subjects under fed conditions. The results of study 752/16 are consistent with bioequivalence as defined for the pre-specified criteria; the 90% confidence intervals are within the predefined acceptance limits; 111.06% (108.56 - 113.62%) for C_{max}, 109.15% (105.79 – 112.61%) for AUC, and 108.56% (105.11 – 112.13%) for AUC_{inf}.

The CHMP noted that the C_{max} was higher for the test compared to the reference product for the studies LBS-005-18 and 752/16, while AUC_{0-t} and AUC_{inf} were larger for the test product in study 752/16 and a trend in this direction was also seen for study LBS-004-18. Overall, these results suggest a somewhat higher bioavailability for the test product, but this observation fells within the bioequivalence pre-specified acceptance ranges. Overall, the CHMP considered that all the obtained results are within the prespecified acceptance ranges for bioequivalence.

With regards to the categorisation of carbamazepine as an NTI drug, the CHMP noted that there is not unanimous classification of carbamazepine as NTI drug. Taking into consideration the guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) which states that *"It is not possible to define a set of criteria to categorise drugs as narrow therapeutic index drugs (NTIDs) and it must be decided case by case if an active substance is an NTI drug based on clinical considerations."* and based on the characteristics of ER formulation of carbamazepine, clinical studies and literature review on pharmacokinetic profile (flattened curve) for carbamazepine, the CHMP agreed that there is no need of tightened C_{max}, even though carbamazepine is classified as Category 1 medicine. The view that carbamazepine is not considered an NTI drug was also supported by the Central nervous system working party (CNSWP) which was consulted during the CMDh procedure.

The CHMP noted that the frequent dosing of immediate release (IR) dosage form of carbamazepine and other anti-epileptic drugs (AEDs) exhibit large fluctuations in peak-to-trough plasma concentrations which result in breakthrough seizures and other adverse events. However, the product under evaluation is an ER formulation which was developed with the aim to reduce peak-to-trough fluctuation (more flattened curve with reduced fluctuation and increased dosing interval) thereby reducing breakthrough seizures in patients.

The applicant has submitted a literature overview which supports that different formulations of carbamazepine (immediate release, extended release, suspension) may vary in bioavailability and it may be prudent to avoid changing formulations (IR to ER, ER to suspension, ER to IR, ER to suspension, etc).

ER formulations of AEDs including carbamazepine minimised the spikes in maximum plasma concentrations (C_{max}) at steady-state and resulted in reduced adverse drug reactions due to reduction in dosing frequency and flattened plasma concentration curve. Direct PK comparison studies of IR and ER formulations (e.g., carbamazepine, divalproate sodium, lamotrigine, oxcarbazepine, levetiracetam,

and phenytoin) have found that dose-normalized ER formulations may or may not be bioequivalent to their IR counterparts, but most ER formulations have a lower fluctuation index compared with the IR versions. This results in more even concentration-time plots.

The applicant has submitted a Cochrane systematic review[1] that summarises the pharmacokinetic behaviour of IR versus ER formulation of carbamazepine. A 2.5-fold fluctuation in peak-to-trough concentrations with IR formulations is noted. Based on this, the applicant argued that the category 1 classification of carbamazepine is more appropriate for IR formulations and for suspension since they exhibit all the relevant characteristics such as fluctuation and higher dosing frequency, in contrast to the ER formulation of carbamazepine.

One study[2] showed that ER carbamazepine produced a significantly lower fluctuation ($p < 0.015$) in serum carbamazepine levels than IR carbamazepine, which was considered to be a result of a significantly lower C_{max} with the ER formulation ($p < 0.01$). This fluctuation difference was associated with significantly fewer AEs globally and fewer intermittent AEs with ER carbamazepine ($p < 0.001$ for both). In addition, monthly seizure frequencies were significantly reduced during treatment with ER carbamazepine ($p = 0.013$).

In another study[3] evaluating the bioequivalence of IR carbamazepine administered four times a day to an ER carbamazepine administered twice daily (Carbatrol), it was shown that the formulations were bioequivalent.

Similarly, when comparing the PK parameters of IR and ER carbamazepine, it was shown that significantly fewer patients reported AEs (n = 26, IR carbamazepine vs. n = 6, CR carbamazepine; $p < 0.001$) and significantly more patients rated tolerability as ''good or very good'' (n = 27, IR carbamazepine vs. n = 47, CR carbamazepine; $p < 0.001$) with the ER versus IR carbamazepine formulation[2].

A study[4] with the reference product Tegretol IR versus Tegretol XR (extended release) established that there were no changes in clinical status when patients were switched from one carbamazepine formulation to the other under steady state. The two products maintained similar steady state trough plasma drug concentrations. Moreover, 98% of patients during Tegretol XR treatment and 97% of patients during Tegretol treatment had plasma concentrations within the therapeutic range. Patients tolerated both products well, and clinically significant drug-related changes in laboratory test results did not occur. The literature concludes that physicians can switch patients whose seizure disorder is well controlled with Tegretol monotherapy to twice-daily treatment with Tegretol-XR at the same daily dose without loss of seizure control or increase in drug-related adverse experiences.

The CHMP also took into consideration the consultation with the CNSWP occurred during the CMDh procedure. The CNSWP noted that the use of carbamazepine ER is associated with fewer adverse events as compared to IR formulations of carbamazepine[5]. The slow titration at initiation of treatment is important and aims to desensitise for adverse events. The CNSWP concluded that from a clinical perspective carbamazepine is not an NTI agent. This conclusion applies even more for the ER formulations which have a less steep absorption and lower C_{max}, less variable plasma fluctuations as compared to the IR formulations.

1 Ilo E. Leppik and Collin A. Hovinga. Extended-rel ease antiepileptic drugs: A comparison of pharmacokinetic parameters relative to original immediate-release formulations, Epilepsia, 2013, 54(1):28–35.
2 Canger et al. Conventional vs controlled-release carbamazepine: a multicentre, double-blind, cross-over study. Acta Neurol Scand 1990, 82:9-13.
3 Garnett et al. Pharmacokinetic Evaluation of Twice-Daily Extended-Release Carbamazepine (CBZ) and Four-Times-Daily Immediate-Release CBZ in Patients with Epilepsy. Epilepsia, 1998, 39(3):274-279.
4 Double-blind crossover comparison of Tegretol-XR and Tegretol in patients with epilepsy. Neurology, 1995, 45:1703-1707.
5 Powell G et al, Immediate-release versus controlled-release carbamazepine in the treatment of epilepsy. Cochrane Database of Systematic Reviews 2016, Issue 12. Art. No.: CD007124. DOI: 10.1002/14651858.CD007124.pub5.

Switching from one ER formulation of carbamazepine to another when tolerance has already been established, despite being considered acceptable by the CNSWP, is not specifically addressed in this procedure. Bioequivalence, which is shown on the population level may not necessarily mean interchangeability for an individual patient. Switching should always be done under careful monitoring of the patient by the treating physician and in line with the current recommendations in the product information.

Taking into consideration all the above, the CHMP considered that for IR carbamazepine formulations, the C_{max} is of importance and should comply with narrow acceptance criteria of 90.00 to 111.11%, whereas for ER formulations the general acceptance criteria of 80.00 to 125.00% for C_{max} and 90.00 to 111.11% for AUC are adequate to demonstrate bioequivalence.

3. Benefit-risk balance

The applicant has submitted a generic application for Carbamazepin Tillomed 200 mg and 400 mg prolonged release tablets, intended for epilepsy, paroxysmal pain of trigeminal neuralgia and prophylaxis of manic-depressive psychoses.

Three bioequivalence studies and one with replicative design have been submitted in support of this application. The acceptance intervals were predefined at 80.00-125.00 % for C_{max} and 90.00-111.11 % for AUC_{0-t}. The results suggest a higher bioavailability for the test product, however it is within the prespecified acceptance ranges for bioequivalence.

The CHMP noted the guideline on bioequivalence which suggest that for NTI drugs and for drugs for which C_{max} is of particular importance for safety, efficacy or drug level monitoring, tighter acceptance ranges of 90.00-111.11% for C_{max} should be applied.

However, based on the characteristics of ER formulation of carbamazepine, clinical studies, literature data on the PK profile of carbamazepine and the CNSWP advise obtained during the CMDh procedure, the CHMP considered that carbamazepine is not considered as an NTI drug with C_{max} of major importance. This conclusion applies even more to the ER formulations of carbamazepine, which they have been shown to minimise the spikes in maximum plasma concentrations and reduce fluctuations in plasma levels leading to reduced break through seizures. Overall, for the ER formulations, AUC is more important and application of stringent criteria for C_{max} is not that essential.

CHMP noted that demonstration of bioequivalence on the population level may not necessarily mean interchangeability for an individual patient. Switching among different products/formulations of carbamazepine should always be done with caution and only when considered appropriate by the treating physician and under close monitoring of the patient.

In view of all the available data and taking into consideration the outcome of the CNSWP consultation, the CHMP is of the opinion that the standard bioequivalence criteria of 80.00-125.00 % for C_{max} should be applied for assessment of bioequivalence between test and reference medicinal product. The observed differences in C_{max} between the products in the submitted bioequivalence studies fall within the predefined bioequivalence limits and do not represent a potential serious risk to public health. Consequently, the bioequivalence between Carbamazepin Tillomed 200 mg and 400 mg prolonged-release tablets and Tegretol Prolonged Release Tablets 200 mg and 400 mg has been sufficiently demonstrated. The benefit-risk of Carbamazepin Tillomed 200 mg and 400 mg prolonged-release tablets is considered positive and therefore the CHMP recommends the granting of the marketing authorisation.

4. Grounds for Opinion

Whereas

- The Committee considered the referral under Article 29(4) of Directive 2001/83/EC.
- The Committee considered the bioequivalence studies and the literature overview submitted by the applicant in relation to the objections raised as potential serious risk to public health.
- The Committee considered the outcome of the central nervous system working party consultation obtained during the CMDh procedure.
- The Committee was of the view that the standard bioequivalence criteria of 80.00-125.00 % for C_{max} should be applied for assessment of bioequivalence between test and reference product.
- The Committee considered that the bioequivalence between Carbamazepin Tillomed 200 mg and 400 mg prolonged-release tablets and the reference product (Tegretol Prolonged Release Tablets 200 mg and 400 mg) has been sufficiently demonstrated.

The Committee, as a consequence, considers that the benefit-risk balance of Carbamazepin Tillomed 200 mg and 400 mg prolonged-release tablets and associated names is favourable and therefore recommends the granting of the marketing authorisation(s) for the medicinal products referred to in Annex I of the CHMP opinion. The product information remains as per the final version achieved during the Coordination group procedure as mentioned in Annex III of the CHMP opinion.