Annex II

Scientific conclusions

Scientific conclusions

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.

The product under evaluation is an extended/prolonged release (ER) formulation of carbamazepine 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.

In order to demonstrate bioequivalence, the applicant has submitted four bioequivalence studies performed with the highest strength (400 mg) of carbamazepine prolonged release tablets against the reference product Tegretol 400 mg. The 90% CI of the acceptance intervals were predefined at 80.00-125.00 % for C_{max} and 90.00-111.11% for AUC_{0-t} and the obtained results are in accordance are within the range of the pre-specified criteria.

The guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) suggests that for drugs with narrow therapeutic index (NTI) 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.

During the CMDh procedure, one of the concerned member states, 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, 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 NTI antiepileptic drug with 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 since all the fed studies are considered failed 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.

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.

Overall summary of the scientific evaluation by the CHMP

The applicant submitted four bioequivalence studies and literature review in order to support the use of the wider acceptance ranges for C_{max}.

The literature review demonstrated that 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. In contrast, 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 pharmacokinetic comparison studies of IR and ER formulations 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 resulted in more even concentration-time plots. [1] [2] [3] The applicant submitted also a Cochrane systematic review [4] that summarises the pharmacokinetic behaviour of IR versus ER formulation of carbamazepine showing that IR formulations and suspension exhibit a 2.5-fold higher fluctuation in peak-to-trough concentrations, in contrast to the ER formulation of carbamazepine.

Overall, it has been sufficiently demonstrated that the ER formulations have the potential to minimise the spikes in maximum plasma concentrations and reduce fluctuations in plasma levels leading to reduced break through seizures.

The CHMP also took into consideration the guideline on the investigation of bioequivalence 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 NTID based on clinical considerations*" and pointed out that there is not unanimous classification of carbamazepine as NTI drug.

Based on the characteristics of carbamazepine ER formulation, the submitted clinical studies, the literature data on the pharmacokinetic profile of carbamazepine and the outcome of the central nervous system working party consultation obtained during the CMDh procedure, the CHMP concluded that carbamazepine is not considered as an NTI with C_{max} of major importance and that this conclusion applies even more to the ER formulations of carbamazepine. For the ER formulations, AUC is more important and application of stringent criteria for C_{max} is not essential.

In view of all of the available data, the CHMP is of the opinion that the standard bioequivalence criteria of 80.00-125.00 % for C_{max} is appropriate for the assessment of bioequivalence between test and reference 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 / 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 / 400 mg prolonged-release tablets is considered positive and therefore the CHMP recommends the granting of the marketing authorisation.

1 Double-blind crossover comparison of Tegretol-XR and Tegretol in patients with epilepsy. Neurology, 1995, 45:1703-1707.

2 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.

3 Canger et al. Conventional vs controlled-release carbamazepine: a multicentre, double-blind, cross-over study. Acta Neurol Scand 1990, 82:9-13.

4 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.

Grounds for the CHMP 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 200mg 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.