CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-251

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	12/17/08
From	Norman Hershkowitz, MD, PhD
NDA/BLA # **Supplement#**	22251 000
Applicant	GSK
Date of Submission	11/28/07
PDUFA Goal Date	9/28/08
Proprietary Name / **Established (USAN) names**	Lamictal ODT/ Lamotrigine
Dosage forms / Strength	Oral Disintegrating Tablet/ 25 mg, 50 mg, 100 mg, and 200 mg tablets
Proposed Indication(s)	Epilepsy, Bipolar Disorder
Recommended:	Approval

Introduction

Lamictal, available as a tablet and chewable tablet, is indicated in the treatment of a number of epilepsies (partial, primary generalized tonic-clonic and Lennox-Gastaut) and Bipolar Disorder. The Sponsor has submitted the present NDA to support approval for a new formulation that consists of an oral disintegrating tablet for patients who may have difficulty swallowing whole tablets. The evidence for approval is described below.

CMC/Device

Dr Wilson performed the CMC review and recommends approval. CMC noted that the approval letter should contain the following informtion "we grant an 18 month expiry for all four tablet strengths of Lamictal® (lamotrigine) Orally Disintegrating Tablets when packaged in the commercial container closures (30-count HDPE bottles, (b) (4) t HDPE bottles, and (b) (4) blister packs) and stored at controlled room temperature [20oC – 25oC (68oF – 77oF)], with excursions permitted between 15oC – 30oC (59oF – 86oF)."

Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviwer was Dr Fisher. Although there was some initial concern regarding polyethylene (PE) excipient the Sponsor provided adequate informtion to support the safety of levels of PE in the formulation. Pharmacology did have labeling recomendations which have been executed.

Clinical Pharmacology/Biopharmaceutics

Two pharmacokinetic studies were performed. These were reviewed by Dr. Carol Noory. The first was a pilot study (LBI108614) that compared two potential ODT formulations to the IR tablet formulation. The formulation identified in this study was then examined in a pivotal bioequivalence trial (LBI108617). The latter trial was a four-arm parallel-group study designed to demonstrate the bioequivalence of the ODT to the Lamictal IR tablet and to determine the effect of food and water on the ODT. Dr. Noory concluded that the ODT was comparable to the marketed product (within the range of 80 to 125%) and that no food effect was apparent. There was also no differnce between swallowing the tablet whole or allowing it to disintegrated in the mouth. The Clinical Pharmacology Review contained labeling recommendations have been included in the division's editing of the label.

DSI audit

DSI audited the clinical and analytic portions of the pivotal trial, LBI108617. The reviewers included Drs. Subramaniam, Chen and Raha. In a review written on September 8, 2008 they note a 483 was issued to GSK following inspection. The principal issue was that the study could not be reconstructed in its entirety because the firm did not retain electronic data copies and electronic audit trails for chromatography. All that was available were pdf copies of chromatograms. This impacted DSI's ability to evaluate the reasons for rejecting a number of runs because of QC failures and the changing of integration parameters in 25% of samples. There was also a failure to maintain some original pdf copies for auditing a number of other issues such as the justification for re-injections as a result of "poor chromatography" rejection of validation run and peak integrations modification.

The Sponsor responded to the 483 and DSI reviewed the response on 11/12/08. In that review it is noted that the Sponsor believed that the pdf allowed for an accurate reconstruction and evaluation of the original electronic records. The DSI responded that while this allowed for verification of final drug concentration, it does not allow for an "evaluation of bioanyltical data to assure that reported concentrations were obtained in a scientifically sound, consistent, and unbiased manner." DSI again noted that pdf copies fail to demonstrate the reason for reintegration, but also add that the firm did not manually document why reintegration was warranted. In response to GSK's contention that electronic auditing was unnecessary DSI pointed out that inadequate manual records were maintained to reconstruct data and that adequate manual records should have been maintained in absence of an electronic audit trail.

Clinical pharmacology was asked to perform a recalculation of bioequivalent calculations, excluding run that required reevaluations in the analysis. Clinical Pharmacology performed this and demonstrated that even with the exclusion of data in question[1] bioequivalence standards were met for all comparisons with regard to for AUC and Cmax. A separate calculation was performed to detrmine the adequacy of power by Dr Schuimann, of biostatistics. Power was determined to be acceptable.

[1] 32 to 33 out of 53 to 54 patients were analyzed. The range is given as there were multiple comparisons: i.e. this consisted of simple comparison of ODT to IR as well as examination of a food effect etc.

The DSI division's predominant issue in the present audit appears concentrate runs that required recalculation. When these cases were eliminated and a calculation was performed "bioequivalence standards" were still met. A calculation of power indicated the data to be acceptable. This reviwer believes that this post hoc calculation mitigates DSI's concern and provides a justification of accepting the data. The Sponsor should, however, be warned to provide an adequate audit trial in future applications.

Clinical

Dr Sheridan performed the Clinical review. As he noted the efficacy is based solely on equivalence demonstrated in the clinical pharmacology studies. The safety data included 194 patients form these studies exposed to ODT. No new adverse events, other then those expected from lamictal, was observed. No significant local oral mucosa irritation was noted.

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/s/

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MEDICAL OFFICER