CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22-509

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	1/28/10
From	Norman Hershkowitz, M.D, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	22509 (000)
Applicant	Glaxo Smith Kline Pharmaceutical Co.
Date of Submission	3/31/09
PDUFA Goal Date	1/31/09
Proprietary Name / **Established (USAN) names**	Lamotrigine extended-release / Lamictal XR
Dosage forms / Strength	XR Tablets: 25 mg, 50 mg, 100 mg, and 200 mg.
Proposed Indication	Primary Generalized Tonic Clonic Seizures (PGTC) Adult patients and children $\geq$ 13
Recommended:	Approval

1. Introduction

Lamotrigine (Lamictal®) is an approved anticonvulsant used for the adjunctive treatment of partial onset seizures, primary generalized tonic-clonic and generalized seizures of Lennox-Gastuat syndrome in patients. It is also labeled for conversion to monotherapy in the treatment of partial seizures. The drug is available in three formulations including a tablet, chewable dispersible orally disintegrating tablets, all of which are usually dosed in a BID regimen. On 11/30/09 a new additional slow release formulation (Lamictal XR) was approved for the adjunctive treatment of partial seizure in patients 13 years old and above. This decision was based upon the demonstration of similar bioavailability with the IR formulation, as demonstrated through pharmacokinetic studies, and one phase 3 randomized double blind study (study LAM100034) that demonstrated efficacy in this seizure subtype. The Sponsor now requests approval for the use of Lamictal XR in the treatment of Primary Generalized Tonic Clonic (PGTC) seizures for adults and children 13 years old and above. The IR formulations are presently approved for this indication in adults and children 2 years old and above.

2. Background

In a case where an XR preparation is newly developed for a seizure indication, and where an IR is already labeled, pharmacokinetic studies demonstrating similar bioavailability and a single controlled efficacy/safety with additional safety extension trials are considered sufficient in establishing "substantial evidence." Pharmacokinetic studies were previously reviewed and found acceptable in the prior application, for the approval of Lamictal XR for the treatment of partial onset seizures (POS). In a teleconference on August 23, 2007 between the Agency and GSK it was agreed that along with the demonstration of similar bioavailability a

single a randomized placebo control trial (study LAM100036), could support approval of Lamictal XR for adjunctive treatment of primary generalized tonic-clonic seizures in patients. This application contains this study along with additional safety informtion. The safety informtion in this application includes the aforementioned study along with additional extension study exposure. The Sponsor has also submitted, as part of this application, safety data that was previously reviewed, and which served as the basis of the approval for Lamictal XR in the treatment of POS.

3. CMC/Device

Not applicable.

4. Nonclinical Pharmacology/Toxicology

Not applicable.

5. Clinical Pharmacology/Biopharmaceutics

See section 7

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Dr Steven Dinsmore preformed the clinical review and Dr Steve Bai performed the statistical review.

Efficacy was evaluated by a single international, multicenter, double-blind, randomized, placebo-controlled, parallel-group study in patients 13 years old and above (n=128). This trial was relatively typical in design except for its long experimental period, which was required because of the need for a slower titration period to avoid serious skin reactions. With this exception it is similar to that used for other anticonvulsant drug approvals, and is acceptable to me and the Medical Reviewer, Dr Dinsmore. The trial consist of an 8 week Baseline followed by a 19 week Double-Blind phase (consisting of 7 weeks of upward drug titration and 12 weeks of Maintenance). Patients were permitted to continue into an open label extension if they so decided. According to Dr Dinsmore patients were required to have a “confident diagnosis of primary generalized tonic clonic (PGTC) seizures with a confirmation over a period of 4 weeks prior to baseline with no interictal evidence of partial seizures. A single drug treatment group was compared to a placebo group (1:1 randomization). Patients in the single drug treatment group were targeted to a Lamictal dosage according to the concomitant anticonvulsants metabolic effect on Lamictal with the intention of achieving similar exposure

across different groups. In essence this constitutes a single targeted dose exposure with the allowance to limited dosage adjustment for reasons of efficacy or tolerability[1]. These dosages are based upon the labeled doses for the IR formulation. The primary efficacy endpoint was percent change from Baseline in weekly PGTC seizure frequency during the double-blind Treatment Phase. This or similar endpoints are routinely used in such studies and are considered acceptable. A number or other endpoints were examined as secondary endpoints. The primary anlysis was performed on a modified intent to treat population that included patients receiving drug who had at least one post-baseline measure. It is noteworthy that while the predominate seizure experienced by these patients were PGTC seizures patients were also noted to have other generalized type seizures including absence, myoclonic, tonic, clonic and atonic.

Demographic variables were generally evenly distributed across both treatment groups with a slight preponderance of patients taking only one concomitant anticonvulsant in the Lamictal group (67%) as compared to that of the placebo group (51%). Off note, the majority of patients were from outside the US. Thus, 19% and 12% of the placebo and drug groups coming form the US. The majority of patients came form India. The primary endpoint analysis was to be carried out was to be an ANCOVA with a two-tailed analysis ($p< 0.05$). However, the Sponsor performed a Wilcoxin Rank Sum test in their final study report. This is presumably because the final data was not normally distributed leaving a non-parametric anlysis more appropriate. Dr Steve Bai, the statistics reviewer notes that this analysis is more appropriate then the ANCOVA, which would have been a "problematic" analysis. I agree. I would also note that a Wilcoxin-Rank Sum is the analysis that was performed for the approval of Lamictal XR for POS. The results of this analysis is presented in the table below, which is derived from the statistical review.

Statistics	Placebo	LTG XR
N	72	69
Median (Range)	32.1 (-427, 100)	75.4 (-100, 100)
Estimate Difference[a]	31.6	
95% CI for Difference	15.8, 47.9	
p-value	<.0001	

[Source: Reviewer's results]

a. Hodges Lehman estimates for the median treatment difference, 95% CI and p-value are based on a Cochran-Mantel-Haenszel Rank Sum test.

As apparent the results demonstrated a statistical difference between both groups using the protocol driven p value. The statistics reviewer was able to reproduce the Sponsor's final conclusions. The protocol specified secondary endpoints that examined seizure reduction through other seizure counts (50% responder rates, reduction during the titration or maintenance period, time to reach 50% reduction in seizures) were statistically significant.

[1] Thus for subjects on VPA the targeted dose was 200mg/day with an allowance to increase or decrease by a maximum of 50mg if needed. Subjects on anticonvulsants that induced Lamictal metabolism the targeted dose was 500mg with an allowance to increase or decrease by a maximum of 100mg. Subjects on other regimens had a targeted of 300mg/day with an allowance to increase or decrease by a maximum of 100mg.

Health outcome result secondary endpoints such as SSQ, ESS, POMS and QOLIE-31P failed to achieve statistical significance. Investigator's Global Assessment proved to be statistically significant in favor of drug.

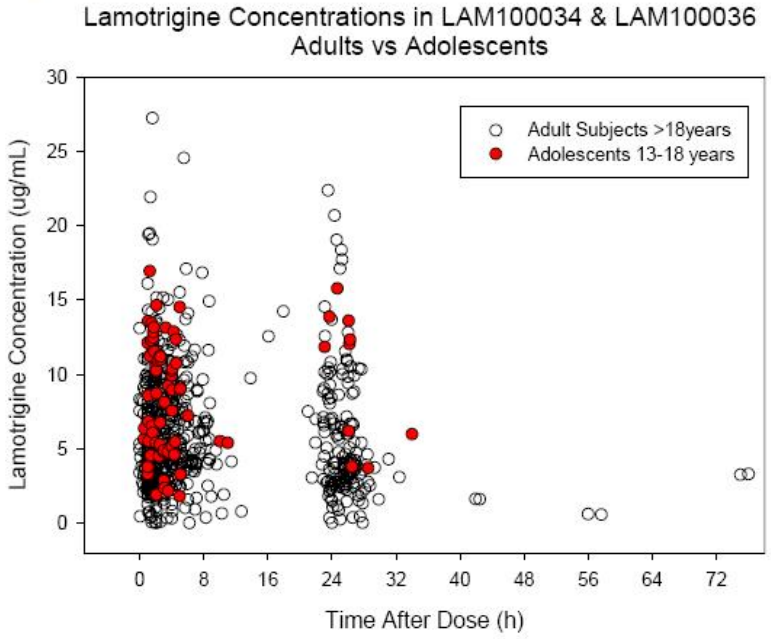
Two subpopulation issues are of relative importance, country of origin and age. These will be discussed below.

As noted above, this study used a targeted dose dosing scheme that allowed for a limited adjustment of final dose. Dr. Dinsmore performed an anlysis which demonstrated that final dosages achieved were similar to that recommended in labeling for POS.

With regard too country of origin, the prior application examining Lamictal XR use in patients with POS revealed a markedly smaller treatment effect (Drug-Placebo) in the US population as compared to populations outside the US with a 4% versus 27% treatment difference, respectively. At that time I concluded that the differences likely resulted from differences in high incidence of concomitant valproic acid use (which inhibits Lamictal metabolism) in the non-US sites, limited power of subset analysis and an unusually high placebo effect in the US population. The present study demonstrated a smaller difference in treatment effect between the two populations for PGTC seizures then prior that observed in the prior study. Thus tehre was a study a 22.2% treatment effect in the US population and a 34.5% treatment difference in the non-US population. Dr Dinsmore points out that there still is an increase in valproic acid use in the drug as compared to placebo groups in non-US versus US as well as an increased placebo effect in the US sites. While the differences in concomitant drug use and placebo effect may have influenced the final conclusions, I belive that the study results indicate effectiveness in the US population and that some. A sub-analysis performed by the statistics reviewer failed to find a significant interaction by country, further supporting these conclusions.

There was some disagreement regarding the adequacy of the data in the prior application requesting Lamictal XR treatment for POS in children 13 to 16 years old. In that study few patients were exposed to drug (n=5) to this age group. Despite this the pharmacokinetic reviewer at that time (Dr. Tandon) felt that there was significant evidence that the drug acted similar pharmacokinetically in adults and children. Considering this fact and that similar dosing is indicated in this children's age group as it is for adults, the data where found adequate for labeling. Nonetheless, to clarify and confirm prior decision about pharmacokinetics in these age groups the Sponsor was requested to perform an additional analysis for all patients (n=9) exposed to drug in the present and prior controlled studies. The results of this analysis are presented in the figure below.

Figure 6-2



This anlysis confirms prior similarity of the two populations. Dr. Tandon agreed, through an email, that populations are equivalent. Both I and Dr. Dinsmore concur that there is adequate data to justify labeling in this younger population.

In conclusion I concur with the medical reviewer, Dr. Steven Dinsmore and the statistics reviewer, Dr, Steve Bai, that this study presents evidence of the efficacy of Lamictal XR in the treatment of PGTC seizures in patients 13 years old and above.

8. Safety

The safety of Lamictal XR is already backed by data acquired and reviewed for the approval of the IR formulation of Lamictal. Some of the data submitted for safety review by the Sponsor was previously reviewed in the application for POS. The controlled database included the previously reviewed POS study (LAM100034) as well as the new study (LAM100036) examining PGTC seizures. Additional extension trial data are also included as well as data from a "conversion to monotherapy."

At the time of the 120 day safety update a total of 662 subjects were treated with lamotrigine XR in All Clinical Studies Grouping. A total of 558 subjects were exposed to lamotrigine XR for 24 weeks, and 270 subjects for 52 weeks. Distribution of dose appeared similar to that of the anticipated labeling. Dr. Dinsmore belives these exposures are adequate and I agree. It is, however, worth noting that only 35 patients under 16 years of age were exposed to Lamictal XR for at least 24 weeks or longer. This is a small number but the adequacy of this data is supported by prior pediatric exposures to the IR formulation of this drug.

Dr Dinsmore notes that 6 deaths were noted to occur in the complete XR development program. Four of these were reviewed by the FDA as part of the POS application and at that time were not thought to constitute a new signal. Dr Dinsmore believes that the two new deaths do not obviously appear to be drug related. I agree. This includes a case of hepatocellular carcinoma and another of hip fracture, small bowel obstruction and MI.

Dr Dinsmore has reviewed the new serious adverse events in this database. Twenty-one new such events were reported, which were not previously reviewed. The most common events were seizures as might be expected, with 2 cases of status epilepticus. The high incidence for status epilepticus is noted in the Warnings of the present label. Additional common events included 3 fractures (2 in the elderly $\geq$ 70 years old), 2 neoplasms (1 hepatic and 1 brain), and 2 cases of pancreatitis. Examinations of the narratives suggested that neoplasm were likely not drug related. It is difficult to attribute the fractures directly to the drug, but it is not unreasonable that the drug may have been related considering that impairment of balance and coordination are noted in the label to be common adverse events. Moreover, considering the fact that 2 events occurred in the elderly, it is meaningful to note that the geriatric section of the present label notes a potential increase in the sensitivity of the elderly population with a warning in dosing. Because of the two cases of pancreatitis Dr Dinsmore performed datamining on the post marketing database. An EB05 of 0.6 was observed. This is not a significant signal. Other serious events are either labeled (rash and ataxia) or could not be attributed to drug.

Dr. Dinsmore discuses discontinuations resulting from adverse events. He notes that, in the completed placebo control database (LAM 100034 and LAM 100036), 4 (2%) subjects in the placebo group and 10 (5%) subjects in the LTG XR group discontinued because of adverse events. Dropouts in the complete database reflected the incidences of common adverse events. Thus, dizziness and rash were common causes of drug discontinuation. No new signals were apparent.

Dr Dinsmore note, under the rubric of "significant adverse events, that there were 20 occurrences of rash in the complete database, including safety follow-up. None were coded as Stevens Johnson syndrome, although one required hospitalization and steroid treatment. He notes, and I agree, that the present label is adequately labeled serious rashes.

Dr Dinsmore notes that the most common adverse events during dose escalation in the controlled trial data base (LAM100034, LAM100036), such that the drug group rate is greater then placebo and which reached a minimum of 2%, were nausea, diarrhea, dizziness, and somnolence, in descending order. This changed when patients were examined during maintenance to dizziness, tremor, and vomiting, in descending order. Dr Dinsmore notes a greater prevalence of GI adverse events during titration and greater prevalence of CNS adverse event during maintenance and speculates there may be a difference resulting from different degrees of habituation. I would add that this may be so, but the differences may result from different rates of drop outs in these groups, which were not examined. Dr Dinsmore also notes that headache was the most common adverse event in the complete database (controlled and uncontrolled studies), but it appears in the controlled data base that headaches occurred at no greater frequency then that observed in the placebo group. In summary Dr Dinsmore notes

that the common adverse events in this database are similar to that of other anticonvulsants, in general, and to that observed for the IR Lamictal formulation. I agree. Informtion on the common adverse events will be included in the label.

Examination of potentially significant labs for all controlled studies did not reveal a definitive signal. No definitive changes were observed in vital signs. Previous formal EKG QT studies did not indicate QT prolongation. Dr Dinsmore notes that the tQT team "concluded that "it unlikely that lamotrigine XR administration is associated with QT interval prolongation or serious ventricular arrhythmias. However, we acknowledge that a different observer might reasonably come to a different conclusion given the flaws in study SCA104648." Of note in my examination of the QT data, there appeared to be a small shorting of the QT interval (approximately 6 msec). This has been observed with sodium channel blocking agents. The magnitude of this change appears smaller then that observed for other such drugs and the significance of such shortening is not completely clear. There was no obvious QT signal observed in the present trials database. There was, however, a suggestion of PR prolongation, another common finding observed in other sodium channel blocking anticonvulsants.

Dr. Dinsmore noted there were no new significant blood chemistry findings. A number of patients experienced low neutrophile counts. Many of these had low pre-drug baseline values. None were reported as associated with drug discontinuations or serious adverse event. The label presently adequately labeled. The Warning notes the potential fro for blood dyscrasias.

Because of literature reports, the Sponsor performed an examination of the potential that Lamictal might increase the incidence of myoclonic seizures. While one patient was noted to discontinue drug because for myclonus, the Sponsor and Dr. Dinsmore concluded that there was no evidence for this. I agree, but I would also add that the present data may not be adequately large to definitively answer the question. Dr. Dinsmore did perform datamining on postmarketing data which revealed an EB05 for myoclonic epilepsy and myoclonus, 1.26 and 1.01 respectively, both not considered significant.

The Sponsor performed additional post-marketing analyses. Because of a suggestions in the literature that Lamictal may produce a significant effect in the delayed rectifier in nonclinical studies, the Sponsor performed an analysis of the rate of sudden death comparing it to other anticonvulsants. Lamictal was less frequently associated with sudden death then other anticonvulsants examined (fifth of thirteen studied drugs). It is noteworthy sudden unexpected death in epilepsy (SUDEP) has already been analyzed in the original IR formulation database with the conclusion that such deaths are no greater then the published background rate. Dr Dinsmore datamining, using the Empirica Signal program, confirmed the Sponsor's conclusion. Moreover, as noted above the QT studies found no evidence of QT lengthening as might be expected with a drug that blocks the delayed rectifier. Both the Sponsor and Dr. Dinsmore performed a number of additional datamining for issues of blood toxicity, multiorgan hypersensitivity, and liver toxicity. The Sponsor concludes that the present labeling adequately represents such risk. Dr Dinsmore concurs as do I.

In summary, no new safety signals were identified.

9. Advisory Committee Meeting

Not applicable

10. Pediatrics

The pediatric patients studied in this application were limited in number and only included patients older then 13 years old. For efficacy conclusions the reader is referred to section 7. Dr Dinsmore noted that, from the data presented in the submission, there was no obvious safety signal specific to this population. Additional informtion, drawn from the larger database, derived from previous studies using the IR formulation has identified some adverse events which were more common in the pediatric population, most notably serious skin reactions, these are noted in the present XR label.

The pediatric data were presented to PERC. There was consensus between PERC and DNP that:

- Pediatric study requirement for ages birth up to 2 years should be waived because the necessary studies are impossible or highly impracticable. This is because there are too few children in this age group with the disease to study.

- This product is appropriately labeled for use in ages 2 years to 12 years for this indication. Therefore, no additional studies are needed in this pediatric group.

- The Sponsor fulfilled the pediatric study requirement for ages 13 years to 16 years.

11. Other Relevant Regulatory Issues

No other relevant issue was identified. As per Dr Dinsmore, financial disclosures and DSI audits were found acceptable.

12. Labeling

There were only minor changes made to the label. The reader is referred to the approval letter.

13. Recommendations/Risk Benefit Assessment

I belive the application should be approved, with labeling specifying use as adjunctive treatment PGTC seizures for adults and children 13 years and older. No post marketing Commitments or Requirements are needed. A REMS is required, which includes a comprehensive MedGuide. The product already has a REMS, but an update is needed. The REMS originates from the need for class labeling regarding the risk of suicidality.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22509	ORIG-1	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE	LAMICTAL XR(LAMOTRIGINE)ORAL TABLETS

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/s/

NORMAN HERSHKOWITZ
01/28/2010