CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-115

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	5/27/09
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	22115 000 BZ
Applicant	Glaxo Smith Kline Pharmaceutical Co.
Date of Submission	7/10/08
PDUFA Goal Date	5/31/08
Proprietary Name / **Established (USAN) names**	Lamotrigine extended-release Lamictal XR
Dosage forms / Strength	
Proposed Indication	1. Adjunctive Treatment of Partial Seizures
Recommended:	Approval

1. Introduction and Background

Lamotrigine (Lamictal®) is an approved anticonvulsant used for the adjunctive treatment of partial seizures, primary generalized tonic-clonic and generalized seizures of Lennox-Gastuat syndrome in patients >2 years of age. It is also labeled for conversion to monotherapy in the treatment of partial seizures. The drug is presently available in three formulations including a tablet, chewable dispersible and orally disintegrating tablets, all of which are usually dosed in a BID regimen. The present submission consists of a response to an approvable letter (dated 9/21/07) for an application of a new extended release formulation (Lamictal XR). The application requests approval of this new formulation for a once-a-day dosing in the adjunctive treatment of partial seizures. The original application consisted of a single pivotal efficacy study (LAM100034) which examined patients ≥13 years old. Also included in this application were 7 PK studies, the principal of which examined single and multiple dose pharmacokinetics, dose proportionality, dosage strength equivalency, food effect and the conversion from the immediate release dosage form to the proposed extended release dosage form and a drug interaction study with esomeprazole. Included in these studies was short-term trial (LEP103944) conducted in patients with epilepsy that evaluated the pharmacokinetics in patients who were converted from immediate release (IR) lamotrigine to XR lamotrigine and then back to IR lamotrigine. Population PK data from the single efficacy was also used for approval.

The following points were addressed as requiring a response in the aforementioned approvable letter:

- Although efficacy was observed to be statistically significant when the study was viewed as a whole, no significant treatment effect was observed when the US sub-set, which constituted 36% of the complete study population. Thus, the median percentage change from baseline in seizure frequency (i.e. primary efficacy endpoint) for XR lamotrigine in foreign sites is 50 % Vs. 23% for placebo and the median percentage change from baseline in seizure frequency for XR lamotrigine in U.S. sites is 37 % vs 33% for placebo. A detailed exposure response was recommended to further investigate this discrepancy.
- The above geographic disparity in effect was troublesome particularly in view of problems identified in 2 Korean sites. A majority of sites were non-US with many unconventional countries being represented (Russian Federation, Ukraine, India, Korea, Chile, Brazil, Argentina). Because of this additional informtion was requested regarding 1) monitoring and inspections of sites, 2) Standard Operating Procedures.
- Because the integrity if data was in question in 2 Korean sites: 1) reanalyzes of data after corrections for the Korean sites, 2) Findings of the audit from these two sites, 3) description of the differences between Sponsor's audit and inspections between Korean sites and other sites. In general the company was requested to address the divisions concern for other sites as a result of the problems identified at the Korean site.

2. CMC/Device

No new CMC issues were identified.

3. Nonclinical Pharmacology/Toxicology

There are no nonclinical issues included in the approvable letter.

4. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology reviewer, Veneeta Tandon, found no issues, but the reader is referred to Efficacy and Pediatric section for pertinent PK issues related to the efficacy review.

5. Clinical Microbiology

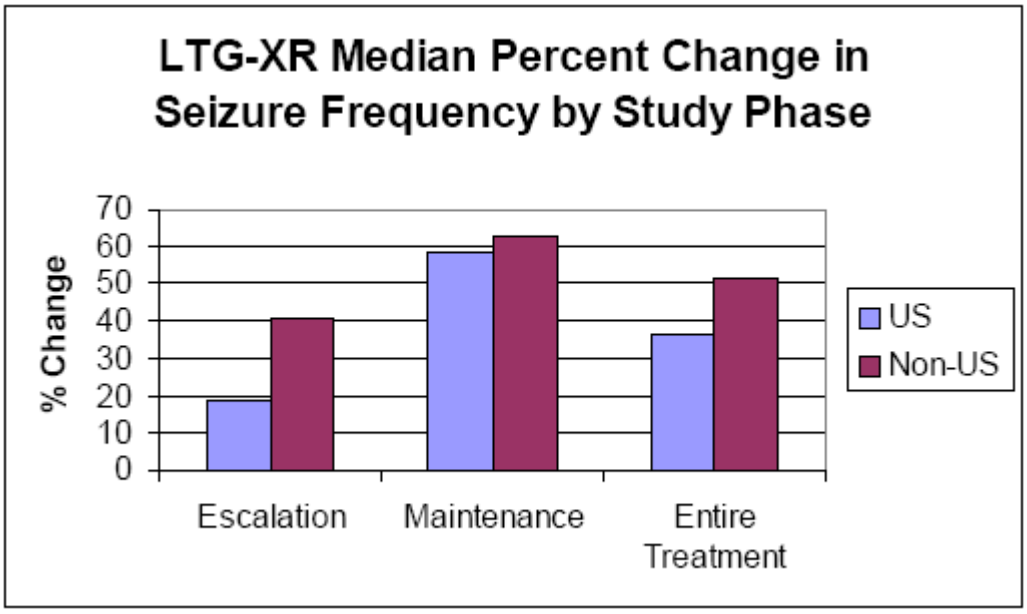
Does not apply.

6. Clinical/Statistical- Efficacy

The single efficacy study (LAM100034) was a double-blind placebo control that included an 8 week baseline period and 19 week experimental period (n=236). Patients were randomized to a target dose, which was in the middle to high range of dosing as proposed in the label. The actual range was dependent on the presence the concomitant medications (inducers, inhibitors and no effect on glucuroidation metabolism). Patients were permitted to be titrated up or down depending on efficacy and/or tolerability. The endpoint consisted of percent reduction in seizure frequency form baseline. As previously noted, the primary analysis of the primary endpoint was statistically superior to placebo ($p < 0.0001$). This significance appeared to be driven by non-US sites, which made up 64% of the n size. Thus the FDA noted in the aforementioned approval letter that:

> "the median percentage change from baseline in seizure frequency (i.e. primary efficacy endpoint) for XR lamotrigine in foreign sites is 50% vs. 23% for placebo and the median percentage change from baseline in seizure frequency for XR lamotrigine in U.S. sites is 37% vs. 33% for placebo"

The Sponsor has argued that the differences can be accounted for by the greater use of valproic acid (VPA), which inhibit Lamictal metabolism and therefore increases Lamictal levels, in the non-US sites. Dr Kapcala, the clinical medical reviewer, notes that while this may in part contributed to the discrepancy, the effect of a greater number of patients in the non-US subset would also increase Lamictal drug levels during the escalation (final steady state will be achieved earlier when valproic acid is present) as well as the maintenance phase, and as both phases are included in the final calculation, should also contribute to observed differences. This effect is apparent in that much greater treatment effect is obvious during the escalation period in the non-US sites as compared to the US sites (see the figure below). This, in part, supports the contention that the differences were not a result of factors intrinsic to individuals in the two populations but differences in concomitant drug use in that population.



Dr. Masse, the statistical reviewer expressed a general concern that there was no statistical evidence that the difference observed between non-US and US sites resulted from VPA use differences, but he points out the limitations of statistical subgroup analysis.

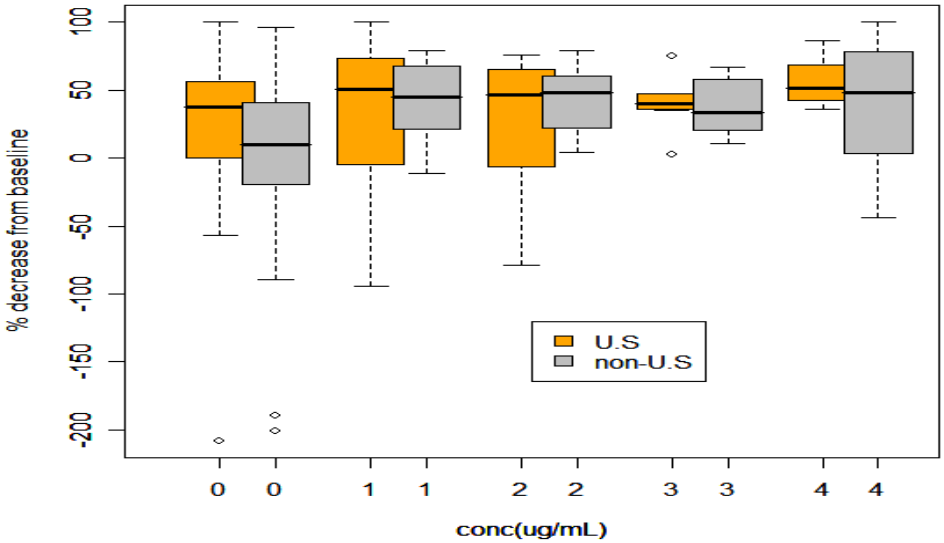
To further explore potential for differences in drug exposure causing differences in seizure efficacy the Sponsor performed a comparison of PK parameter between both populations. An examination of spot concentrations (in two epochs: <12 hours post dose and >12 hours post dose) revealed an increase in median spot concentrations of Lamictal in the non-US population by approximately 15 to 20%. Dr. Kapcala concluded that the difference in this data is not meaningful. This reviewer would concur that from a statistical point of view that such differences is probably not statistically significant, but considerations of statistical sub-group analysis, particularly post-hoc, are fraught with difficulty, as such studies are not designed with sufficient power to discern such differences. I believe that this does, however, suggest a greater trend for exposure in the non-US group.

Another contributing factor, pointed out by Dr Kapcala, was the difference in placebo effect in patients not treated with valproic acid, which constituted the majority of US patients. Thus, although the percent change in seizures were similar for lamotrigine treated groups for European and US sites, the placebo effect is greater then 60% greater for the US as compared to the non-US sites.

The Sponsor argues that a greater number of patients in the US population can be considered refractory to seizures, as based upon the number of anticonvulsants they had used in the past. Dr Kapcala rightfully points out flaws in this analysis.

The Sponsor performed a concentration/response analysis and concludes a positive slope for both US and non-US treatment groups. Dr Kapcala questions this analysis as he believes that the inclusion of placebo results in the positive slope. I agree that a plateau is apparent, but considering the design of the study a plateau would be expected as patients were specifically titrated to a clinical effect. Nonetheless, Dr. Kapcala does agree that a drug effect is apparent in both US and non-US sites when comparing placebo to all other exposures. But, he stresses that the magnitude of effect may be different between US and non-US sites. I believe that a conclusive statement in the differences between these groups is limited by the power of such sub-grouped data and that all we can do with such limited data is a trend analysis. Such an analysis suggests efficacy in both US and non-US sites. In support of this A separate analysis by the pharmacometric team, which included Drs Joo Yeon Lee, Sripal Mada, and Hao Zh, concluded that “the difference in effectiveness between the U.S. and non-U.S. sites, as measured by percentage change from baseline, is likely due to the difference in lamotrigine exposure levels between the U.S. and non-U.S. sites, not due to the response difference.”

An analysis of concentration/response (dividing concentration into quartiles) for US and non-US group’s analysis performed by the pharmacometric group at the request of Dr Kapcala demonstrated a similar relation albeit with a smaller treatment effect (see below). As pointed out by Dr. Kapcala, the difference in treatment effect is likely a result of differences in placebo response.



These data demonstrate a number of previously raised issues: 1)the large placebo effect in the US population, 2) Similar absolute effect in both US and non-US sites, 3) lack of an obvious concentration/ response relation over the measured range (i.e. a plateauing).

Because of the plateauing, Dr Kapcala does not believe dosing has been adequately explored. As I noted above I believe the plateau is likely an artifact of the experimental design in that the study had target doses, but patients were permitted to be titrated up or down depending on efficacy and/or tolerability. Indeed if all patients were titrated for reason of efficacy no rising phase of a dose response curve would be expected. The only was to truly explore dose or concentration dependence is to perform a concentration or dose randomized multiple arm study.

In conclusion, I believe similar efficacy would be expected in both US and non-US populations. The differences observed in the present study likely resulted form differences in concomitant medication use, limited power of subset analysis and an unusually high placebo effect in the US population. This conclusion is strengthened by the fact that IR formulations of the drug have been shown to be effective in the US population and the XR and IR formulations exhibit similar pharmacokinetic behavior.

7. Safety

As part of the approvable letter the Sponsor was requested to provide additional vital sign analysis, with a particular emphasis on identifying orthostatic cahnges, Dr. Kapcala concluded that there was no clear cut data to suggest any change in the present label was necessary.

The Sponsor provided a safety update, the data of which they argued, demonstrated a similar profile as is already known for this agent. Dr. Kapcala agreed with the Sponsor.

8. Advisory Committee Meeting

Does not apply.

9. Pediatrics

The efficacy study conatied 10 patients between ages 13 and 16 years old. No younger patients were studied. Examination of central tendency statistics revealed a trend in efficacy when examining the median change in seizure frequency with an 86% decrease for drug and 30% decrease for placebo. The reduction based on mean was not as obvious with 17% for drug and 13 % for placebo. This, however, is a small sample and definitive conclusions would be difficult to make. Dr Kapcala notes that this is "consistent with a possible therapeutic effect," but he cautions about concluding such an effect from limited data. This reviewer agrees with Dr Kapcala. But I would add that the data is supportive and other sources of informtion should be examined.

Thus, PK data was examined. Only 4 patients provided PK data points, as part of the full study population PK sampling. In his "eyeballing guestimate" Dr Kapcala believes that the mean exposures trended higher then that experienced by older adults, although actually lower for that experienced by young adults. However, Dr Veneeta Tandon, clinical pharmacology reviewer and acting team leader, expressed the view that these data are still consistent with similar PK behavior between adults in this pediatric population. Thus she notes:

> Although there are few subjects between the age range of 13-18 years, additional PK study is not necessary in this age group because (i) concentrations (and dosing regimen) were similar to the adults and there were at least 4-6 samples per subject; (ii) effectiveness of lamotrigine IR in the age range 12-18 years has been established and dosing in partial seizures for the IR formulation is same for ages 12 and older; (iii) relative bioavailability to the IR formulation in patients is known (overall 90% relative BA), hence overall the exposures are not expected to be very different.

Although it is noteworthy that in her review Dr. Tandon defined a pediatric group as patients 13 to 18 years old. upon personal discussions with her she felt that the same conclusions apply for patients 13 to 16 years old. This reviewer agrees with Dr. Tandon. Thus, I belive this data strongly supports labeling for ages 13 to 16 years old. This conclusion is also supported by the fact that as an IR formation the drug is approved for both adult and this pediatric (13- 16 years) patients at the same dosage regimen.

The application has been discussed with the PERC committee and PREA requirements will be waived for children 1 month to 12 years, as it is already adequately labeled at this dosage (as an IR formulation). A waiver will be granted for patients less then 1 month, as there are too few agents with this disorder to make such a study practicable.

Dr Kapcala also argues that only 34 patients of the pediatric age group were included in the safety database. Some safety differences were noted in common adverse events, but this reviewer feels that this is likely a result of the limited sample size. Also noted was one case considered a "pancreatitis." The data for this case, however, is incomplete and Dr Kapcala

has requested additional informtion. Pancreatitis is presently only reported in the post marketing section. There, however, is nothing that would lead one to believe that this risk factor is greatest in pediatric at the present time. Also of note was a single pediatric case of persistent elevated diastolic blood pressure was observed. As this patient's baseline was low it was not deemed to be an adverse event. A more structured analysis of the database did not lead to suspicion of blood pressure alterations in the population in general. It is noteworthy that this patients did experience high serum concentrations of lamotrigine because of his unusually low body weight. Nonetheless, there is no present corroborative data in both adult and pediatric database to suggest that elevated blood pressure is a potential side effect. The case is also mitigated by the fact that the baseline blood pressure was low and while subsequent blood pressures changes were high, absolute blood pressures were not far out of that expected.

In conclusion, Dr. Kapcala recommends additional efficacy and safety data. I, howver, believe that an approval can be granted for ages >12 years of age.

10. Other Relevant Regulatory Issues

Various materials were requested from the Sponsor to better analyze the integrity of the database of the principle efficacy trial. These are summarized and discussed in the following billeted points:

- Standard Operating Procedures were requested by the division. Dr Kapcala reviewed these and believes them to be "reasonable."
- Additional informtion was requested on the Sponsor's monitoring and/or inspection of the pivotal efficacy trial. DR Kapcala has reviewed these and found them adequate in regard to both the safety and efficacy database.
- A reanalysis that included corrected data from the Korean study sites was submitted. This data were include in the present submission (see above) and are the foundation for which the above efficacy conclusions were reached.

Because of the irregularities identified at the Korean sites, 4 additional Russian sites were chosen for inspections. Dr. A El-Hage has written a review of such inspections and concluded that the data integrity appears acceptable in supporting the pending application.

11. Labeling

See proposed labeling letter sent to Sponsor.

12. Recommendations/Risk Benefit Assessment

Dr Kapcala recommends 2 PMRs: 1) A study to better examine efficacy in the pediatric population age 13 to 16 years old, 2) A study to better explore dose response relation in the complete population.

Dr Kapcala reason for recommending further explorations of dose response relation are described above. It is my opinion this investigation is not necessary. In the past this division has requested such studies for presently marketed drugs, but only when there was compelling data to suggest that the recommended doses were inappropriate. I do not believe the evidence reaches this level such (see above). It should also be noted that the drug is labeled not for a single dose, but for a range of doses and that label recommends the dose be titrated. In neurological practice such a titration regimen is routine. While I believe that more informtion could improve dosing, I do not think there is compelling data to suggest that such data is necessary. `

With regard to a study to explore efficacy in an older pediatric population, I do not believe that such a study is necessary for reasons noted in the above Pediatric section. This includes PK data that indicates similar pharmacokinetic behavior in children as that demonstrated in adults and a trend analysis of efficacy in this population. Had this been a completely new medicinal entity, such data would note adequate and an additional study would have been recommended, but as a drug that has a long track record for pediatric use at, I believe the data is sufficient to support the use on this pediatric population.

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/s/

Norman Hershkowitz
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MEDICAL OFFICER