MEMORANDUM

DATE: May 6, 2009

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 22-115

SUBJECT: Action Memo for NDA 22-115 for the use of Lamictal XR (lamotrigine) Extended-Release Tablets 25 mg, 50 mg, 100 mg, and 200 mg

NDA 22-115 for the use of Lamictal XR (lamotrigine) Extended-Release Tablets 25 mg, 50 mg, 100 mg, and 200 mg, as adjunctive treatment for partial seizures in patients down to the age of 13 years old, was submitted by GlaxoSmithKline on 11/22/06. The application contained the results of a single controlled trial (Study 34). The division issued an approvable letter on 9/21/07. In brief, the letter noted that, although the study reached a clear statistically significant difference between drug and placebo, there was a discrepancy in the results between US and non-US centers. Specifically, the treatment effect was not significant in the US (37% median percent change from baseline in seizure frequency on XR compared to 33% for placebo) but was highly significant in the non-US sites (50% vs 23% XR vs placebo, respectively). Approximately 36% of the patients were US patients. The letter asked the sponsor to further evaluate this discrepancy, including a request for additional exposure-response analyses.

An additional troubling factor was that the sponsor had detected significant deficiencies in the 2 Korean sites, and the fact that many of the foreign sites were in countries for which we have little experience (Russian Federation, Ukraine, India, Chile, Brazil, Argentina) raised further questions about the integrity of the data. For this reason, we asked the sponsor numerous questions about their inspections of other sites in the study. Finally, we asked the sponsor to perform additional analyses of vital sign data.

The sponsor responded to the Approvable letter with a submission dated 7/10/08. The application has been reviewed by Dr. Antoine El-Hage, Division of Scientific Investigations, Dr. Tristan Massie, statistician, Dr. Abiola Olagundoye, SEALD team, Drs. Joo Yeon Lee and Sripal Mada, Office of Clinical Pharmacology, Dr. Leonard Kapcala, medical officer, and Dr. Norman Hershkowitz, Neurology Team Leader.

Regarding the critical question about the differential effects in the US and non-US sites, Drs. Massie, Lee, Mada, and especially Kapcala have performed extensive re-analyses of the data. Although, as the reviewers point out, there is no explanation provided for this discrepancy that can be considered definitive, I

believe that there are certain findings that can be considered sufficient to establish that the differential response seen is of no significant importance.

Specifically, and critically in my view, the response during the maintenance phase of the study was essentially similar, and statistically significantly in favor of drug, in the US and non-US sites. Further, as noted by Drs. Lee and Mada, lamotrigine levels in non-US sites were somewhat higher than in US sites, and this is explainable by the greater proportion of patients in the non-US sites taking concomitant valproate (27%) than in the US sites (9%). The difference between the overall results in the US and non-US sites is entirely attributable to a difference in response between the US and non-US in the titration phase. As Dr. Kapcala points out, the titration schedule in patients receiving concomitant valproate results in these patients achieving effective lamotrigine plasma levels sooner than those not receiving concomitant valproate, and as noted, there was a significant discrepancy between the US and non-US sites in the degree of concomitant valproate use. In my view, these findings, taken together, provide a reasonable explanation of the geographic differences seen in the overall response. Also, as Dr. Kapcala notes, there was a significantly higher placebo response in the US than in the non-US sites. This also affected the treatment effects seen. In my view, though this is true, this does not undermine the conclusion that there is considerable evidence of a treatment effect in the US sites.

It is also worth noting that there is no discernible difference in exposure-response between the US and non-US, and that the slope (including placebo) is non-zero in both areas, again suggesting essentially similar responses in both regions. Dr. Kapcala does note that there is a minimal exposure-response without placebo, suggesting that patients are being treated with higher doses than might be necessary. In this regard, he also questions Drs. Lee and Mada's conclusion that the discrepancy in seizure reduction is due to higher lamotrigine levels in the non-US sites secondary to increased valproate use, because higher levels do not seem to be associated with an increase in seizure control. Although this might be true (it is true that the difference in plasma levels related to differential valproate use is minimal), these are levels associated with the **maintenance** phase, and this observation is consistent with similar drug effects during the maintenance phase; i.e., similar plasma levels result in similar drug effects. I find the observation that "therapeutic" lamotrigine levels were likely to have been achieved quicker in the titration phase in patients treated with valproate (this occurred three times as frequently in the non-US sites) coupled with the clear finding of essentially identical (and significant) seizure responses during the maintenance phase, powerful support for the view that the treatment is effective, and has been shown to be so, in both the US and non-US sites.

Regarding the question of the integrity of the data in the study, DSI has inspected 4 sites in the Russian Federation, and has found them acceptable. In addition, the sponsor has performed comprehensive data verification audits at all study

sites. These audits resulted in minor changes to the data that had no effect on the result. Further, the sponsor's extensive SOPs for monitoring the study were found to be acceptable.

Finally, Dr. Kapcala has offered 2 recommendations.

First, he has concluded that effectiveness has not been demonstrated in patients below the age of 17, and recommends that the sponsor perform pharmacokinetic (PK) studies in patients 13-16 years old in Phase 4. I disagree. Dr. Vaneeta Tandon of the Office of Clinical Pharmacology reviewed the pharmacokinetic data in the 13-16 year old patients in her review of 9/6/07 and found that the PK in these patients, although based on a relatively few patients, was essentially the same as in adults; I see no reason to question this finding. Further, Dr. Kapcala is not convinced that effectiveness has been shown in this sub-group. Although I agree that there are only a few patients in this group, the effect was clearly numerically in favor of drug compared to placebo, and I see no reason to conclude that there is a decreased response in this population compared to the response seen in adults.

He also recommends that the sponsor be required to perform a fixed-dose study in Phase 4, to better define the dose response, especially because he suggests that patients may be receiving larger doses than necessary (see above). Although I believe that it is certainly possible that better dose response data could be obtained in the case of many drugs, I do not believe that, at this point, there is compelling evidence that patients are systematically being overdosed with Lamictal products. Further, although under FDAAA the Agency has the authority to require certain studies be performed in Phase 4 (so-called Post Marketing Requirements, or PMRs), I do not believe that a fixed dose effectiveness trial would qualify as a PMR. For these reasons, I do not believe that it is critical that the sponsor perform a fixed dose study.

For the reasons cited above, then, I have concluded that this application should be approved. At the time of this writing, the division has not yet agreed with the sponsor regarding the language for the package insert. When this agreement has been reached, the application can be approved.

Russell Katz, M.D.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Russell Katz
5/8/2009 07:36:14 PM
MEDICAL OFFICER