CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-764/S-011
20-241/S-017

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Patent Information Pursuant to 21 C.F.R. § 314.53

for

LAMICTAL® (lamotrigine) Tablets

NDA 20-241

The following is provided in accord with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name: LAMICTAL®

Active Ingredients: Lamotrigine

Strength(s): 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg

Dosage Form: Tablets

U.S. Patent	Expiration Date	Type of Patent	Patent Owner	U.S. Agent
4,602,017	22 July 2008	Composition/ Formulation Method of Use	SmithKline Beecham Corp.	SmithKline Beecham Corp.

The undersigned declares that U.S. Patent No. 4,602,017 covers the formulation, composition and/or method of use of LAMICTAL® (lamotrigine) Tablets. This product is currently approved under section 505 of the Federal Food, Drug and Cosmetic Act.

Please address all communications to:

David J. Levy, Ph.D.
Vice-President and Patent Counsel
GlaxoSmithKline
Corporate Intellectual Property Department
Five Moore Drive
Research Triangle Park, NC 27709
(919) 483-2723

Respectfully submitted,

Date: 25 January 2002

David J. Levy, Ph.D.
Attorney for Applicant
GlaxoSmithKline

NDA 20-241 & 20-764
Lamictal (lamotrigine)

Supplemental New Drug Application for
Lamictal Bipolar – Delays Depressive Episodes
In Patients with Bipolar I Disorder

DEBARMENT CERTIFICATION

Glaxo Wellcome hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

23 JAN 2002

Charles E. Mueller
Head, North American Clinical Compliance
World Wide Compliance

Date

MEMORANDUM

DATE: April 3, 2003

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-241/S-017 & NDA 20-764/S-011

SUBJECT: Action Memo for NDA 20-241/S-017 & NDA 20-764/S-011, for the use of Lamictal Tablets and Chewable Dispersible Tablets in the Long-Term Management of Patients with Bipolar Disorder

NDA 20-241/S-017 & NDA 20-764/S-011, for the use of Lamictal Tablets and Chewable Dispersible Tablets in the Long-Term Management of Patients with Bipolar Disorder, were submitted by SmithKline Beecham Corporation, on 6/5/02. The application contains reports of 12 controlled trials, including short-term trials in patients with bipolar depression, bipolar mania, unipolar MDD, longer-term trials in rapid bipolar cyclers, and 2 long-term randomized withdrawal trials in patients with bipolar disorder, Studies 2003 and 2006. All studies other than the latter two did not distinguish Lamictal from placebo.

The review team (Dr. Cara Alfaro, clinical reviewer, Dr. Yeh-Fong Chen, statistician, Dr. Kofi Kumi, Office of Clinical Pharmacology and Biopharmaceutics, and Dr. Thomas Laughren, Psychiatric Drugs Team Leader) recommends that the division consider the application Approvable.

I agree, and wish to make only a few comments.

As all reviewers describe, the statistical analysis plans for both studies were amended after the trials were completed, but before the data were unblinded. Also, as all reviewers note, the amended primary analyses (to be the same for both studies), was found to be unacceptable to the team, for the reasons they state (the proposed primary analysis considered almost all premature discontinuations to be affective events). Instead, Dr. Alfaro considered a different analysis for Study 2003 to be more appropriate.

Specifically, she proposed that the primary analysis include as an affective event only those events that led to discontinuation that, upon inspection, could reasonably be considered to be affective episodes. This involved a re-inspection of some of the events that led to discontinuation. However, not all events that led to discontinuation were re-examined.

Dr. Alfaro did re-examine those events for which there was reason to believe that the available data could provide an explanation for the patients' discontinuation. Specifically, patients' whose reasons for discontinuation were listed as Lost to

Follow-up, Consent Withdrawn, and Protocol Violation, did not have their records re-examined, because these categories were checked off in boxes on the Case Report Forms, and there was no expectation that additional clarification was contained in the records.

When the analyses were performed with the appropriate patients included (along with the exclusion of patients from Center 55466, for the reasons Dr. Alfaro describes), the p-value for the 200 mg + 400 mg group (the protocol-specified primary comparison) vs placebo was 0.034.

An examination of the clinical and statistical reviews reveals that a similar analysis was not performed for Study 2006, although, in my view, it should have been, because we believe that it is the appropriate approach to analyzing the trial. The review team felt, reasonably, that, because analyses that considered more, and fewer, patients than the preferred analysis were strongly significant, this implies that our preferred analysis would also be so. While reasonable, I asked Dr. Chen to perform the analogous analysis to the one on which we are relying in Study 2003. She informed me that that the p-value for the drug-placebo contrast was 0.02.

I agree with the review team that the analyses proposed by the sponsor were inappropriate, and that the analyses performed by the team are more appropriate, and should serve as the primary basis for our decision.

I also believe that the numerous changes to the studies and analyses (truncation of the 50 and 400 mg dose groups in Study 2003, termination of the lithium group in, and early termination of, Study 2006, and revision of the analysis plans for both studies) did not pose any bar to an adequate assessment of the studies, given that these changes all occurred prior to the breaking of the blind.

I also believe that the recommended monotherapy dose should be 200 mg/day. It is clear that, in both studies, 200 mg was the dose considered primary by the sponsor (it was the only dose group not truncated in Study 2003, and it was the target dose in Study 2006; although patients could receive up to 400 mg/day in the latter study, the average dose achieved was 211 mg/day).

The presence of so many studies in which Lamictal was not distinguished from placebo at first may appear troubling, but it is, of course, not uncommon for these studies to not distinguish drugs known to be effective from placebo. It is also, of course, possible, that Lamictal is ineffective as an acute treatment for bipolar disorder, but effective only as long-term maintenance treatment, either because it may lack intrinsic activity, or because the required slow titration precludes its utility in this setting.

In any event, I agree with the review team that Studies 2003 and 2006 establish that Lamictal is effective as maintenance treatment in patients with bipolar

disorder. I also agree with Dr. Laughren that the data indicate (based on a pooled analysis of the studies) that Lamictal delays the time to an affective episode of both types (depression and mania).

Finally, the drug should be explicitly indicated for patients with bipolar disorder who are not experiencing an acute affective episode (that is, in patients who have been stabilized on standard treatments), given that there is no evidence that Lamictal is effective in these patients.

For these reasons, I will issue the attached Approvable letter, with appended draft labeling.

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
4/4/03 10:39:40 AM
MEDICAL OFFICER

Alfaro concluded that the data do not suggest that this approach importantly increases the risk of rash, and I agree.

Safety Update

This update covered the period from 9-1-02 to 2-28-03, and included data from 6 ongoing studies. It also included a literature update regarding safety. There were no new, important safety findings that emerged from this safety update, and no new information that would impact on labeling.

Regulatory Status Update

As of 3-21-03, lamotrigine has been approved for bipolar disorder in 12 countries, and applications are pending in [redacted] countries.

Labeling

We reached agreement on final labeling with the sponsor on June 17, 2003. The one remaining controversial issue was whether or not data on [redacted] could go into labeling. We had

[redacted]

Conclusions and Recommendations

I believe that GSK has submitted sufficient data to support the conclusion that lamotrigine is effective and acceptably safe in the maintenance treatment of bipolar disorder. I recommend that we issue the attached approval letter with the mutually agreed upon final labeling.

cc:
Orig NDAs 21-440/S-017 & 20-764/S-011
HFD-120
HFD-120/TLaughren/RKatz/PAndreason/CAlfaro/JWare
DOC: MEMLAMBP.APE1

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

/s/

Thomas Laughren
6/17/03 10:12:26 AM
MEDICAL OFFICER

Ware, Jacqueline H

From: Feeney III, John J
Sent: Friday, April 04, 2003 10:30 AM
To: Ware, Jacqueline H
Subject: Lamictal NDA 20-241/SLR-018

I reviewed the proposed changes to carton and container labeling. I believe they are acceptable.

The studies supporting this supplement were conducted under IND 49,916, which was originally submitted 1-30-96. The original supplement for this expanded indication was submitted 6-5-02.

We decided not to take this supplement to the Psychopharmacological Drugs Advisory Committee (PDAC).

2.0 CHEMISTRY

As lamotrigine tablets and chewable tablets are already approved, there were no CMC issues requiring review for this NDA.

3.0 PHARMACOLOGY

As lamotrigine tablets and chewable tablets are already approved, there were no pharm/tox issues requiring review for this NDA.

4.0 BIOPHARMACEUTICS

The sponsor conducted 2 drug interaction studies as part of this program. One study looking at the effect of steady state dosing with bupropion (300 mg/day) on a single 100 mg dose of lamotrigine found no pharmacokinetic effect on lamotrigine. Another study looking at the effect of steady state dosing with lamotrigine (100 mg/day) on co-administered lithium (300 mg bid) found no pharmacokinetic effect on lithium. The sponsor's proposed language in labeling regarding these data is acceptable.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Overview of Efficacy Data

As noted earlier, the two efficacy studies submitted in support of the claimed indication for lamotrigine come from a very extensive bipolar development program for this drug including, in addition to these two studies, 13 other completed efficacy studies (2 long-term trials in rapid cyclers; 3 short-term trials in bipolar MDD; 2 short-term bipolar mania trials; 3 short-term trials in unipolar MDD; and 3 open-label continuation trials). On face, the 8 short-term trials produced no interpretable efficacy data (7 were considered "failed" and one was "negative," i.e., one of the acute mania trials). Of the 2 long-term trials in rapid cyclers, 1 was open label, and the second, although a placebo-controlled add-on study, was too small to contribute any useful information. We are also aware of

3 additional trials in bipolar, 2 ongoing open label trials, and an active-controlled trial that has been terminated.

Thus, the focus of this review was on two randomized withdrawal studies involving an open run-in period to induce response or ensure stability, followed by randomization to either lamotrigine, lithium, or placebo. For one study (2003), the index episode was bipolar MDD, and for the other study (2006), the index episode was bipolar mania or hypomania.

5.1.2 Study SCAB2003

This was a multicenter study involving 38 US and 41 nonUS sites. The open-label run-in phase of this trial was conducted on an outpatient basis (weekly visits) and involved adult bipolar I patients whose most recent bipolar episode was a major depressive episode (MDE)(DSM-IV). Patients could enter this phase if they either had a current MDE, or had a MDE within the past 60 days and still either had depressive symptoms or were receiving treatment for depressive symptoms. This phase lasted from 8 to 16 weeks, and involved treatment with lamotrigine (target dose of 200 mg/day) plus any other psychotropics deemed necessary (n=966). Dosing with lamotrigine was very gradual: 25 mg/day for weeks 1-2; 50 mg/day for weeks 3-4; 100 mg/day for week 5; and then up to a maximum dose of 200 m/day during week 6 and beyond, if tolerated, during the remainder of this open phase. Their were special instructions for dosing patients already taking either valproate or carbamazepine (see later). The following criteria needed to be met before randomization into the double-blind, parallel group, withdrawal phase:
-Response, defined as CGI-S ≤ 3 for 4 consecutive weeks,
-Withdrawn from all concomitant psychotropics (i.e., other than lamotrigine)
-Receiving ≥ 100 mg/day of lamotrigine, with stable dose for at least 2 weeks

Patients meeting these criteria (n=480) were randomized to: lamotrigine (fixed doses of 50, 200, or 400 mg/day); lithium (0.8-1.1 mEq/L); pbo. Dosing with lamotrigine to the 400 mg target dose was as follows: 100 mg/day for week 1; 200 mg/day for week 2; 300 mg/day for week 3; and then 400 mg/day for week 4 and subsequently; 50 mg patients received this dose from day 1; 200 mg patients were dosed at 100 mg for week 1, and then 200 mg thereafter. The protocol was amended during the course of the study to restrict enrollment to only the 200 mg/day and placebo groups, due to difficulties achieving full enrollment. There was an observation period of up to 76 weeks for clinical events intended to represent relapse to a mood episode, of any type (i.e, manic, hypomanic, mixed, or depressed). Patients were seen weekly for 4 weeks, then q 2 weeks for 1 month, and then monthly.

These patients were roughly 50:50 male to female, predominantly white, and the mean age was about 43. The modified ITT population (referred to as the "efficacy population" in Dr. Alfaro's review) for statistical analysis (including all randomized patients who received at least 1 dose of assigned treatment and had baseline and at least one post-randomization efficacy assessment, or who reached the TIME endpoint) was as follows: lamotrigine 200 or 400, n=165; lithium, n=120; pbo, n=119. Completion proportions for these groups (based on ITT, and including patients who met TIME criteria but stayed in the trial) were as follows: lamotrigine 200 or 400, 67% (114/171); lithium, 63% (76/121); pbo, 65% (78/121).

The original protocol specified TIME(Only) as the primary outcome, i.e., time to the first mood episode (any of 4 types) requiring additional pharmacotherapy or ECT. The survival analysis was designed to combine data for the 200 and 400 mg/day groups for comparison with placebo. Kaplan-Meier curves were estimated, and groups were compared on survival using the Log Rank Test. An 8-28-01 amendment, after completion of the trial, but prior to datalock on 2-11-02, changed the primary endpoint to TIME(ABE), defined as meeting TIME(Only) criteria or being prematurely discontinued prior to reaching TIME for reasons other than AEs not deemed related to bipolar symptomatology. Thus, TIME(ABE) included discontinuations for any reason other than this narrow group (i.e, protocol violations, "other," lost to followup, consent withdrawn, and AEs deemed related to bipolar symptomatology [mania, hypomania, etc]). Apparently, the only such cases that were looked at in detail to determine if they could reasonably be considered bipolar events were the discontinuations for AEs. A third outcome, TIME(SIS), i.e., survival in the study, was defined to include patients discontinuing for any reason or meeting TIME(ONLY) criteria. However, with this amendment, TIME(Only) and TIME(SIS) were designated as secondary outcomes. TIDep and TIMan were additional secondary outcomes defined as those subsets of TIME(Only) for emergent MDEs, or for manic, hypomanic, or mixed episodes, respectively [i.e., these endpoints did not include premature discontinuations other than those that met TIME(ONLY) criteria].

While the sponsor had amended the analysis plan to focus on TIME(ABE) on 8-28-01 as noted, this change was not made clear in the submission and, thus, was not noted or responded to. It was not until the review that we became fully aware of the implications of designating TIME(ABE) as the primary endpoint. Our concern about TIME(ABE) was that it included many events that had never been assessed with regard to whether or not they, in fact, represented bipolar events. As noted, the only such cases that were looked at in detail to determine if they could reasonably be considered bipolar events were the discontinuations for AEs. Consequently, we derived a new endpoint, TIME(BipEvent), to include the following: (1) all events meeting criteria for the TIME(ONLY) endpoint; (2) discontinuations for AEs deemed related to bipolar symptomatology (there were 3 of these); and (3) discontinuations for "other," where other=lack of efficacy (there were 6 of these). We performed the analyses for this new endpoint, but in these analyses, always excluded data from site #55466 (see below for reasons).

The numbers of subjects meeting criteria for having events in each of the 6 key TIME analyses are as follows (Note: Lamotrigine will always refer to the combined 200 and 400 mg/day groups):

review, 6 cases were reclassified, and the key analyses were re-done with these changed classifications (see below).

-Deletion of Site #55466: Dr. Alfaro discovered in the course of her review that the sponsor had closed this site for GCP violations, but had, nevertheless, included data from the 11 patients at this site in the efficacy analyses (they argued that the violations would not have affected the integrity of the data). Dr. Alfaro disagrees, and I do as well. Thus, the 5 key analyses were re-done with the efficacy data for these 11 patients deleted (see below).

Study 2003
Summary of Revised P-Values (lamotrigine vs pbo) Resulting from DNDP Re-Analyses Based on Recoding of TIME Events (Recoding) and Deletion of Site #55466 Data (#55466 Deleted)

Endpoints Analyzed	Sponsor's Analyses	DNDP: Recoding	DNDP: #55466 Deleted	DNDP: Recoding & #55466 Deleted
	P-Value[1]	P-Value	P-Value	P-Value
TIME(ABE)	0.004	0.004	0.010	0.010
TIME(SIS)	0.003	0.004	0.007	0.008
TIME(Only)	0.029	0.030	0.059	0.062
TIME(BipEvnt)	-----	-----	0.034	-----
TIMan	0.339	0.394	0.365	0.419
TIDep	0.047	0.042	0.097	0.088

1 P-value for difference in survival distributions between lamotrigine and placebo using Log Rank Test

Thus, on our preferred endpoint [TIME(BipEvnt)], the results were still statistically significant in favor of lamotrigine over placebo (p=0.034), even with deletion of the problematic site.

Separate analyses done by Dr. Chen looking at individual dose groups vs placebo suggested that the 200 mg/day group may be the most effective dose (Chen, p. 29).

Exploratory analyses were done looking at the effects of age and gender. The gender analyses suggested that most of the effect was coming from men, while the age analyses suggested that most of the effect was coming from> 40. There were too few non-white patients to justify subgroup analyses based on race. It is difficult to know how to interpret such posthoc subgroup analyses.

Comment: Both Drs. Alfaro and Chen considered this a positive study in support of a claim of maintenance efficacy for lamotrigine in bipolar disorder, and I agree.

5.1.3 Study SCAB2006

This was a multicenter study involving 40 US and 40 nonUS sites. This study was similar in most respects to 2003, except for 2 differences: (1) the index patients had a manic or hypomanic episode; and (2) this was a flexible dose study. The open-label run-in phase of this trial was conducted on an outpatient basis (weekly visits) and involved adult bipolar I patients whose most recent bipolar episode was a manic or hypomanic episode (DSM-IV). Patients could enter this phase if they either had a current manic/hypomanic episode, or had such an episode within the past 60 days and still either had manic/hypomanic symptoms or were receiving treatment for manic/hypomanic symptoms (n=349).

Patients meeting criteria for entry in the double-blind phase (same as in 2003; n=175) were randomized to: lamotrigine (range of 100-400 mg/day, with a target dose=200 mg/day); lithium (0.8-1.1 mEq/L); pbo. All lamotrigine patients were started on a dose of 200 mg/day; those who tolerated that dose but were not fully responding could be titrated up to a maximum dose of 400 mg/day, and those not tolerating 200 mg/day could be reduced to 100 mg/day. Dose increments (up or down) were in 100 mg/day dosage units and at minimum intervals of 1 week. The protocol was amended during the course of the study to eliminate the lithium group, and finally was terminated in November, 1998 due to enrollment problems. All currently enrolled patients were discontinued and not followed for the duration of the 76 week observation period. This practice raised a concern that the sponsor might have done an interim analysis and used this as a basis for stopping the study. However, the sponsor denied conducting any such analyses. As in 2003, there was an observation period of up to 76 weeks for clinical events intended to represent relapse to a mood episode, of any type (i.e, manic, hypomanic, mixed, or depressed). Patients were seen weekly for 4 weeks, then q 2 weeks for 1 month, and then monthly.

These patients were roughly 50:50 male to female, predominantly white, and the mean age was about 41. The modified ITT population (referred to as the "efficacy population" in Dr. Alfaro's review) for statistical analysis (including all randomized patients who received at least 1 dose of assigned treatment and had baseline and at least one post-randomization efficacy assessment) was as follows: lamotrigine, n=58; lithium, n=44; pbo, n=69. Completion proportions for these groups (based on ITT, and including patients who met TIME criteria but stayed in the trial) were as follows: lamotrigine, 53% (31/59); lithium, 41% (19/46); pbo, 70% (49/70). The mean lamotrigine daily dose achieved was 177 mg/day.

The statistical plan, along with modifications, were exactly as in 2003.

The numbers of subjects meeting criteria for having events in each of the sponsor's 5 key TIME analyses are as follows:

Study 2006 Summary of Revised P-Values (lamotrigine vs pbo) Resulting from DNDP Re-Analyses Based on Recoding of TIME Events (Recoding)		
Endpoints Analyzed	Sponsor's Analyses	DNDP: Recoding
	P-Value[1]	P-Value
TIME(ABE)	0.023	0.022
TIME(SIS)	0.030	0.029
TIME(Only)	0.018	0.014

1 P-value for difference in survival distrubutions between lamotrigine and placebo using Log Rank Test

Exploratory analyses were done looking at the effects of age and gender. The gender analyses suggested that most of the effect was coming from both men and women, while the age analyses again were suggestive that much of the effect was coming from> 40. There were too few non-white patients to justify subgroup analyses based on race. It is difficult to know how to interpret such posthoc subgroup analyses.

Comment: Dr. Alfaro considered this a positive study in support of a claim of maintenance efficacy for lamotrigine in bipolar disorder, and I agree. Dr. Chen considered this a positive study in support of a claim of maintenance efficacy for lamotrigine in bipolar disorder only if we can accept the sponsor's explanation of why they terminated the study; since there is no basis for making a case against their explanation, I think we need to accept it.

5.1.2 Combined Analyses for Studies 2003 and 2006

The sponsor also provided data for a combined analysis of studies 2003 and 2006. Although this was not a primary analysis, I think it is informative, particularly regarding the individual events of manic and depressive relapse, since the individual studies were not powered for these separate endpoints.

The results of the sponsor's analyses for the 5 key endpoints are as follows:

I think labeling needs to be very clear for whom this drug would be indicated, i.e., patients who are essentially in remission following an acute affective episode, of any type, and who are being considered for maintenance treatment to delay the time to affective relapse, again, of any type. Thus, I disagree with the sponsor's focus on only depressive relapse.

Since these trials did not adequately explore dose response, labeling will need to target the dose targeted in the trials, i.e., 200 mg, but also note that patients in at least one of the trials showing efficacy were dosed in a range of 100 to 400 mg/day (with a mean dose of about 177 mg/day).

5.2 Safety Data

This was a very large program, involving 15 completed clinical efficacy and safety studies, as well as the 2 PK studies. The cut-off date for the original submission was 10-31-01, and there were safety updates on (1) 10-4-02, covering the period from 11-1-01 to 3-31-02, and on (2) 2-26-03. There was a total lamotrigine exposed population of n=2272. The mean duration of exposure was 134 days, and the total person-time of exposure was 832 PY. The mean lamotrigine dose was 122 mg/day. Overall, the assessment of adverse events, including those from the 10-4-02 safety update, did not reveal any adverse events not previously recognized for this drug, and the profile of adverse events in bipolar patients did not appear to differ substantially from that seen in epilepsy. [Note: The safety update from 2-26-03 was not reviewed during this cycle, however, it appeared to include mostly data from the final report for study SCA40910 that was already reviewed.] The following events and issues merit specific mention:

-Deaths and Suicides: There were 10 deaths overall, 9 on lamotrigine and 1 on placebo. 7 of the 10 deaths were likely suicides, and none of the remaining deaths could be reasonably attributed to lamotrigine; for the pool of all the controlled trials, the rates of suicide and suicide attempt were equivalent for lamogtrigine and placebo, and in fact were the expected rates in this population.

-Rash: There were 3 serious rashes in lamotrigine patients (3/2272=0.1%), and 1 in a placebo patient; none of these represented TEN; in the controlled trials, 3% of lamotrigine subjects withdrew with rash vs 1% of placebo; however, the overall risk of rash in the controlled trials was roughly equal (7% for lamotrigine vs 6% for pbo).

-Mania: There was no indication of an induction of mania by lamotrigine.

-Seizures: Overall, there were 4 patients reported to have "convulsions" either during lamotrigine treatment, or following the discontinuation of lamotrigine. One of these was a case of status occurring about 9 days after stopping lamotrigine abruptly for rash (4/832 PY). While all 4 cases were confounded by concomitant medications and/or comorbidity, a role for lamotrigine cannot be ruled out.

-Discontinuation of Lamotrigine: The labeling for lamotrigine recommends tapering over 2 weeks for patients with epilepsy coming off of this drug. However, the sponsor has suggested that bipolar patients may be abruptly withdrawn. This advice is based on a comparison of patients assigned to placebo with those assigned to continued lamotrigine with regard to discontinuation emergent events

in the first 21 days after randomization. The only event that appeared to be in excess for placebo patients was dizziness. The sponsor has apparently also looked for discontinuation emergent events in the post-treatment phases for all the bipolar controlled trials, and again, found little evidence for a withdrawal syndrome. Nevertheless, because of the reports of seizures, including 2 associated temporally with discontinuation of lamotrigine, Dr. Alfaro has recommended that we not adopt the sponsor's proposal to permit abrupt discontinuation of lamotrigine in bipolar patients. I agree that we can propose tapering, but consider arguments against this practice if proposed by the sponsor.

-Dosing with Lamotrigine after Discontinuation of Valproate:

-Based on the finding that co-administered valproate decreases the clearance of lamotrigine by roughly 50%, the sponsor is recommending in labeling that prescribers immediately double the dose of lamotrigine after discontinuing valproate. Apparently, this same advice was included in the protocols for the pivotal trials, i.e., during the run-in phase when patients were being phased onto lamotrigine alone from whatever combinations they were taking. There were 83 patients during that phase reported to be on lamotrigine and valproate, and presumably these patients would have had their lamotrigine doses doubled. We have asked the sponsor for confirmation that this practice was followed, and for whatever data were generated to support the safety of this practice. We have not yet gotten a response, and will wait to finalize this language in labeling until we have seen these data.

5.3 Clinical Sections of Labeling

We have made a number of changes to the sponsor's proposed labeling for this new indication in the draft labeling that is included in the approvable package.

6.0 WORLD LITERATURE

The sponsor provided 32 published papers pertinent to the efficacy and safety of lamotrigine in bipolar disorder. Dr. Alfaro reviewed these papers and did not discover any important new safety information regarding this product.

7.0 FOREIGN REGULATORY ACTIONS

It is my understanding that lamotrigine is approved for the maintenance treatment of bipolar disorder in 5 countries (Czech Republic; Latvia; New Zealand; Panama; and Romania), and applications are pending in [redacted] other countries.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

As noted, we did not take this supplement to the Psychopharmacological Drugs Advisory Committee (PDAC).

9.0 DSI INSPECTIONS

Three sites that contributed patients both to studies 2003 and 2006 (Calarese; Fieve; Reimherr) were inspected. While there were some minor deficiencies, the data from all 3 sites were deemed acceptable.

10.0 LABELING AND APPROVABLE LETTER

10.1 Labeling Attached to Approvable Package

As noted, we have made a number of changes to the sponsor's proposed labeling.

10.2 Foreign Labeling

We do not have labeling language for the 5 countries where lamotrigine has been approved for bipolar disorder. We have requested this information.

10.3 Requests for Additional Information in Approvable Letter

The approvable letter will include our proposed labeling, along with requests for additional safety data to address several concerns, as noted.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that GSK has submitted sufficient data to support the conclusion that lamotrigine is effective and acceptably safe in the maintenance treatment of bipolar disorder. I recommend that we issue the attached approvable letter with our labeling proposal and the above noted requests for updates, in anticipation of final approval.

cc:
Orig NDAs 21-440/S-017 & 20-764/S-011
HFD-120
HFD-120/TLaughren/RKatz/PAndreason/CAlfaro/JWare
DOC: MEMLAMBP.AE1

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/s/

Thomas Laughren
3/18/03 07:44:35 AM
MEDICAL OFFICER

1) **Protocol 105-605 (SCAB 2003)** entitled: "A Multi-Centre, Double-Blind, Double-Dummy, Placebo and Lithium-Controlled, Randomized, Fixed-Dose Evaluation of the Safety and Efficacy of Lamotrigine in the Long-Term Prevention of Relapse and Recurrence of Mania and/or Depression in Patients with Biopolar I Disorder"
2) **Protocol 105-606 (SCAB 2006)** entitled: "A Multi-Centre Double-Blind, Double-Dummy, Placebo and Lithium-Controlled, Randomised, Flexible-Dose Evaluation of the Safety and Efficacy of Lamotrigine in the Long-Term Prevention of Relapse and Recurrence of Mania and/or Depression in Patients with Bipolar I Disorder.

Subjects who were currently or recently manic/hypomanic (SCAB2006) or depressed (SCAB2003) were stabilized while receiving a combination of lamotrigine and other medications or lamotrigine alone for up to 16 weeks and were then randomized to double-blind study medication over a long period (maximum 76 weeks). The primary efficacy measure was the time to intervention (pharmacotherapy or electroconvulsive therapy) for a mood episode (manic, hypomanic, mixed or depressive) or one that was emerging.

The inspection assignments were issued August 2, 2002 for three domestic sites: Dr. Calabrese for protocol SCAB 2003; Drs. Fieve and Reimherr, for both protocols SCAB 2003 and SCAB 2006. The purpose of these assignments was to validate data in support of pending NDA 20-241/SE1-017 and 20-764/SE1-011 using oral lamotrigine for long-term relapse prevention and recurrence of depression and/or mania in Bipolar I Disorder.

II. INSPECTIONAL FINDINGS

The following sites were inspected:

NAME	Location	Assignment Date	Dates of EIR received	Classification
Dr. Calabrese	Cleveland, OH	8/2/2002	10/7/02	VAI
Dr. Fieve	New York, NY	8/2/2002	11/12/02	VAI
Dr. Reimherr	Salt Lake City, UT	8/2/2002	10/25/02	VAI

CALABRESE, M.D.

For protocol SCAB 2003, a total of 32 subjects was enrolled in open-label, preliminary phase for 8-16 weeks followed by randomized phase using fixed dose of lamotrigine (200 mg/day), lithium (serum level of 0.8-1.1 m Eq/L) or placebo for up to 76 weeks of double-blind treatment. Sixteen of 32 subjects did not complete the preliminary phase of the study; 15 of the remaining 16 subjects enrolled in the randomized phase were discontinued or withdrew from the study (16 subjects due to lack of efficacy; 8 subjects due to adverse events). Only one subject completed the study at this site. No deaths reported at this site during the study. Dr. Calabrese explained high dropout rate for this study based on the study design.

An audit of 12 subjects' records was conducted. Inspection revealed that Dr. Calabrese did not

promptly report a serious adverse event for four subjects to the IRB (subject #4899, 4892, 4908, 4912) and he did not submit the final study report to the IRB. All subjects signed informed consent. Data appear acceptable.

REIMHERR, M.D.

Protocol SCAB 2006 - subjects were enrolled in the Long-Term Prevention of Relapse and Recurrence of Depression and/or Mania over a long period (a maximum of 76 weeks) in patients with Bipolar I Disorder who experienced a recent manic or hypomanic episode. The subjects were enrolled in open-label, preliminary phase for 8-16 weeks of lamotrigine (100 mg/day minimum dose for last 2 weeks), followed by randomized phase using flexible dose of lamotrigine, lithium or placebo for double-blind treatment.

A total of 16 subjects listed in the enrollment, 2 subjects were listed twice with two subjects numbers each as they were screened and re-enrolled (ie, subject 20804/20807; 20808/20809). Thus, there were a total of 14 subjects in the study; 10 subjects were randomized and 6 subjects reportedly completed the study end point. There were no deaths at this site during the study. Two subjects had SAE (#20800 withdrew from study because of hospitalization for suicidal ideation; #20807 was hospitalized for pancreatitis). One subject #20798 developed a rash and the subject was dropped from the study.

An audit of 5 subjects' records was conducted. Dr. Reimherr did not promptly report serious adverse event to the IRB for two subjects (#20800, 20807).

Protocol SCAB 2003 - subjects were enrolled in the Long-Term Prevention of Relapse and Recurrence of Depression and/or Mania over a long period (a maximum of 76 weeks) in patients with Bipolar I Disorder who experienced a recent major depressive episode. The subjects were enrolled in open-label, preliminary phase for 8-16 weeks of lamotrigine, followed by randomized phase using fixed dose of lamotrigine (200mg/day), lithium (serum level titrated to 0.8 to 1.1 meq/L) or placebo for double-blind treatment of this SCAB 2003 study.

A total of 42 subjects was enrolled; 4 subjects were withdrawn from study after screening (#12701 did not meet entrance criteria, #12715 withdrew consent, 12718 for positive urine drug screen for amphetamine and #12735 for abnormal TSH); 10 subjects were randomized following preliminary phase of the study.

During this study, one subject (#12702) committed suicide by cutting his throat and bleeding from carotid artery on 1/16/98. One subject (#12698) was hospitalized for overdose of approximately 14-30 tablets of lorazepam on 3/24/98 and was discontinued from the study. One subject (#12722) was pregnant during the study; the subject elected to have abortion and was continued in the study.

An audit of 6 subjects' records was conducted. Dr. Reimherr did not promptly report serious adverse event to the IRB for two subjects (#12702, 12698). All subjects signed informed consent. Several minor record keeping deficiencies were noted for both protocols. Overall, data appear

acceptable.

FIEVE, M.D.

Protocol SCAB 2003 – 55 subjects screened; 50 subjects were listed in the enrollment log at the site; 42 subjects enrolled in the preliminary phase; 16 subjects entered the randomized phase. An audit of six subjects' records was conducted. No major objectionable conditions noted except for an incorrect dose titration for subject 5095 who was prescribed 200mg/day of lamotrigine instead of 100 mg/day at week 4 and subject 5092 received 50 mg/day of lamotrigine on week 2 instead of 25 mg/day during the preliminary phase. Of 55 subjects screened, 54 subject received adequate informed consent. One subject received informed consent for protocol 105-606(SCAB 2006).

Protocol SCAB 2006 – 22 subjects screened; 19 subjects were enrolled in preliminary phase; 9 subjects entered the randomized phase. The number of subjects who completed the study endpoint was not specified in the EIR. An audit of five subjects' records was conducted. No major objectionable conditions reported. All study subjects signed the informed consent. However, it was noted that 10 subjects did not sign the updated version of informed consent. Overall, data appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As stated above, there were some record keeping, IRB reporting and informed consent deficiencies. Overall, I recommend that data from these 3 sites that had been inspected appear acceptable for use in support of this NDA.

Key to Classifications
NAI = No deviation from regulations. Data acceptable
VAI = Minor deviations(s) from regulations. Data acceptable
VAIr= Deviation(s) form regulations, response requested. Data acceptable
OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection completed but EIR still pending

Ni A. Khin, M.D., Medical Officer
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

cc:
NDA 20-241/SE1-017; 20-764/SE1-011
Division File
HFD-45/Program Management Staff (electronic copy)
HFD-47/c/r/s
HFD-47/Khin
HFD-47/Friend
HFD-45/RF

rd: NK:12/26/02

O:\NK\CIS\NDA20241SE1017 Lamictal Bipolar CIS.doc

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

/s/

Ni Aye Khin
12/27/02 10:24:21 AM
MEDICAL OFFICER
Original Paper Version was reviewed and concurred by Dr. El-Hage on 12/27/02

prevention of a disease." In this case, the primary outcome measure in the pivotal studies submitted in support of this new indication is affective relapse, and thus, if approved, Lamictal would get a claim for delay in time to affective relapse. In our view, the drug product, lithium, is already approved and widely used for this outcome.

Accordingly, a standard review classification has been designated for these applications with a user fee goal date as indicated above.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the application numbers listed above at the top of the first page of any communications concerning these applications. All communications concerning these supplemental applications should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, call Jacqueline H. Ware, Pharm.D., Regulatory Management Officer, at (301) 594-5533.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

172 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

__X__ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

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
8/5/02 12:44:29 PM

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA: 20-241/S-017 20-764/S-011	Efficacy Supplement Type SE1	Supplement Number: N20-241/S-017 & N20-764/S-011
Drug: Lamictal (lamotrigine) Tablets Lamictal (lamotrigine) Chewable Dispersible Tablets	Applicant: GlaxoSmithKline	
RPM: Jackie Ware	HFD-120	Phone # 301-594-5533
Application Type: (✓) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

	❖ Application Classifications:	
	• Review priority	(✓) Standard ( ) Priority
	• Chem class (NDAs only)	
	• Other (e.g., orphan, OTC)	
	❖ User Fee Goal Dates	June 22, 2003 (2nd review cycle) April 6, 2003 (1st review cycle)
	❖ Special programs (indicate all that apply)	(✓) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
	❖ User Fee Information	
	• User Fee	(✓) Paid
	• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
	• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
	❖ Application Integrity Policy (AIP)	
	• Applicant is on the AIP	( ) Yes (✓) No
	• This application is on the AIP	( ) Yes ( ) No
	• Exception for review (Center Director's memo)	
	• OC clearance for approval	
A.	❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(✓) Verified
B.	❖ Patent	
	• Information: Verify that patent information was submitted	(✓) Verified
	• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
	• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will	( ) Verified

	not be infringed (certification of notification and documentation of receipt of notice).	
C.	❖ Exclusivity (approvals only)	
	• Exclusivity summary	✓
	• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes (✓) No
D.	❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	
	Copy all information	
E.	❖ Actions	
	• Proposed action	(✓) AP ( ) TA ( ) AE ( ) NA
	• Previous actions (specify type and date for each action taken)	AE on April 4, 2003
	• Status of advertising (approvals only)	(✓) Materials requested in AP letter ( ) Reviewed for Subpart H
	❖ Public communications	
	• Press Office notified of action (approval only)	(✓) Yes ( ) Not applicable
	• Indicate what types (if any) of information dissemination are anticipated	(✓) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
F.	❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
	• Division's proposed labeling (only if generated after latest applicant submission of labeling)	June 18, 2003
	• Most recent applicant-proposed labeling	June 12, 2003
	• Original applicant-proposed labeling	June 5, 2002
	• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	June 17, 2003 telecon June 6, 2003 email to firm March 23, 2003 memo
	• Other relevant labeling (e.g., most recent 3 in class, class labeling)	Not applicable
G.	❖ Labels (immediate container & carton labels)	
	• Division proposed (only if generated after latest applicant submission)	Not applicable
	• Applicant proposed	April 21, 2003 June 5, 2002
	• Reviews	see CMC review
	❖ Post-marketing commitments	Not applicable
	• Agency request for post-marketing commitments	
	• Documentation of discussions and/or agreements relating to post-marketing commitments	
H.	❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	8/5/02 letter 12/6/02 letter
I.	❖ Memoranda and Telecons	7/2/02 telecon
	❖ Minutes of Meetings	
	• EOP2 meeting (indicate date)	
	• Pre-NDA meeting (indicate date)	February 1, 2002

	• Pre-Approval Safety Conference (indicate date; approvals only)	
	• Other	
K.	❖ Advisory Committee Meeting	
	• Date of Meeting	
	• 48-hour alert	
L.	❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	Not applicable
	Summary Review	
M.	❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	6/17/03 TL Memo 4/4/03 DD Memo 3/18/03 TL Memo
	Clinical Information	
Mc.	❖ Clinical review(s) *(indicate date for each review)*	6/17/03 3/14/03
N.	❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	Not applicable
O.	❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	In clinical review (Mc)
P.	❖ Pediatric Page(separate page for each indication addressing status of all age groups)	✓
Q.	❖ Demographic Worksheet *(NME approvals only)*	Note applicable
R.	❖ Statistical review(s) *(indicate date for each review)*	3/18/03
S.	❖ Biopharmaceutical review(s) *(indicate date for each review)*	7/22/02 #1 7/22/02 #2 3/4/03
	❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	Not applicable
U.	❖ Clinical Inspection Review Summary (DSI)	
	• Clinical studies	12/27/02
	• Bioequivalence studies	Not applicable
	CMC Information	
V.	❖ CMC review(s) *(indicate date for each review)*	6/9/03 11/7/02
W.	❖ Environmental Assessment	
	• Categorical Exclusion *(indicate review date)*	in CMC review (V)
	• Review & FONSI *(indicate date of review)*	Not applicable
	• Review & Environmental Impact Statement *(indicate date of each review)*	Not applicable
	❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	Not applicable
	❖ Facilities inspection (provide EER report)	Date completed: **Not applicable** ( ) Acceptable ( ) Withhold recommendation
	❖ Methods validation - **Not applicable**	( ) Completed ( ) Requested ( ) Not yet requested
	Nonclinical Pharm/Tox Information	
	❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	4/15/03
	❖ Nonclinical inspection review summary	Not applicable
	❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	Not applicable

	❖ CAC/ECAC report	Not applicable

Regulatory Issues & Other Items

7/2/02

Ware, Jacqueline H

Subject:	N20-241/S-017 and N20-764/S-011 - Lamictal Bipolar applications
Entry Type:	Phone call
Company:	GlaxoSmithKline
Start:	Tue 7/2/02 1:09 PM
End:	Tue 7/2/02 1:19 PM
Duration:	10 minutes
Contacts:	Eric Benson
Categories:	Business, Phone Calls

Following our internal filing meeting for the above applications, I phoned Mr. Benson to inform him of the following:
1. The applications were considered provisionally fileable at this point because key statistical information was not locatable in the application. I promised to contact him later today with more specifics on this problem. I emphasized that once this specific request was relayed to him, the Division expected GSK to submit a response within 2 weeks. [I noted that there were about 30 day remaining in the initial 60-day filing review period.]
2. The Division determined that these applications would be reviewed under a standard review clock, not under priority review as requested, with a PDUFA goal date of April 6, 2003. Our rationale for this decision was that the primary outcome measures for the submitted pivotal studies were for affective disorder relapse and that lithium was already approved for this indication.
3. These applications would still be taken to an advisory committee, but not in November 2002. They would likely go after sometime early 2003. The advisory committee contact person was Sandy Titus, phone # 301-827-6764. In addition, the August 8th meeting with the Division to prepare for the advisory committee meeting would be canceled and would be rescheduled sometime in the future when appropriate.
4. I asked when the safety data for studies LAM30046, SCA40910, and SCA40912 would be provided. Mr. Benson stated that the data from SCA40910 would likely be available by the end of 2002, but he was unsure if GSK planned to submit it to these applications. He indicated that GSK planned to submit the efficacy and safety results from study SCA40910 in a [redacted] to the Lamictal NDAs. He also stated that he would check on the availability of the data from the other 2 studies and get back to me.
5. I asked Mr. Benson if he had included in the applications reference to the pediatric deferral and waiver that the Division had granted for this indication at the February 1, 2002 preNDA meeting. Mr. Benson stated that he had not. For administrative and regulatory reasons, I asked him to submit this information as an amendment to these applications.

Mr. Benson thanked me for my phone call and indicated his appreciation for the information.

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

/s/

Jackie Ware
7/2/02 02:29:26 PM
CSO

June 5, 2002

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709

Tel. 919 483 2100
www.gsk.com

Leah Andrews, Consumer Safety Officer
Office of Regulatory Affairs
Food and Drug Administration
Atlanta District Office
60 8th Street, NE
Atlanta, GA 30309

Re: NDA 20-241; LAMICTAL® (lamotrigine) Tablets
NDA 20-764; LAMICTAL® (lamotrigine) CD (lamotrigine) Chewable Dispersible Tablets
General Correspondence: CMC Field Copy

Dear Ms. Andrews:

In accord with revised 21CFR 314.50 (k)(3), a field copy of the Chemistry, Manufacturing and Controls section of the supplemental submission of New Drug Applications 20-241 and 20-764 is provided herewith.

In compliance with the requirements set forth in 21 CFR 314.50 (k)(3), GlaxoSmithKline certifies that the field copy is a true copy of the Chemistry, Manufacturing and Controls submission to these NDAs, as described in 21 CFR 314.50 (d)(1), contained in the archival and review copies of the applications as submitted to the Division of Neuropharmacological Drug Products.

If you have any questions or comments regarding this submission, please do not hesitate to contact me at (919) 483-5857.

Sincerely,

Mary Faye S. Whisler

Mary Faye S. Whisler, Ph.D.
Assistant Director
New Submissions, North America

Organization of Application
These applications are submitted in accordance with the *Guidance for Industry, Providing Regulatory Submission in Electronic Format-NDAs, January 1999* and incorporates agreements reached in the February 1, 2002 Pre-sNDA meeting with representatives of the Division. The submissions are virus-free and confirmed via VirusScan NT 4.0.3a (4204).

Each submission is comprised of one digital tape (approximately 4 gigabytes) as the electronic archive copy and labeled ELECTRONIC REGULATORY SUBMISSION FOR ARCHIVE. The format of the digital tape is NT server 4.0 with NT backup. Review copies of the technical sections are not provided, however, the submission does include the following as agreed at the Pre-sNDA meeting:

- One paper copy of the Final Clinical Study Reports for pivotal studies SCAB2003, SCAB2006 and supportive studies SCAB2005 and SCAA2012 for the statistical reviewer
- Patient profiles of key demographic and safety data for patients who died, discontinued due to an adverse event or experienced a serious adverse event in the clinical studies presented in this application. Please note that data collected varied across studies; for example, electrodardiogram and laboratory data was not collected in all studies. These profiles can be found in the "CRT/Profiles" folder.
- Datasets from the pivotal and supportive studies as SAS transport files. These can be found in the "CRT/Datasets" folder.
- Programs to recreate primary and key secondary efficacy analyses in pivotal and supportive clinical studies. These can be found in the "CRT/Programs" folder.

User Fee
The sNDA for NDA 20-241 has been assigned User Fee ID #4341. It is our understanding that both these sNDAs qualify for bundling under this same User Fee. This User Fee has been mailed under separate cover on May 30, 2002 to the following address:

Food and Drug Administration (360909)
Mellon Client Services Center
500 Ross Street
Pittsburgh, PA 15262-0001

Certifications
Debarment: GlaxoSmithKline (GSK) has included a certification in this sNDA confirming it has not used in any capacity the services of any person debarred under 306(a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

Investigator Financial Disclosure: In compliance with the requirements set forth in 21 CFR 54.4, GSK has included a certification (Form FDA 3454) covering financial interest information for clinical investigators participating in clinical studies supporting the approval of the sNDA.

Field Copy: In compliance with the requirements set forth in 21 CFR 314.50(d)(1), GSK certifies that a field copy of the Chemistry, Manufacturing and Controls section of this sNDA along with a copy of FDA Form 356(h) and the Overall NDA Summary Volume is being provided to the FDA Atlanta District office under separate cover to the following address:

Office of Regulatory Affairs
Food and Drug Administration
Atlanta District Office
60 8th Street, N.E.
Atlanta, GA 30309
Attention: Leah Andrews

Future Interactions with the Division/Meeting Request

Over the past six years, GSK has had several interactions with the Division regarding the development of lamotrigine for use in the management of bipolar disorder and we appreciate the Division's thoughtful advice and guidance throughout the development. We look forward to continuing these productive interactions during the review of this application and hereby request a meeting with the Division, to occur soon after its 45 Day Review of the application. Our objective for this meeting is to agree next steps in preparation for the Psychopharmacological Drugs Advisory Committee meeting that we understand will be convened to address aspects of this sNDA. I plan to follow up with Dr. Doris Bates of the Division to make the necessary arrangements.

If there are any questions or comments regarding this application please contact the undersigned at (919) 483-3627.

Sincerely,

Eric B Benson

Eric B. Benson
Senior Director
Regulatory Affairs, Psychiatry

Question 2. Does the Agency concur that the design of studies SCAB2003 and SCAB2006 could support our proposed dosing instructions?
FDA Response: This will be a matter for review. GSK confirmed that the target dose will be 200 mg.

Question 3. Does the Agency concur with the proposal for the ISE?
FDA Response: Yes, as presented in the briefing book. Agency review will concentrate on the two pivotal studies.

Question 4. Does the Agency concur with the planned strategy for analysis in the ISS?
FDA Response: Yes, as presented in the briefing book.

Question 5. Does the Agency continue to concur with our proposal for presentation of adverse event (AE) data in the package insert for LAMICTAL?
FDA Response: The Division agreed with this proposal, which involves separate presentations of AEs associated with bipolar disorder and those associated with epilepsy.

Question 6. Does the Agency concur with our plans for assessing adverse events of special interest?
FDA Response: It was noted that there was a suggestion that emergent mania might be looked at from the standpoint of its being an adverse event. The Division asked how mania would be evaluated as an AE; the individual studies did not separate drug from placebo in manic relapse as an efficacy endpoint. Also, the studies were not defined prospectively as equivalence trials or powered to serve as such.

GSK acknowledged the Division's concerns. In fact, the firm felt it might be unnecessary to consider this approach since an analysis has been conducted on the combined studies (2003 and 2006); which apparently does show a statistically significant effect of drug vs. placebo in the prevention of manic episodes.

Question 7. Does the Agency continue to concur with our plans for specific CRFs, tabulations, and narratives to be supplied for patients who died, discontinued due to an adverse event, or experienced a serious adverse event?
FDA Response: The Division will need line listings for dropouts due to adverse events; FDA typically expects to see these listings for all events leading to discontinuation. Preferred term, verbatim term, etc. should be included in these listings; providing them will simplify the process of identifying patients who dropped out of studies.

GSK indicated that they are providing this information in each individual study report, and that it will also be in the ISS.

Question 8. Does the Agency agree to consenting to a partial waiver of the under-11-year-old age group in this disorder?
FDA Response: The Division explained that present policy is to grant a waiver for ages below 13, to request pediatric studies in ages 13 through 17, and to grant a pediatric deferral so that presently planned submissions may be filed and acted upon without the initial inclusion of pediatric studies. Documentation of this statement in these minutes constitutes both a waiver and a deferral, as presented above, for the supplemental application being discussed.

Question 9. Does the Agency grant consent to the request for deferral of a study in pediatric subjects age 11 through 17 years until after approval of this application and not before the fourth quarter of 2002?
FDA Response: See Question 8, above.

Question 10. Does the Agency agree that this application meets the criteria for a priority review?
FDA Response: The Division explained that one factor weighing against a priority review would be the fact that lithium is available and widely used in the maintenance treatment of bipolar disorder. However, GSK were encouraged to include a request and justification for priority review status in the application at time of submission.

Question 11. Does the Agency concur with our proposal to make electronic copies of the reports for legacy studies the archival copy given the fact that they do not fully comply with its guidance and does the agency concur that inclusion of these reports in the electronic archival copy would not result in a refusal to file?
FDA Response: GSK clarified that the deviations from guidance generally apply to font size, and the Division indicated that as long as the pages in question could be 'zoomed' to enlarge the fonts, the files should be acceptable.

Question 12. Does the Agency require paper review copies and if so could this be limited to paper copies of all non-clinical pharmacology and toxicology reports and the text, tables, and figures (but not listings) from the reports of legacy studies in Item 6 and Item 8?
FDA Response: GSK clarified that the nonclinical reports referred to here include studies on the mechanism of action of the drug. The clinical reviewer requested electronic copies; however, the statistical reviewers would prefer to receive paper copies as well, of the study reports for the two pivotal clinical studies and the supportive studies. Only one copy of these reports will be needed by the statisticians. **Important Note:** The needs of the nonclinical pharmacology / toxicology review team will be addressed in a separate communication.

Question 13. Does the Agency concur with our proposals to include 1) case report tabulations for the pivotal and supportive studies and 2) patient profiles for subjects who discontinue from the pivotal studies due to an adverse event?
FDA Response: The Division requested patient profiles for deaths and other SAEs and for dropouts due to AEs. These profiles should be provided for all such events arising out of the entire exposed population in the bipolar development program. For the purposes of accessing the information in electronic format, GSK agreed to prepare patient profiles with all variables displayed over time, and to provide these in .pdf format so that the reviewer will not need to construct profiles from multiple different data domains.

GSK will create and provide a sample for this information so that the Division can see the presentation and provide feedback prior to submission.

Question 14. Does the Agency concur with the proposal for covered studies for the purposes of financial disclosure?
FDA Response: The Division concurs with the proposal as presented on page 28 of the briefing book.

Additional Discussion Points. In addition to the items discussed above, the Division raised the following questions:

1. Dr. Katz asked to what extent dosing recommendations had been evaluated which involve withdrawal of concomitant medications, i.e. other mood stabilizers. GSK confirmed that the trial design had used dose tapering / drug withdrawal practices which matched the current labeling of the medications involved; only study 2001 included a rapid titration.

2. In terms of the indication being proposed, vs. that which was the protocol specified primary outcome, the Division confirmed that 'delay of depression' appears to be a reasonable proposal, based on currently available information. FDA's review will examine the initial hypothesis as tested to determine, if possible, the source of the treatment effect seen; in this context, the fact that the combined studies show a statistically significant effect for emergence of mania is reassuring.

3. GSK also provided a package of information with regard to the truncation of the flexible-dose pivotal study (attenuation of the outer arms, concomitant enrichment of the 200 mg dose arm). This information has not yet been reviewed. The format of statistical data proposed for provision with the submission differs from that initially requested, but is considered acceptable by the Statistics Review Team.

PLEASE SEE ELECTRONIC SIGNATURE PAGE.
DRS. BATES AND LAUGHREN ARE SIGNING THESE MINUTES FOR THE ATTENDEES;
DR. KATZ WILL SIGN THEM TO INDICATE ACCEPTANCE FOR DIVISION INTERNAL RECORDS AND FOR EXTERNAL RELEASE.
NOTE: ELECTRONIC SIGNATURES APPEAR ON LAST PAGE OF DOCUMENT, FOLLOWING ANY ATTACHMENTS.

Doris J. Bates, Ph.D.
Regulatory Project Manager

Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drugs Group

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

/s/

Doris Bates
2/25/02 04:30:10 PM

Thomas Laughren
2/26/02 08:08:13 AM

Russell Katz
2/28/02 02:49:55 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-241/S-017
NDA 20-764/S-011

INFORMATION REQUEST LETTER

SmithKline Beecham Corporation
d/b/a GlaxoSmithKline
Attention: Eric B. Benson
Senior Director, Regulatory Affairs, Psychiatry
Five Moore Drive; P.O. Box 13398
Research Triangle Park, NC 27709

Dear Mr. Benson:

Please refer to your June 5, 2002 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamictal (lamotrigine) Tablets and Lamictal (lamotrigine) Chewable Dispersible Tablets.

We are reviewing the clinical section of your submission and have the following questions regarding your pivotal trial, SCAB2006.

1. Why were all currently enrolled subjects in SCAB2006 prematurely discontinued rather than followed for the duration of the prespecified time interval (76 weeks or TIME)?
2. When was the decision made to terminate SCAB2006?
3. Were any interim analyses performed for SCAB2006?

We are basing the above questions on the following information. According to the study report for SCAB2006, this study was initiated on August 14, 1997 and terminated early on December 10, 1999 "because of difficulty achieving enrollment goals". The study report further states that "subjects active in the trial at the time of study termination were evaluated at a standard 'study closeout visit' and a 'follow-up visit' that would have occurred at the natural end of the study". In addition, data provided to us indicates that approximately 25 to 35% of subjects were prematurely discontinued from SCAB2006 due to study termination; the stated reason for early termination of the study was due to difficulty achieving enrollment goals.

We request a prompt written response to the above questions in order to continue our evaluation of your supplemental new drug applications. We also ask that you provide copies of appropriate internal documents to support your response.

If you have questions, call Jacqueline H. Ware, Pharm.D., Regulatory Project Manager, at (301) 594-5533.

Sincerely,

{See appended electronic signature page}

Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drugs Group
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Thomas Laughren
12/6/02 03:43:00 PM