CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-251

MEDICAL REVIEW(S)

MEMORANDUM

DATE: May 7, 2009

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 22-251

SUBJECT: Action Memo for NDA 22-251, for the use of Lamictal ODT (lamotrigine) Orally Disintegrating Tablets 25 mg, 50 mg, 100 mg, and 200 mg

NDA 22-251, for the use of Lamictal ODT (lamotrigine) Orally Disintegrating Tablets 25 mg, 50 mg, 100 mg, and 200 mg, was submitted by GlaxoSmithKline on 11/28/07. The division issued a Complete Response (CR) letter on 12/24/08. The CR letter asked the sponsor to submit revised labeling and a Medication Guide as well as revised carton and container labeling. In addition, the letter asked the sponsor to submit a Risk Evaluation and Mitigation Strategy (REMS), to include a Medication Guide and a timetable for assessment of the success of the REMS.

The sponsor had submitted the REMS prior to the issuance of the CR letter (they had anticipated such a request from the division, because they were aware that the Agency would require a REMS consisting of a Medication Guide). The formal response to the CR letter was submitted on 12/24/08, the same day that the letter was issued. These events occurred with this timing because the sponsor was aware that the Agency was imposing class labeling for anti-epileptic drugs (AEDs) that described the results of a meta-analysis of 11 AEDs that demonstrated an increase in suicidal behavior and ideation in controlled trials, and that a Medication Guide incorporating this information would be required.

The response to the CR letter has been reviewed by Dr. Marc Stone, safety team reviewer, Dr. Elizabeth Donohoe and team, Division of Risk Management, Office of Surveillance and Epidemiology, and LaShawn Griffiths, Division of Risk Management. The review team finds that the labeling and the REMS submitted by the sponsor adequately address the requests in the CR letter.

I agree. For this reason, I will issue the attached Approval letter, with appended REMS.

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 08:48:36 AM
MEDICAL OFFICER

MEMORANDUM

DATE: December 7, 2008

FROM: Director
Division of Neurology Products/HFD-120

TO: File, NDA 22-251

SUBJECT: Action Memo for NDA 22-251, for the introduction of an orally disintegrating form of Lamictal (lamotrigine), Lamictal ODT

NDA 22-251, for the introduction of an orally disintegrating form of Lamictal (lamotrigine), Lamictal ODT 25, 50, 100, and 200 mg tablets, was submitted by GlaxoSmithKline (GSK) on 11/28/07. Lamictal is already approved as an oral tablet as adjunctive treatment for partial seizures, generalized seizures of Lennox-Gastaut Syndrome (LGS), primary generalized tonic-clonic seizures, conversion to monotherapy for partial seizures, and maintenance treatment for bipolar disorder. The current application contains the results of a definitive bioequivalence study (comparing the 200 mg ODT formulation to the currently marketed formulation 200 mg tablet).

The application has been reviewed by Dr. Philip Sheridan, medical officer, Carol Noory, Office of Clinical Pharmacology (OCP), Dr. Edward Fisher, pharmacologist, Dr. Zachary Oleszczuk, Division of Medication Error Prevention and Analysis (DMEPA), Dr. Wendy Wilson, chemist, and Dr. Sriram Subramaniam, Division of Scientific Investigations (DSI).

Ms. Noory has concluded that the sponsor has demonstrated the bioequivalence of the ODT formulation to the marketed tablet, and Drs. Sheridan, Fisher, Wilson, and Oleszczuk find no reason to withhold approval at this time (although Dr. Oleszczuk recommends that the sponsor inform practitioners about the differences among the various lamotrigine products at the time of launch of the ODT).

However, Dr. Subramanian has concluded that, based on the DSI inspection of GSK (and not of the inspection of the CRO that performed the bioequivalence study), the application should not be approved at this time.

Specifically, in his review dated 9/8/08, Dr. Subramanian notes numerous deficiencies primarily in GSK's record-keeping related to the analyses of the data in the definitive bioequivalence study (it is important to note that the inspection of GSK's records was a complete inspection; that is, all of the records for all patients were examined, not just a subset of the records [see below]). In particular, DSI found that:

1) the firm's audit trail did not allow the reconstruction and data processing of analytic runs
2) the audit trail feature of the software GSK used to collect and analyze the data was disabled, according to GSK worldwide policy
3) original chromatograms and results for analyses that were re-performed were not retained
4) other documentation failures occurred

The sponsor has responded to these concerns (that were presented to GSK in a 483). Dr. Subramanian reviewed the company's responses in a review dated 11/12/08. In brief, the sponsor presumably believes that the records that they did submit permit an adequate reconstruction of the original and final study results, although they did agree to retain certain records (that were not retained in this study) in the future. Clearly, DSI has concluded that GSK's responses and the data submitted do not allow for a complete reconstruction of the study.

In brief, as I understand the deficiencies, numerous analytic runs were re-done because of QC failures (albeit relatively minor failures), and the reasons for these failures could not be documented. Further, a number of chromatograms were re-integrated, again without documented reasons. In addition, DSI found that the integration parameter sets for 25% of the runs were different from those used for the initial runs, again without documented explanation. Also, several chromatograms were, according to the sponsor, of "very poor quality", and these runs were re-done, though the original records were not retained.

In order to examine the impact of these deficiencies on the study results, Ms. Noory re-analyzed the study with data from any subject with questionable data removed. Originally, the study was analyzed with data from 54 subjects; the re-analysis included data from 32 subjects. The results of the re-analyses demonstrated bioequivalence of the two products, with the exception of the ratio of the Cmax of the ODT fed/fasted, which had a lower bound of the 90% CI of 77.

Further, because bioequivalence depends upon a showing of "equivalence", and not superiority, we were interested in the power of the truncated, re-analyzed, study to demonstrate a difference between the ODT and marketed tablet (if there was one). Don Schuirmann of the Office of Biostatistics examined this question; he found that the probability for passing the BE criteria for AUC was about 0.05%. He further comments that it is possible to pass the BE criteria when the ratio of geometric means is 1.0, due to extreme variability or very small sample size, could be essentially just as likely when the products are not bioequivalent as when they are bioequivalent (the outcome we are worried about here). However, as he notes, that is not the case here, given that the chances of passing the BE criteria if the ratio of geometric means is 1.0 is about 10 times greater than the chance of passing the BE criteria if the ratio of geometric means is 0.8 or 1.25. As he concludes, then, although the power of the study to demonstrate BE for AUC is relatively low, "…it is still substantially more likely to

pass if… [the products] are equivalent than it is if…[the products] are not equivalent." (see his note to Dr. Vaneeta Tandon, OCP).

COMMENTS

As originally analyzed, the definitive BE study demonstrates that Lamictal ODT and Lamictal Tablets are bioequivalent. However, DSI has identified numerous deficiencies in the record-keeping for the analyses of plasma levels that, in their view, make the study results, as presented by GSK, unreliable, primarily, as I understand it, because the reasons for numerous re-analyses were not adequately documented and/or justified.

We have discussed these findings in two meetings between members of the review teams of DNP, OCP, and DSI.

Inadequate documentation of study conduct and results (especially when various important outcomes are re-analyzed) is a serious deficiency in a new drug application. Given that we depend entirely on the integrity of the data submitted to us in order to make regulatory judgments, deficiencies in these matters obviously can have a critical impact on our decisions, and must be taken very seriously.

It must also be noted, however, that few studies are conducted and/or documented perfectly, and we are often called upon to make judgments about the seriousness of the particular deficiencies noted in these areas when we are faced with making a decision about a specific application.

In the case here, the staff of DSI has concluded that the errors made by GSK are of sufficient severity to warrant a conclusion that the results, as submitted, are unreliable.

I take seriously DSI's conclusions, and certainly defer to their expertise in assessing the nature and severity of the findings, and also the inadequacies of the sponsor's responses to these findings.

However, the fact that the inspection included all records for this study affords us the opportunity, in my view, to examine any possible (or at least any reasonable; see below) effect that the questionable data might have had on the results as presented. Specifically, re-analyzing the study without the data from any subject whose data was in any way questionable should adequately address any concerns about the effect of said questionable data on the results as presented.

In this regard, as noted above, such a re-analysis has shown that, even with almost half of the data removed, the finding of BE is robust, and questions about the appropriate power of such a truncated study have been, in my view, adequately answered by Mr. Schuirmann.

However, as Mr. Schuirmann also notes, it is still possible that the finding of BE is misleading, because it is possible that the original data from the over 20 patients that was removed could have, if included, given rise to a finding of a lack of bioequivalence. That is, the product could have performed so poorly in those patients that inclusion of their data could have driven the entire study to a finding of non-bioequivalence. I find such a possibility vanishingly small.

It is also possible, I suppose, that the findings seen in the DSI inspection could be considered so significant that, despite the conclusion that the data do support a finding of bioequivalence, the application should not be approved because: 1) they raise questions about the overall integrity of the study/submission, and/or 2) they are at such great variance from acceptable study conduct that this, in and of itself, justifies not approving the application.

Regarding possibility (1), although I take these findings seriously, and as I noted above, I defer to DSI's conclusions about the adequacy of GSK's responses, I find nothing in the application to suggest to me that the integrity of the application as a whole is undermined. And as regards possibility (2), I am sufficiently satisfied that the data, both as originally and as re-analyzed, establish the bioequivalence of the ODT and tablet formulations according to our usual and accepted standards. Once this conclusion has been reached, it seems to me that to withhold approval of the application based on GSK's deviation, in this case, from acceptable study conduct standards would be inappropriate. I have concluded that the products are bioequivalent; the findings of the DSI inspection do not undermine that conclusion, and such a finding, in my view, provides an adequate justification for approving the application. I have discussed my intentions with the staff of DSI; although I believe it is fair to say that they still recommend that the application should not be approved, I also believe it is accurate to state that they accept my decision to approve the application.

However, before the application can be approved, there is another issue that must be resolved.

Because Lamictal ODT is an antiepilepsy drug (AED), it must have in place a Risk Evaluation and Mitigation Strategy (REMS) related to the Agency's conclusion, based on a meta-analysis of 11 AEDs, that labeling for all AEDs must contain statements about an increased risk of suicidal behavior and suicidal thinking (suicidality). In addition, all AEDs must have a Medication Guide describing these effects. The sponsor has submitted a REMS, but too late in the review cycle for it to have been reviewed. The REMS must be reviewed and found acceptable before the application can be approved.

For these reasons, then, I will issue the attached Complete Response letter.

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
12/23/2008 12:34:48 PM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	22251
Submission Code	N000
Letter Date	November 28, 2007
Stamp Date	November 28, 2007
PDUFA Goal Date	September 28, 2008
Reviewer Name	Philip H. Sheridan, M.D.
Review Completion Date	December 3, 2008
Established Name	Lamotrigine orally disintegrating tablet
(Proposed) Trade Name	Lamictal ODT
Therapeutic Class	Antiepileptic Drug
Applicant	GSK
Priority Designation	S
Formulation	Orally disintegrating tablet
Dosing Regimen	Bioequivalent to Lamictal
Indication	Epilepsy, Bipolar Disorder
Intended Population	Adults

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Approval

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

Distinctive tablets to avoid confusion with other Lamictal products.

Labeling (see medication error discussion in section 10.2 of this review)

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The Lamictal Orally Disintegrating Tablet (ODT) is an immediate-release tablet which is designed to disintegrate rapidly in the mouth and be swallowed without the need to take it with water. It uses a taste-masking approach (Eurand's Microcap technology) and flavorings to offset the slightly bitter taste of lamotrigine.

The application is based on the demonstration of bioequivalence between the currently marketed LAMICTAL™compressed tablets and the new lamotrigine ODT.

1.1. Overall Safety Evaluation Plan and Narratives of Safety

1.3.2 Efficacy

No new efficacy data was submitted. Approval is based on safety and bioequivalence.

1.3.3 Safety

Two bioequivalence studies have been conducted with the ODT formulation of lamotrigine in healthy volunteers.

For each study, the Safety Population was comprised of all subjects who received a dose of lamotrigine. Laboratory data, vital signs and ECG parameters were summarized by treatment using descriptive statistics as absolute values and changes from baseline. In addition, values of laboratory data, vital signs and ECG parameters which fell outside a pre-defined, expanded normal range indicative of potential clinical concern (PCC) were flagged and summarized by treatment.

No deaths or serious adverse effects occurred during the two studies. Adverse effects observed were comparable in patients receiving single dose Lamictal ODT and Lamictal IR. There were no significant local adverse effects involving the oral cavity from the Lamictal ODT preparation.

1.3.4 Dosing Regimen and Administration

Given bioequivalence, the proposed dosage regimen is the same as for the currently marketed Lamictal IR tablets. The Lamictal Orally Disintegrating Tablet (ODT) is an immediate-release tablet which is designed to disintegrate rapidly in the mouth and be swallowed without the need to take it with water.

1.3.5 Drug-Drug Interactions

Given bioequivalence, the interactions are expected to be the same as for the currently marketed Lamictal IR tablets.

1.3.6 Special Populations

Lamictal ODT is not indicated for the pediatric population. Lamictal CD is an already marketed chewable-dispersible dosage form appropriate for the pediatric population.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

This summary of clinical safety summarizes the clinical safety data from two clinical pharmacokinetic studies conducted in adult subjects with lamotrigine formulated as an Orally Disintegrating Tablet (ODT). The ODT is an immediate-release tablet which is designed to disintegrate rapidly in the mouth and be swallowed without the need to take it with water, and uses a taste-masking approach (Eurand's Microcap technology) and flavorings to offset the slightly bitter taste of lamotrigine. The application is based on the demonstration of bioequivalence between the currently marketed, LAMICTAL™ compressed tablets and the new lamotrigine ODT in a pilot study (LBI108614) and pivotal study (LBI108617).

2.2 Currently Available Treatment for Indications

Lamictal IR tablet is currently marketed for these indications:

Epilepsy—adjunctive therapy in patients ≥2 years of age:
- partial seizures
- primary generalized tonic-clonic seizures
- generalized seizures of Lennox-Gastaut syndrome

Epilepsy—monotherapy in patients ≥16 years of age: conversion to monotherapy in patients with partial seizures who are receiving treatment with carbamazepine, phenobarbital, phenytoin, primidone, or valproate as the single AED.

Bipolar Disorder in patients ≥18 years of age: maintenance treatment of Bipolar I Disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy.

Lamictal ODT is proposed as a bioequivalent alternative dosage form for Lamictal IR tablets for adult patients who have difficultly swallowing. For pediatric patients, there is a currently marketed chewable-dispersible dosage form, Lamictal CD.

2.3 Availability of Proposed Active Ingredient in the United States

Not applicable

2.4 Important Issues With Pharmacologically Related Products

Not applicable

2.5 Presubmission Regulatory Activity

Lamictal (lamotrigine) tablets were originally approved on December 27, 1994, for NDA 20-241. A second NDA was approved for Lamictal CD (lamotrigine chewable dispersible) tablets, NDA 20-764, on August 24, 1998.

Lamictal ODT is proposed for approval based on two bioequivalence studies. The Agency agreed to the design of the "pivotal" bioequivalence study, LBI108617, at the End-of-Phase-2 meeting held on April 26th, 2007 and the final protocol of Study LBI108617 submitted under IND 76,557, Serial Number 0011 dated May 7, 2007.

2.6 Other Relevant Background Information

Not applicable

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Acceptable. See CMC review.

3.2 Animal Pharmacology/Toxicology

Bioequivalent to Lamictal IR.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Clinical safety data from two clinical bioequivalence studies

4.2 Tables of Clinical Studies

Table 1 Summary of Exposures and Treatments Administered in Studies LBI108614 and LBI108617

Treatment Code/Description		Number of subjects
Study LBI108614		
A	25mg lamotrigine ODT, fasted/disintegrate in the mouth without water	16
B	200mg lamotrigine ODT fasted/disintegrate in the mouth without water	16
C	25mg lamotrigine IR fasted/swallowed with water	16
D	200mg lamotrigine IR fasted/swallowed with water	16
Study LBI108617		
C	200mg lamotrigine ODT fasted/disintegrate in the mouth without water	54
D	200mg lamotrigine IR tablet fasted/swallowed with water	54
E	200mg lamotrigine ODT high fat meal/disintegrate in the mouth without water	54
F	200mg ODT fasted/swallowed with water	53
G	200mg ODT fed/swallowed with water[1]	1

1. Subject 336 received lamotrigine ODT 200 mg, fed with water in error, designated regimen G for the purposes of reporting.

4.3 Review Strategy

This reviewer has reviewed the final study reports of studies LBI108614 and LBI108617, the clinical overview, the summary of clinical safety submitted by the sponsor. I also reviewed the reviews of CMC, Clin Pharm, and DSI.

4.4 Data Quality and Integrity

The Division of Scientific Investigations (DSI) has raised concerns regarding the analysis of some of the bioequivalence doses. These updated concerns are summarized in the DSI memorandum dated November 12, 2008 which updates the DSI report dated September 8, 2008 concerning the FDA audit of bioequivalence study LBI 108617. DSI is concerned that study reconstruction is not possible because the sponsor only retained PDF copies of the chromatograms without also retaining the electronic data and audit trail generated by the chromatography acquisition and integration software. Also, data from original runs that were rejected and reanalyzed were not retained.

As a result, DSI concluded that the accuracy of 37% of analytical runs in study LBI 108617 cannot be assured. DSI's review of the Sponsor's response to the September 8, 2008 memorandum found the response "unsatisfactory". However, after further in-house discussion with DSI and the Clinical Pharmacology team, I have concluded that the demonstration of

bioequivalence is still valid even given the less than optimal documentation of some of the analytical runs of study LBI 108617.

4.5 Compliance with Good Clinical Practices

4.6 Financial Disclosures

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

5.2 Pharmacodynamics

5.3 Exposure-Response Relationships

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The application is based on the demonstration of bioequivalence between the currently marketed, LAMICTAL™ compressed tablets and the new lamotrigine ODT.

Indications will be the same as for LAMICTAL™ compressed tablets.

6.1.1 Methods

6.1.2 General Discussion of Endpoints

6.1.3 Study Design

6.1.4 Efficacy Findings

6.1.5 Clinical Microbiology

6.1.6 Efficacy Conclusions

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

In total, 194 healthy subjects have received lamotrigine ODT.

In Study LBI108614, 64 subjects received a single dose of lamotrigine, of whom 32 received an ODT. All subjects completed the study.

In Study LBI108617, 216 subjects received a single dose of lamotrigine, of whom 162 received an ODT. Three subjects withdrew consent due to personal reasons prior to the follow-up visit although they contributed both safety and PK data up to Day 7.

Table 1 summarizes the doses of ODT and LAMICTAL IR administered and number of subjects receiving each treatment in the two studies.

7.1.1 Deaths

There were no deaths in the two studies submitted.

7.1.2 Other Serious Adverse Events

There were no Serious Adverse Events in the two studies submitted.

7.1.3 Dropouts and Other Significant Adverse Events

There were no dropouts in Study LBI108614.

Three subjects in Study LBI108617 withdrew consent due to personal reasons prior to the follow-up visit although they contributed both safety and PK data up to Day 7.

7.1.3.1 Overall profile of dropouts

Not applicable

7.1.3.2 Adverse events associated with dropouts

Not applicable

7.1.3.3 Other significant adverse events

7.1.4 Other Search Strategies

Not applicable

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

7.1.5.3 Incidence of common adverse events

The most common treatment-emergent AEs (TEAEs), defined as AEs occurring in more than one subject in any treatment group, in LBI108614 and LBI108617 are summarized in Table 4 and Table 5, respectively (See 7.1.5.4).

In LBI108614, overall, 33% of subjects reported a TEAE: 25%, and 31% of subjects, respectively, receiving 25 mg and 200 mg ODT and 44% and 31% of subjects, respectively, receiving 25 mg and 200 mg IR tablets. The most common TEAEs over all treatments were headache (13%), pharyngolaryngeal pain (6%), lip ulceration (3%) and dizziness (3%). The percentage of subjects reporting headache was higher in the 200 mg IR group, but numbers of subjects with individual AEs was low, and the group sizes too small to draw any conclusions about tolerability differences between the treatments.

Reviewer note:
With regard to the symptom of lip ulceration (3%) in LBI108614, the 2/64 subjects experiencing this were both in the 200 mg lamotrigine IR group rather than in either of the ODT groups.

In LBI108617, overall, 28% of subjects reported a TEAE: 26% receiving 200 mg ODT, fasted, 24% receiving 200 mg IR tablet, fasted, 28% receiving 200mg ODT, fed and 34% receiving ODT swallowed with water, fasted. The one subject who accidentally received the incorrect food allocation, and took 200 mg ODT swallowed, fed, had no AEs.

The overall frequency of AEs was similar for the four treatments, although slightly higher when the ODT was swallowed with water in the fasting state compared to the other three treatments. Since the ODT disintegrated in the mouth, fasted was bioequivalent to the IR tablets, fasted, and the ODT disintegrated fasted was bioequivalent to the ODT swallowed with water, fasted, tolerability differences between the treatments are not expected. The slightly lower average lamotrigine Cmax following the ODT in the fed state has not had any apparent affect on tolerability.

In LBI108617, the most common TEAEs over all treatments were headache (10%), diarrhea (3%) and nausea (3%). Headache was somewhat more frequent in the ODT fed group (19%) compared to the other three groups (6-9%), but these headaches were generally mild and of short duration, and potentially related to study conditions.

In summary, the frequency and nature of adverse events was similar between the ODT and IR tablet in both studies. No new safety concerns or new pattern of AEs were associated with ODT administration.

The lack of mouth symptoms associated with the oral disintegration of ODT is discussed below in section 7.1.5.5.

7.1.5.4 Common adverse event tables

Table 4 Summary of the Most Frequently Reported (>1 subject in any treatment group) Adverse Events During Study LBI108614 (Safety Population)

AE preferred term	25mg lamotrigine ODT	200mg lamotrigine ODT	25mg lamotrigine IR	200mg lamotrigine IR	All subjects
Number dosed	N=16	N=16	N=16	N=16	N=64
Number (%) with any TEAE	4 (25)	5 (31)	7 (44)	5 (31)	21 (33)
Headache	2 (13)	2 (13)	1 (6)	3 (19)	8 (13)
Dizziness	0	0	0	2 (13)	2 (3)
Lip ulceration	0	0	0	2 (13)	2 (3)
Pharyngolaryngeal pain	1 (6)	2 (13)	1 (6)	0	4 (6)

Data Source: LBI108614 Table 10.8

Table 5 Summary of the Most Frequently Reported (>1 subject in any treatment group) Adverse Events During Study LBI108617 (Safety Population)

AE Preferred term	200mg ODT disintegrated fasted	200mg IR fasted	200mg ODT disintegrated fed	200mg ODT swallowed fasted	200mg ODT swallowed fed[1]
Number dosed	N=54	N=54	N=54	N=53	N=1
N (%) with any TEAE	14 (26)	13 (24)	15 (28)	18 (34)	0
Headache	5 (9)	4 (7)	10 (19)	3 (6)	0
Diarrhoea	3 (6)	0	1 (2)	2 (4)	0
Nausea	2 (4)	2 (4)	1 (2)	1 (2)	0
Rhinitis allergic	0	0	1 (2)	2 (4)	0
Cough	0	0	0	2 (4)	0
Upper respiratory tract infection	0	0	2 (4)	0	0

Source Data: LBI108617 Table 10.2
1. Subject 336 received lamotrigine ODT 200 mg, fed with water in error.

7.1.5.5 Identifying common and drug-related adverse events

In LBI108614, 14% of all the subjects reported a drug-related AE: 25%, and 13% of subjects, respectively, receiving 25mg and 200mg ODT and 6% and 13% of subjects, respectively, receiving 25mg and 200mg IR tablets. The most common drug-related AEs were headache, dizziness and pruritus; the only ones occurring in more than one subject in the study.

In LBI108617, 11% of subjects reported a drug-related AE: 6% of subjects in the 200mg ODT fasted group and 13% of subjects in each of the other three treatment groups. The most common drug related AEs were headache (2-9% across the treatment groups) and

nausea (2-4% across the treatment groups).

Overall, the frequency of drug-related AEs was low, reflecting the single dose design and short duration of the studies, with no evidence of clinically relevant treatment differences.

Rash is an AE of special concern for lamotrigine products. In the two studies presented here, a parallel-group design was selected to avoid repeated administration of single doses of lamotrigine to healthy subjects as it was considered that repeated administration of single doses of lamotrigine in excess of 25mg (rather than using the recommended dose titration schedule) could increase the risk of skin rash.

No serious rashes were reported in either studies. In LBI108614, two subjects reported skin disorders, both of which were mild and considered drug-related. Subject 107 (25mg lamotrigine ODT) had a mild, flat, blotchy, red rash on his back and upper chest (preferred terms: rash macular and rash erythematous) accompanied by itching on his back which started approximately 4 hours post-dose and lasted approximately 19 hours. Subject 139 (200mg lamotrigine ODT) had mild erythema and itching (preferred term: pruritus) on her right forearm which started approximately 8 hours post dose and lasted for 31 hours and a further episode of pruritus on her upper body after 2 days which lasted for 9 hours. Both cases resolved without treatment.

In LBI108617, four subjects reported skin disorders: one case of rash, one of pruritus, one of contact dermatitis and one case of a dermal cyst. All were considered mild and unrelated to treatment.

As the ODT is allowed to disintegrate in the mouth, the oral cavity is exposed to drug for longer than with a conventional, swallowed tablet, so AEs relating to mouth symptoms or taste were of interest. There were very few AEs relating to mouth symptoms and none relating to taste. One subject in LBI108614 who received 25mg lamotrigine ODT reported mild tongue numbness (preferred term: hypoaesthesia oral), within a minute of taking the ODT which lasted 10 minutes and was considered drug-related. In LBI108617, one subject who received 200mg lamotrigine ODT reported mild mouth pain (preferred term oral pain) which started 1 day 8 hours post-dose and was not considered drug-related. Two cases of mild dry mouth occurred 2-3h post-dose, one after 200mg ODT allowed to disintegrate in the mouth and one after 200mg ODT swallowed with water.

Overall, there was nothing to suggest the ODT was associated with a clinically important incidence of mouth symptoms.

7.1.5.6 Additional analyses and explorations

Not applicable.

7.1.6 Less Common Adverse Events

Not applicable.

7.1.7 Laboratory Findings

In both LBI108614 and LBI108617, laboratory data were collected at screening, pre-dose and at follow-up. No laboratory value was reported as an AE in either study and no trends in the laboratory data were observed to suggest a drug effect.

7.1.7.1 Overview of laboratory testing in the development program

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

7.1.7.4 Additional analyses and explorations

7.1.7.5 Special assessments

7.1.8 Vital Signs

In LBI108614, one AE was reported which potentially related to vital signs: one subject in the 200mg lamotrigine ODT group reported an AE of postural dizziness approximately two hours post-dose, but no recording of vital signs was made during this event to suggest that there was any underlying blood pressure change. In LBI108617, there was one AE relating to vital signs: Subject 482 (200mg IR) had a mild AE of tachycardia, beginning 3 h 20 minutes post-dose and lasting for 18 minutes. A heart rate of 100 beats per minute was recorded during this period, compared to a pre-dose value of 84bpm, and no other symptoms were reported.

In both studies, there was a trend for the mean systolic and diastolic blood pressures to be slightly lower (4 to 10mmHg for systolic and 2 to 3mmHg for diastolic) at the 24h and 48h

post-dose readings, compared to the pre-dose value following all doses. These differences are probably explained by the post-dose recordings being taken following a period of prolonged rest whilst subjects were in the clinical pharmacology unit, and differences in the time of day the pre-dose and post-dose recordings were made. Mean heart rate in LBI108614 was lower (8-12 beats per minute) 24h post-dose whilst in LBI108617, there was little difference from pre-dose.

In both studies, occasional observations were outside the pre-defined range of potential clinical concern but none were of actual clinical concern.
For further details see the clinical trials reports for LBI108614 [HM2007/00153/

7.1.8.1 Overview of vital signs testing in the development program

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

7.1.8.4 Additional analyses and explorations

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

7.1.9.4 Additional analyses and explorations

7.1.10 Immunogenicity

7.1.11 Human Carcinogenicity

7.1.12 Special Safety Studies

7.1.13 Withdrawal Phenomena and/or Abuse Potential

7.1.14 Human Reproduction and Pregnancy Data

7.1.15 Assessment of Effect on Growth

7.1.16 Overdose Experience

7.1.17 Postmarketing Experience

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

7.2.1.2 Demographics

Table 2 Summary of Demography in Study LBI108614

	25mg lamotrigine ODT	200mg lamotrigine ODT	25mg lamotrigine IR	200mg lamotrigine IR	Total
Number of Subjects	16	16	16	16	64
Age (y) Mean (SD)	31.8 (10.29)	26.6 (8.24)	27.7 (9.47)	31.9 (10.98)	29.5 (9.86)
Range	19 - 51	19 - 53	19 - 48	19 - 51	19 - 53
Sex, n (%)					
Female	7 (44)	7 (44)	5 (31)	8 (50)	27 (42)
Male	9 (56)	9 (56)	11 (69)	8 (50)	37 (58)
BMI (kg/m²) Mean (SD)	25.3 (2.21)	24.0 (2.75)	24.5 (3.15)	23.9 (2.83)	24.4 (2.75)
Weight (kg) Mean (SD)	77.2 (11.01)	75.5 (12.63)	77.5 (14.60)	71.5 (12.44)	75.4 (12.66)
Ethnicity, n (%)					
Hispanic or Latino	2 (13)	2 (13)	1 (6)	0	5 (8)
Not Hispanic or Latino	14 (87)	14 (87)	15 (94)	16 (100)	59 (92)
Race, n (%)					
Mixed Race	0	1 (6)	0	0	1 (1.6)
American Indian or Alaskan Native	0	0	0	1 (6)	1 (1.6)
White/Caucasian/European	16 (100)	15 (94)	16 (100)	15 (94)	62 (97)

Data Source LBI108614 Table 9.1 and Table 9.7.

7.2.1.3 Extent of exposure (dose/duration)

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

7.2.2.2 Postmarketing experience

7.2.2.3 Literature

7.2.3 Adequacy of Overall Clinical Experience

Lamictal ODT is bioequivalent to Lamictal IR.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

7.2.5 Adequacy of Routine Clinical Testing

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

7.2.8 Assessment of Quality and Completeness of Data

7.2.9 Additional Submissions, Including Safety Update

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

7.4.1.2 Combining data

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

7.4.2.2 Explorations for time dependency for adverse findings

7.4.2.3 Explorations for drug-demographic interactions

7.4.2.4 Explorations for drug-disease interactions

7.4.2.5 Explorations for drug-drug interactions

7.4.3 Causality Determination

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Bioequivalent to currently marketed Lamictal IR tablets.

8.2 Drug-Drug Interactions

Bioequivalent to currently marketed Lamictal IR tablets.

8.3 Special Populations

Bioequivalent to currently marketed Lamictal IR tablets.

8.4 Pediatrics

Lamictal ODT is indicated for adults. An alternative pediatric preparation, Lamictal Chewable and Dispersible is available for the pediatric population.

8.5 Advisory Committee Meeting

Not applicable

8.6 Literature Review

Not applicable

8.7 Postmarketing Risk Management Plan

Packaging and tablet appearance are distinctive to avoid confusion with other Lamictal products.

Labeling discussion of potential medication errors is being added (see section 10.2 of this review).

8.8 Other Relevant Materials

Not applicable

9 OVERALL ASSESSMENT

9.1 Conclusions

The Lamictal ODT dosage form has been shown to be bioequivalent to the currently marketed Lamictal IR. The safety profile observed during the two bioequivalence studies was similar to that of Lamictal IR.

9.2 Recommendation on Regulatory Action

Approval

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

See section 8.7.

9.3.2 Required Phase 4 Commitments

9.3.3 Other Phase 4 Requests

9.4 Labeling Review

The sponsor has proposed to adopt PLR format labeling. A single label will be used for currently marketed Lamictal tablets and Lamictal CD tablets as well as for the proposed Lamictal ODT.

The new PLR labeling incorporates a CBE submitted May 7, 2007 which is discussed in section 10.2 of this review.

9.5 Comments to Applicant

Agreement on the new PLR labeling may require some further discussion.

10 Appendices

10.1 Review of Individual Study Reports

See Clinical Pharmacology review of bioequivalence studies and Section 7 Safety of this review.

10.2 Line-by-Line Labeling Review

Agency approved labeling is shown as Appendix 1. This is the first time that Lamictal prioducts have had PLR labeling. The same label will be used for the currently marketed Lamictal IR (NDA 020241) and Lamictal CD (NDA 020764) as well as the proposed Lamictal ODT (NDA 22251).

The sponsor submitted similar PLR labeling with this NDA incorporating a previously unreviewed CBE submitted to Lamictal IR (NDA 020241) and Lamictal CD (NDA 020764) on May 7, 2007.

(b) (4)

Reviewer Note:
This is based on a published retrospective study by L J Hirsch et al (Epilepsia 47(2):318-322, 2006) which found that a hisroty of rash to other antiepileptic drugs was the strongest predictor for nonserious Lamictal-associated rash with an Odds ratio of about 3. This wording is appropriate.

(b) (4)

Reviewer Note:
This is an editorial update of information for the physician to communicate to patients. This wording is appropriate.

Reviewer Note:
This is based on a published retrospective study by L J Hirsch et al (Epilepsia 47(2):318-322, 2006) which found that a hisroty of rash to other antiepileptic drugs was the strongest predictor for nonserious Lamictal-associated rash with an Odds ratio of about 3. This wording is appropriate.

Reviewer Note:
This addresses two issues. One is the longstanding confusion between Lamictal and other non-AED medications such as Lamisil or Lomotil. The other issue is the potential confusion among the dosage forms of lamotrigine which upon approval of this NDA will include Lamictal [Lamictal IR], Lamictal CD, and Lamictal ODT. In the near future, Lamictal XR is also likely to be approved. Therefore this is an appropriate addition to the labeling.

(b) (4)

Reviewer Note:
This is an editorial update of information for the patients, including the rash-predictor discussed above. This wording is appropriate.

52 Page(s) Withheld

_____ Trade Secret/Confidential (b4)

__X__ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical Review Section-_____

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

/s/

Philip Sheridan
12/19/2008 02:50:12 PM
MEDICAL OFFICER

Norman Hershkowitz
12/19/2008 02:55:51 PM
MEDICAL OFFICER