CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-251

OTHER REVIEW(S)

Review and Evaluation of Clinical Data

NDA: 20-241, 20-764, 22-115, 22-251
Sponsor: Glaxo SmithKline
Drug: Lamotrigine (Lamictal®)
Material Reviewed: Proposed labeling and Medication Guides
Subject: Anticonvulsant-associated suicidality
Reviewer: Marc Stone, M.D.
Submission Dates:
Date Review Completed:

The Division asked the manufacturers of all antiepileptic drugs to submit labeling language and Medication Guides that discuss the risk for suicidal thoughts and behaviors associated with the use of these medications. The Division's request was based on the results of a meta-analysis of randomized, placebo-controlled controlled, clinical trial data that found an increased risk of suicidal thoughts and behaviors with antiepileptic drugs. The Division specifically requested class labeling, including a WARNING statement or WARNINGS and PRECAUTIONS statement for PLR labels, an Information for Patients statement, as well as a Medication Guide, and a Risk Evaluation and Mitigation Strategy (REMS). The Division also asked manufacturers to include language informing prescribers and patients about the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This memo reviews GSK's response to the Division's request for their antiepileptic drug, lamotrigine (Lamictal®).

There was some discussion concerning how to integrate warnings concerning suicidality both into labeling and into a comprehensive Medication Guide. Current labeling for lamotrigine contains a boxed warning about the risk of severe skin reactions including Stevens-Johnson syndrome. There are also substantial concerns with hypersensitivity reactions, multiorgan failure and blood dyscrasias. GSK proposed that suicidality be listed after hypersensitivity but before multiorgan failure and blood dyscrasias. It was, however, eventually decided that the three conditions evoke similar clinical concerns and their warnings should be listed consecutively after skin reactions and take precedence over suicidality. In addition, it was decided that long-time concerns over name confusion between Lamictal® and other drugs, particularly Lamisil®, causing medication errors merited provision of specific information in the Medication Guide intended to assist patients in identifying and avoiding this problem. With integration of these changes, the labeling, Medication Guide and REMS appear to be satisfactory.

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/s/

Marc Stone
4/23/2009 11:39:42 AM
MEDICAL OFFICER

Sally Yasuda
4/23/2009 11:54:16 AM
INTERDISCIPLINARY

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	March 25, 2009
To:	Russell Katz, M.D. Director **Division of Neurology Products**
Through:	Jodi Duckhorn, MA, Team Leader **Division of Risk Management**
From:	LaShawn Griffiths, MSHS-PH, BSN, RN Patient Product Information Reviewer **Division of Risk Management**
Subject:	DRISK Review of Patient Labeling (Medication Guide),
Drug Names; Application Type and Number; Applicant:	• Lyrica (pregabalin); NDA 21-446; Pfizer, Inc. • Keppra (levetiracetam); NDA 21-035; UCB Pharma, Inc. • Zonegran (zonisamide); NDA 20-789; Eisai Medical Research, Inc. • Lamictal (lamotrigine); NDA 22-251, NDA 22-115, NDA 20-241, NDA 20-764; GlaxoSmithKline • Topamax (topiramate); NDA 20-505; Ortho-McNeil-Janssen Pharmaceuticals, Inc.
OSE RCM #:	2009-85

1 INTRODUCTION

- Pfizer, Inc. submitted a New Drug Application (NDA 21-446) for Lyrica (pregabalin) capsules on October 30, 2003.
- UCB Pharma, Inc. submitted a New Drug Application (NDA 21-035) for Keppra (levetiracetam) tablets and oral solution on February 1, 1999.
- Eisai Medical Research, Inc. submitted a New Drug Application (NDA 20-789) for Zonegran (zonisamide) capsules on March 19, 1997.
- GlaxoSmithKline, submitted a New Drug Application
    - (NDA 22-251) for Lamictal (lamotrigine) Orally Disintegrating tablets on November 28, 2007 pending approval.
    - (NDA 22-115) for Lamictal (lamotrigine) Extended Release tablets; XR on November 22, 2006 pending approval.
    - (NDA 20-241) for Lamictal (lamotrigine) tablets on September 16, 2006.
    - (NDA 20-764) for Lamictal (lamotrigine) Chewable Dispersible tablets on September 16, 2006.

FDA has determined that Lyrica (pregabalin), Keppra (levetiracetam), Zonegran (zonisamide), Lamictal (lamotrigine), and Topamax (topiramate) pose a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use. FDA has determined that Lyrica (pregabalin), Keppra (levetiracetam), Zonegran (zonisamide), Lamictal (lamotrigine), and Topamax (topiramate) are products with a serious a significant public health concern that meet one of the three criteria for a Medication Guide as set forth in 21 CFR 208.1: these products have serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decision to use or continue to use.

In a letter dated December 16, 2008 the Division of Neurology Products (DNP) informed the sponsors that a REMS is necessary for Lyrica (pregabalin), Keppra (levetiracetam), Zonegran (zonisamide), Lamictal (lamotrigine), and Topamax (topiramate). The only elements of the REMS will be a Medication Guide and a timetable of submission of assessments of the REMS.

This review is written in response to a request from the Division of Neurology Products (DNP) for the Division of Risk Management to review the sponsors' proposed Medication Guides (MG). A review of the sponsors' proposed REMS was completed by DRISK under a separate cover.

2 MATERIAL REVIEWED

- Draft LYRICA (pregabalin) Medication Guide (MG) submitted on January 14, 2009, revised by DNP, and provided to DRISK on March 2, 2009
- Draft KEPPRA (levetiracetam) Medication Guide (MG) submitted on January 15, 2009, revised by DNP, and provided to DRISK on March 3, 2009
- Draft ZONEGRAN (zonisamide) Medication Guide (MG) submitted on January 15, 2009, revised by DNP, and provided to DRISK on March 11, 2009

- Draft LAMICTAL (lamotrigine) Medication Guide (MG) submitted on December 24, 2008, revised by DNP, and provided to DRISK on March 3, 2009
- Draft TOPAMAX (topiramate) Medication Guide (MG) submitted on January 16, 2009, revised by DNP, and provided to DRISK on March 3, 2009

3 DISCUSSION

The purpose of patient directed labeling is to facilitate and enhance appropriate use and provide important risk information about medications. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

In our review of the MG, we have:

- simplified wording and clarified concepts where possible,
- ensured that the MG is consistent with the PI,
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20.
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the MG. Comments to the review division are ***bolded, underlined and italicized***.

We are providing the review division a marked-up and clean copy of the revised MG. We recommend using the clean copy as the working document.

All future relevant changes to the PI should also be reflected in the MG.

4 CONCLUSIONS AND RECOMMENDATIONS

1. In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We recommend that the Sponsor reformat the Medication Guides using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

2. To enhance patient comprehension, materials should be written at a 6^{th} to 8^{th} grade Flesch Kinkaid reading level, and have a Flesch Reading Ease score of at least 60% (60% corresponds to an 8^{th} grade reading level).

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_____Deliberative Process (b5)

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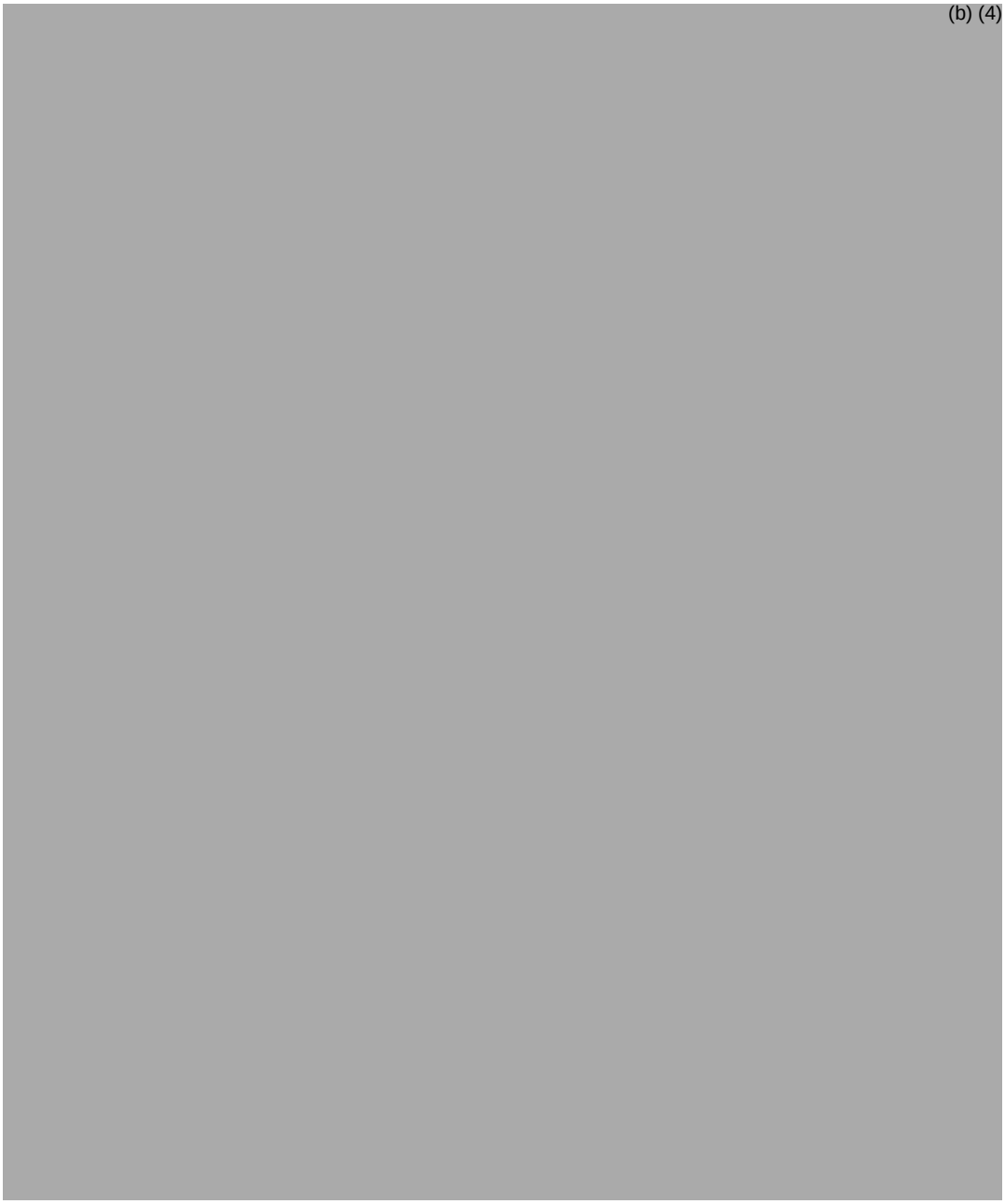

LAMICTAL (lamotrigine)

DRAFT Lamictal Medication Guide reading scores:

Flesch Reading Ease: 51.0%

Flesch-Kincaid Grade Level: 9.5

Our revised scores are:

Flesch Reading Ease: 55.6%

Flesch-Kincaid Grade Level: 8.7

1) If the Orally Disintegrating Tablets formulation is approved, it should be added to this Medication Guide so that there is one Medication Guide for all formulations of the product. Information should be added to the various sections of the Medication Guide as appropriate, including *but not limited to* the "How should I take" section, and the "ingredients" section.

2) The heading (b) (4) was removed. The purpose of patient information is to enhance appropriate use and provide important information to patients about medicines. The above information is risk management that should be done at the pharmacy. All (b) (4) have been removed because this information is not information that is usually included in patient information. However, DDMAC feels that this information is important and should be conveyed to the patient. If there is something specific to this medication versus other medications that a patient should know about to prevent medication errors, the Review Division should clarify and change as appropriate, while ensuring that the Medication Guide is consistent with the PI.

3) (b) (4)

4) In the section "How should I take Lamictal?" the statement, "Swallow Lamictal tablets whole. Chewing the tablets may leave a bitter taste" implies that it is alright to chew Lamictal tablets if you can tolerate the taste. The Review Division should clarify if the tablet should be swallowed whole for effectiveness, or if it is simply because of the bitter taste.

5) In the section "How should I store Lamictal?" the Review Division should clarify if the storage instructions are the same for all formulations.

6) In the section "How should I store Lamictal?" a temperature range was added from the PI.

(b) (4)

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/s/

Mary Dempsey
3/31/2009 03:58:02 PM
DRUG SAFETY OFFICE REVIEWER

LaShawn Griffiths
4/2/2009 01:40:26 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
4/2/2009 01:59:30 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 12, 2008

FROM: Sriram Subramaniam, Ph.D.
Xikui Chen, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. CTV 12/11/08
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

TO: Russell G. Katz, M.D.
Director, Division of Neurology Products

SUBJECT: Review of Response to Form 483 for EIR Covering NDA 22-251, Lamictal (Lamotrigine) Orally Disintegrating Tablets, Sponsored by GlaxoSmithKline

This is a follow-up to DSI's report dated 9/8/08 concerning the FDA audit of the following bioequivalence (BE) study. This report evaluates GlaxoSmithKline's (GSK) response to the Form 483 following the bioanalytical audit at their site.

Study LBI-108617: An open-label, randomized, single-dose, parallel-group study to demonstrate bioequivalence of two formulations and the effect of food and water on one formulation of lamotrigine in healthy male and female volunteers.

Background

The clinical and analytical portions of the study were conducted at Covance Clinical Research Unit, Dallas, TX, and GlaxoSmithKline R&D, WorldWide Bioanalysis, Drug Metabolism and Pharmacokinetics (GSK-DMPQ), Research Triangle Park, NC, respectively. No Form FDA 483 was issued at the conclusion of the inspection at Covance Clinical Unit (6/9-13/08). Following the inspection at GSK (8/25-28/08), significant findings were found and Form FDA 483 was issued. DSI's evaluation of the Form 483 was reported to DNP on 9/8/08. DSI found that study reconstruction in its entirety was not possible because the firm 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. Based on the above findings, DSI concluded that the accuracy of 37% of analytical runs cannot be assured. Subsequent to the inspection, GSK submitted their response to the Form 483 (Attachment 1).

DSI's evaluation of GSK's response to the significant Form 483 findings follows.

1. **Complete reconstruction and evaluation of data processing of analytical runs was not possible.**
   a. **Electronic data was not available for analytical runs. Only PDF files of chromatograms and final results were available. PDF files do not allow for understanding the reason for reintegration and the impact of the original integration. For example, in analytical run LBI108617HUSE47 in Study LBI108617, the 30 ng/mL QC (at #83) failed, and lamotrigine peaks for the 800 and 8000 ng/mL QCs at positions 84 and 85 were modified and were barely within acceptance limit of 15% (i.e. 14.46% and 14.62%). The integration of lamotrigine peaks in the original and modified chromatograms (in PDF format) were similar with no readily discernable reason for modification. The lamotrigine response ratios of QC 800 and 8000 in the original chromatograms (1.4068 and 13.973) were higher to those in modified chromatograms (1.392 and 13.927). GSK procedures require rejection of an analytical run when greater than 2 of 6 QCs fail.**

In their response, GSK claimed that scanned versions of chromatograms and final run summary results in PDF format preserve the content and meaning of the original electronic records and allow for a full and accurate reconstruction and evaluation of the study data. Although the PDF format can be used to verify the final drug concentrations reported in the NDA, it does not allow for an evaluation of the bioanalytical data to assure that the reported concentrations were obtained in a scientifically sound, consistent, and unbiased manner. We in DSI do not believe that GSK's claim is justified as discussed below. The following is a brief description of the chromatography acquisition and processing (*in italics*).

Primary bioanalytical data (i.e. chromatography) were captured electronically using the data acquisition and integration software (b) (4). *The resulting chromatograms were integrated electronically using a set of integration parameters to generate peak responses. Integration of individual chromatograms were sometimes modified (i.e., chromatograms were reintegrated).*

DSI Assessment: As GSK did not maintain the electronic data (b) (4) it is not possible to determine if reintegrations were justified and carried out in an unbiased manner. The PDF copies of the chromatograms fail to demonstrate the reason for reintegration and the firm did not manually document why reintegration was warranted. The example of analytical run LBI108617HUSE047, cited in the

Form 483, illustrates the limitation of using chromatograms in PDF format to evaluate the reintegration of analyte peaks. In fact, GSK was unable to explain the reason for integrations. Also, in their response GSK states that "reintegration of the QCs may not have been necessary" for the above run. Evaluating the reason and consistency of integration is critical to assuring accuracy of analytical runs, especially in this study where the inspection found that **majority of reintegrations were limited to calibrators and QCs**, and **QC results in 15% of analytical runs were borderline and barely met run acceptance criterion.**

In their response, GSK claims that the outcome of run LBI108617HUSE047 was not affected when they recalculated the data manually using the chromatograms of original integration. This claim cannot be verified for the following reasons:

1. GSK did not submit the manual calculations in their response,
2. GSK did not confirm that the calibration curve used for the manual calculations was estimated using original integrations as one of the calibrators in the run was also reintegrated without documented justification, and
3. documentation collected during the inspection indicates that QCs in run LBI108617HUSE047 failed to meet run acceptance using the original integrations.

Peak response data electronically processed by GSK's in-house software to generate calibration response and concentrations of QCs and study samples (i.e. run summary results).

DSI Assessment: GSK did not retain run summary results using data from original integrations. Therefore, the impact of original integrations on sample concentrations and the outcome of analytical runs cannot be ascertained. For example, summary result sheets from original integrations or the electronic data for run LBI108617HUSE047 would have demonstrated whether the run was acceptable using data from the original integrations of calibrators and QCs.

In spite of GSK's belief that their record keeping process is consistent with the Part 11 guidance document on electronic records, the PDF files maintained by GSK were insufficient to allow for reconstruction of the study as it was conducted and evaluation of bioanalytical data submitted to the Agency. Electronic data allows for reconstruction and evaluation of integrations and run summary results.

b. The audit trail feature (b) (4). was disabled.

GSK claims that the software's audit trail does not provide any additional benefit over manually recording changes in the study package. However, in the absence of the audit trail, GSK did not maintain a manual record to document the process of establishing integration parameters and reintegration of chromatograms for each analytical run. The inspection found that integration parameter sets used in 25% of the runs were modified in that the parameter sets were different from the integration parameters in the first analytical run (see DSI's 9/8/08 report). The PDF records maintained by GSK provide no justification for changing the integration parameters.

2. Documentation was incomplete:

a. Failure to retain PDF files of original data (i.e. chromatograms, results) for runs that were reinjected.

GSK's claim that the original injections resulted in chromatograms of "very poor quality" and the reasons for reinjection were documented, do not preclude retention of data for the original injections for the 8 analytical runs cited in DSI's earlier report. GSK agreed to retain such data in the future.

b. Failure to archive final chromatograms (i.e. chromatograms v01) for analytical run LBI108617HUSE46 in Study LBI108617.

GSK states that this was an "inadvertent omission". The final chromatograms provided at the conclusion of the inspection do not provide a clear justification for reintegrating low QCs. The original integrations of QCs indicate both low QCs failed resulting in the run not meeting the run acceptance criteria (Exhibit 1).

GSK's response to Form 483 items 2c to 2h and DSI's evaluation of them are not discussed, as they are not likely to affect the study. GSK agreed to correct the objectionable documentation practices listed in Form 483 items 2c to 2h.

Conclusions

Following review and evaluation of GSK's response, DSI maintains that that study reconstruction in its entirety was not possible and that the integrity of subject data from the analytical runs cited in DSI's memo dated 9/8/08 cannot be assured. GSK's response is unsatisfactory and does not alter DSI's conclusions stated in the memo dated 9/8/08.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Sriram Subramaniam, Ph.D.

Xikui Chen, Ph.D.

Final Classifications:
Covance Clinical Research Unit - NAI
GlaxoSmithKline, Durham, NC - OAI (Changed as the response is not acceptable).

cc:
HFD-45/RF
HFD-45/Vaccari
HFD-48/Subramaniam/Chen/Raha/Kaufman/CF
OCP/DCP1/Noory/Tandon
OND/ODEI/DNP/Ware(NDA 22-251)
HFR-SW1540/Martinez
HFR-SE1535/Frazier
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Edit: JAO
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/s/

Xikui Chen
12/2/2008 12:56:36 PM
COMPLIANCE OFFICER
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Sriram Subramaniam
12/2/2008 02:43:22 PM
PHARMACOLOGIST

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 8, 2008

FROM: Sriram Subramaniam, Ph.D.
Xikui Chen, Ph.D.
Abhijit Raha, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. Martin K. Yau 9/8/2008
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

TO: Russell G. Katz, M.D.
Director, Division of Neurology Products

SUBJECT: Review of EIRs Covering NDA 22-251, Lamictal (Lamotrigine) Orally Disintegrating Tablets, Sponsored by GlaxoSmithKline

At the request of Division of Neurology Products (DNP), the Division of Scientific Investigations (DSI) audited the clinical and analytical portions of the following bioequivalence study:

Study LBI-108617: An open-label, randomized, single-dose, parallel-group study to demonstrate bioequivalence of two formulations and the effect of food and water on one formulation of lamotrigine in healthy male and female volunteers.

The clinical and analytical portions of the study were conducted at Covance Clinical Research Unit, Dallas, TX, and GlaxoSmithKline R&D, WorldWide Bioanalysis, Drug Metabolism and Pharmacokinetics (GSK-DMPQ), Research Triangle Park, NC, respectively.

Following the inspection at GSK-DMPQ (8/25-28/08), Form FDA 483 was issued (Attachment 1). No Form FDA 483 was issued at the conclusion of the inspection at Covance Clinical Unit (6/9-13/08). The evaluation of the significant findings follows:

Clinical Site: Covance Clinical Research Unit, Dallas, TX
No significant findings were observed.

Analytical Site: GSK-DMPQ, Research Triangle Park, NC.

1. **The firm's paper and electronic audit trail systems do not allow complete reconstruction and evaluation of data processing of analytical runs.**
   a. **Electronic data was not available for analytical runs. Only PDF files of chromatograms and final results were available. PDF files do not allow for understanding the reason for reintegration and the impact of the original integration.**

   According to GSK-DMPQ, all chromatograms within an analytical run are integrated using a single set of parameters, and individual chromatograms can be further modified. GSK-DMPQ retains the chromatograms of the original and final integrations, and the final run summary results as Adobe Acrobat (*.pdf) files. These pdf files were not sufficient to assess the reason and impact of the integrations. For example, in analytical run LBI108617HUSE047 in Study LBI108617, the 30 ng/mL QC (at #83) failed, and the 800 ng/mL QC (#84) and 8000 ng/mL QC (#85) barely met the 15% acceptance limit (i.e. 14.46% and 14.62%)and lamotrigine peaks were modified (Exhibit 1). The integration of lamotrigine peaks in the original and modified chromatograms (in PDF format) for the 800 and 8000 ng/mL QCs were similar with no readily discernable or documented reason for modification (Exhibits 2 and 3). Although the run summary result for the original integrations was not available, the response ratios and concentrations of 800 and 8000 ng/mL QCs from the original chromatograms indicate that the QCs failed to meet the acceptance limits, resulting in a total 3 of 6 QCs failing in the analytical run (Exhibit 3). GSK-DMPQ procedures require rejection of an analytical run when greater than 2 of 6 QCs fail. Similar issues were noted for analytical runs LBI108617HUSE002, 014, 016, 018, 046*, 048, 049 and 050. In the aforementioned runs, a significant number of QCs were borderline acceptable and calibrators were modified. The run summary sheets for the original integrations were not available to assess the impact of original integrations. Therefore, the reason for the modification and its impact on run acceptance cannot be determined for the above mentioned runs.

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* See Item 2b for details.

b. The audit trail feature in [redacted] (b) (4) was disabled.

[redacted] (b) (4) software was used for data collection and peak integration. The software has a feature to track peak integrations. This feature was disabled by GSK-DMPQ as part of GSK's worldwide policy. GSK-DMPQ stated that they select the most appropriate set of integration parameters for each analytical run, but do not retain audit trail that tracks how they arrived at the final set of parameters. Nonetheless, the audit found that 75% of the analytical runs in the study used the same integration parameters employed in the first analytical run. But the justification for changing the parameters for the remaining 25% of the runs (Table 1) is not known.

2. **Documentation was incomplete:**

a. Failure to retain PDF files of original data (i.e. chromatograms, results) for runs that were reinjected.

The note to files indicated that analytical runs LBI108617HUSE037 through 043 were reinjected due to poor chromatography, and Run LBI108617HUSE018 was reinjected as the 96-well autosampler plate was oriented incorrectly. GSK-DMPQ did not retain the chromatograms and results of the original injections for the above runs. Therefore, although the reinjected runs were successful, the justification for reinjection cannot be confirmed. These reinjections are also not documented on the HPLC/Mass spec user logs.

b. Failure to archive final chromatograms (i.e. chromatograms v01) for analytical run LBI108617HUSE46 in Study LBI108617.

Peak integrations for both low QCs were modified, however, modified chromatograms were not retained for this run. The original chromatograms indicate that both low QCs failed resulting in the run not meeting the run acceptance criteria (Exhibit 4).

c. Failure to retain PDF files for validation run G1267119HUSEVAL001, which is shown on the LC/MS equipment log 99/AEQUIP/0021/00 as having been analyzed on 09Feb07 using HPLC column A.

GSK-PDF did not retain this validation run. The purpose and the reason for rejection are unknown.

GSK-DMPQ was informed that all analytical data should be retained, irrespective of whether the analyses were successful or not.

Other documentation Issues (Form 483 Items 2d to 2h)
In addition, there were other documentation problems, including no documentation of handling of stability samples and working solutions used to prepare calibrators, retrospective corrections to preprinted forms without justification, and incomplete instrument logs. Although these findings are not likely to affect the study, GSK-DMPQ should assure that documentation is contemporaneous, accurate and complete.

Conclusions

Following the above inspection, DSI concludes that reconstruction of analytical run in its entirety is not possible because the firm retained pdf copies of the chromatograms without also retaining the electronic data generated by the chromatography acquisition and integration software. For this reason, the integrity of numerous study runs was not assured as the basis for modifying the integration of individual chromatograms (item 1a) and whole batches (item 1b) cannot be assessed in the absence of the electronic data and audit trail. In particular, the following runs are affected by this issue:

i. The accuracy of analytical runs LBI108617HUSE002, 014, 016, 018, 046, 047, 048, 049 and 050 cannot be assured (Item 1a). GSK should provide justification for the necessity of modifying chromatograms and its impact on run acceptance for the above mentioned runs.

ii. To assure the accuracy of runs listed in Table 1, GSK should justify the use of different integration parameters in the analytical runs (Item 1b).

iii. The necessity for the reinjection of analytical runs LBI108617HUSE018, and 037 through 43 cannot be determined as the data for the original injections were not retained. Data from the reinjected runs are acceptable for the study provided GSK can present documented justification for not accepting the original injections for runs LBI108617HUSE018, and 037 through 43.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Sriram Subramaniam, Ph.D.

Xikui Chen, Ph.D.

Abhijit Raha, Ph.D.

Final Classifications:
Covance Clinical Research Unit - NAI
GlaxoSmithKline, Durham, NC - VAI

cc:
HFD-45/RF
HFD-45/Vaccari
HFD-48/Subramaniam/Chen/Raha/Kaufman/CF
OCP/DCP1/Noory/Uppoor
OND/ODEI/DNP/Ware(NDA 22-251)
HFR-SW1540/Martinez
HFR-SE150/Hubbard
Draft: AR, XC 9/3/08
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/s/

Xikui Chen
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COMPLIANCE OFFICER
Dr. Yau (Acting for Dr. Viswanathan) signed the paper copy on 9/8/2008.