

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-115

OTHER REVIEW(S)

SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 22-115
APPLICANT	GLAXOSMITHKLINE USA
DRUG NAME	Lamictal XR
SUBMISSION DATE	August 28, 2008
SEALD REVIEW DATE	April 7, 2009
SEALD REVIEWER(S)	Abiola Olagundoye, PharmD
	This review does not identify all guidance-related labeling issues and all best practices for labeling. We recommend the review division become familiar with those recommendations. This review does attempt to identify all aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57.

47 Page(s) of Draft Labeling have been Withheld in Full following this page as B4 (CCI/TS)

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/s/

Abiola Olagundoye
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M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: February 4, 2009

TO: Dorothy Demczar, Regulatory Health Project Manager
Leonard Kapcala, M.D., Medical Officer
Division of Neurology Drug Products

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-115

APPLICANT: GlaxoSmithKline

DRUG: Lamictal XR (lamotrigine extended release) tablets

NME: No

THERAPEUTIC CLASSIFICATION: 6 month Review

INDICATION: Adjunctive therapy in subjects with partial seizures

CONSULTATION REQUEST DATE: September 15, 2008

DIVISION ACTION GOAL DATE: February 28, 2009

PDUFA DATE: February 28, 2009

I. BACKGROUND:

GlaxoSmithKline received an approvable letter for NDA 22-115 on September 21, 2007, requesting that the sponsor re-evaluate data obtained from foreign sites participating in LAM100034. As a result, the sponsor reported that it conducted a comprehensive data verification audit on all subjects at all study sites and reported their findings to the Agency. The sponsor has resubmitted a drug application after representing that the sponsor audited all of the sites relative to efficacy, safety, and exposure data.

The review division requested inspection of protocol LAM100034: “A multi-center, double-blind, randomized, parallel group, evaluation of Lamictal extended-release (LTG XR) adjunctive therapy in subjects with partial seizures. The sponsor resubmitted results from protocol LAM100034 in support of NDA 22-115.

The primary objective of study protocol LAM100034 was to assess the efficacy of once daily adjunctive therapy with LTG extended release in subjects with partial seizures. The primary endpoint was to determine the percent change from baseline in partial seizure frequency during the entire double-blind treatment phase (week 19).

The inspection targeted four foreign clinical investigators who enrolled a relatively large number of subjects.

II. RESULTS (by protocol/site):

Name of CI, site #and location	Protocol and # of subjects	Inspection Dates	Final Classification
Gagik Avakian, M.D. Neurological Neurosurgery Department RGMU, Leninskiy Pr., 8 Moscow Russian Federation 117049 Site 079166/021276	Protocol LAM100034 7 subjects	11/10-11/08	Pending (Preliminary classification NAI)
Elena Belousova, M.D. Moscow Pediatrics and Children Surgery Institute Str., Moscow Russian Federation 125412 Site 079171/021281	Protocol LAM100034 6 subjects	11/12-13/08	Pending (Preliminary classification NAI)
Sergev Gromov, M.D. St. Petersburg Research Psychneurological Institute Named after Bekhterev, Bekhtereva str.3 St. Petersburg, Russian Federation 193019 Site 079168/012278	Protocol LAM10034 5 subjects	11/17-18/08	Pending(preliminary classification NAI)

Name of CI, site #and location	Protocol and # of subjects	Inspection Dates	Final Classification
Nadezhda Korolova.M.D. Human Brain Institute, 9 Academician Pavlov str. St. Petersburg, Russian Federation 19376 Site 079165/021275	Protocol LAM100034 8 subjects	11/19-20/08	Pending (preliminary classification NAI)

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations for regulations. Data unreliable.

Pending = Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending.

Protocol LAM100034

1. Gagik Avakian, M.D.

Moscow

Russian Federation

The EIR for this inspection is currently pending. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the EIR.

At this site, a total of 7 subjects were screened; 7 subjects were randomized and 7 subjects completed the study. Six subjects rolled over into the open-label phase of the study, and one subject refused to enter the open label phase due to gastric pain. Informed consent for all subjects was verified. The medical records for all subjects' files were reviewed including drug accountability, concomitant medication, diaries, laboratory results and adverse events. There were no subjects enrolled prior to IRB approval of the protocol and informed consent.

The medical records/source data for all subjects were reviewed in depth, and the source data were compared to case report forms and data listings for primary and secondary efficacy endpoints. In general, the records reviewed were accurate in terms of data entries and reporting of adverse events. There were no limitations to this inspection.

The data appear acceptable in support of the pending application.

2. Elena Belousova, M.D.
Moscow
Russian Federation

The EIR for this inspection is currently pending. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the EIR

At this site, a total of 7 subjects were screened; one subject was reported as screen failure, 6 subjects enrolled and completed the study. Informed consent for all subjects was verified.

The medical records/source data for 6 subjects were reviewed in depth including drug accountability records, and source documents were compared to data listings for primary efficacy endpoints and adverse events. In general, the records reviewed were accurate in terms of data entries and reporting of adverse events. Our investigation found no significant problem that would impact the results. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application.

3. Sergev Gromov, M.D.
St. Petersburg
Russian Federation

The EIR for this inspection is currently pending. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the EIR

At this site, a total of 6 subjects were screened; one subject was reported as screen failure. Five subjects were randomized; 3 subjects completed the study, and one subject entered the open label. Informed consent for all subjects was verified.

The medical records/source data for 6 subjects were reviewed in depth including drug accountability records, concomitant medications, laboratory results, diaries and source documents were compared to data listings for primary efficacy endpoints and adverse events. Subject 2095 withdrew from the study due to adverse events (tremor and weakness). Subject 2094 died unexpectedly and the cause of death was not known to the FDA team during the inspection. In general, the records reviewed were accurate in terms of data entries and reporting of adverse events. Our investigation found no significant problem that would impact the results. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application.

4. Nadezhda Korolova, M.D.
St. Petersburg
Russian Federation

The EIR for this inspection is currently pending. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the EIR

At this site, a total of 9 subjects were screened; one subject was reported as screen failure; two subjects withdrew consent; 8 subjects were randomized (2 received LTG and 6 received placebo) and six completed the study and entered the open-label phase of the study. Informed consent for all subjects was verified.

The medical records/source data for 6 subjects were reviewed in depth including drug accountability records, concomitant medication, laboratory results, diaries and source documents were compared to data listings for primary efficacy endpoints and adverse events. In general, the records reviewed were accurate in terms of data entries and reporting of adverse events. Our investigation found no significant problem that would impact the results. There were no known limitations to this inspection.

The data appear acceptable in support of the pending application

OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspection of Drs. Avakian, Belousova, Gromov and Korolova revealed no significant problems that would adversely impact data acceptability. The EIRs for these inspections are currently pending. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the EIRs. The data submitted from the inspected sites are acceptable in support of the pending application.

{See appended electronic signature page}

Antoine El-Hage, Ph.D.
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/s/

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MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: September 21, 2007

TO: Teresa Wheelous, Regulatory Project Manager
Leonard Kapcala, M. D., Medical Officer
Division of Neurology Products, HFD-120

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
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Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-115

APPLICANT: GlaxoSmithKline.

DRUG: Lamictal XR (lamotrigine extended release) tablets

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Adjunctive therapy of partial seizures in subjects 13 years of age and older.

CONSULTATION REQUEST DATE: June 15, 2007

DIVISION ACTION GOAL DATE: September 1, 2007

PDUFA DATE: September 22, 2007

I. BACKGROUND:

The review division requested inspection of protocol LAM100034: "A multicenter, double-blind, randomized, parallel-group evaluation of Lamictal extended-release adjunctive therapy in subjects with partial seizures." The sponsor submitted results from the following two sites in support of NDA 22-115. The inspections targeted two clinical investigators who enrolled a relatively large number of subjects.

The following two clinical investigators were selected for data audit in support of this application:

Site# 019591/017850 (Sang-Ahm Lee, M.D. – South Korea)

Site# 026966/017849 (Sang- Kun Lee, M.D. – South Korea)

II. RESULTS (by protocol/site):

Name of CI and site #, if known	Country	City, State	Protocol	Inspection Date	EIR Received Date	Final Classification
Sang-Ahm Lee, M.D. Site #019591/017850	South Korea	Seoul	LAM100034	9/14/07	pending	VAI*
Sang-Kun Lee, M.D Site# 026966/017849	South Korea	Seoul	LAN100034	9/10/07	pending	VAI*

* based on e-mail summary information or telephone call from the field investigators.

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

Protocol LAM 100034

1. Sang-Ahm Lee, M.D.

Observations noted below are based on a telephone conversation with the FDA field investigator; the EIR for this inspection is currently pending. Detailed information is not available to this reviewer at this time. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the EIR.

At this site a total of 19 subjects were screened, 16 subjects were randomized, and 3 subjects were reported as screen failures. Adverse events experienced by 6 subjects were not reported, protocol deviations were found for 5 subjects, one subject was non-compliant, and 4 subjects completed the study. All subjects were verified to have signed informed consent prior to entry into the study. The medical records for 19 subjects were reviewed in depth and compared to case report forms and data listings for primary efficacy end points and adverse events. Although no FDA 483 was issued, the investigation found transcription errors in source documents in terms of seizure date and count, protocol violations, and non- reporting of adverse events when compared to case report forms and data listings.

The medical records reviewed disclosed deficiencies that may reflect negatively on the reliability of the data. There were no known limitations to this inspection.

In light of the limited inspectional findings, it is not clear at this time whether the inspectional findings may reflect negatively on the acceptability of the study data.

2. Sang-Kun Lee, M.D.

Observations noted below are based on a telephone conversation with the FDA field investigator; the EIR for this inspection is currently pending. Detailed information is not available to this reviewer at this time. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the EIR.

At this site a total of 11 subjects were screened, 10 subjects were randomized, one subject withdrew consent, 2 subjects discontinued for adverse events, and 7 subjects completed the study. Informed consent for all subjects was verified and no regulatory violations were found. The medical records for 7 subjects were reviewed in depth and compared to case report forms and data listings for primary efficacy end points and adverse events. Although no FORM FDA 483 was issued, the investigation found transcription errors in source documents when compared to case report forms and data listings.

The study records reviewed disclosed transcription errors and corrections, non-reporting of adverse events, and changes in seizure counts. It is not clear at this time whether the inspectional findings may reflect negatively on the reliability of the data. There were no known limitations to this inspection.

OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspection of Dr. Sang-Ahm Lee revealed transcription errors/corrections, protocol violations and under-reporting of adverse events. In aggregate, these deviations may impact data acceptability.

The inspection of Dr. Sang-Kun Lee revealed transcription errors/corrections, and under-reporting of adverse events. In aggregate, these deviations may impact data acceptability.

The sponsor's recent audit findings and our inspectional observations raises concerns about the quality of the data at both sites. Until we review the EIRs, expected by late October, it is difficult to have confidence in the data generated to support the pending application. At that time we will issue a final assessment and recommendation.

In light of the limited inspectional information available and our inability to assess data acceptability at this time, the review division may wish to exclude the results from the two sites in their final analysis. It is our understanding that the sponsor is planning to correct the database and conduct analysis to determine whether to retain part of or exclude the results from the two sites.

Based on the recent findings, the review division should consider additional foreign sites for inspection in order to verify the sponsor's claim that there are no additional sites with similar findings.

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