

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:
22-509**

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22509
Priority or Standard	Standard
Submit Date(s)	March 31, 2009
Received Date(s)	March 31, 2009
PDUFA Goal Date	January 31, 2010
Division / Office	DNP
Reviewer Name(s)	Steven Dinsmore, D.O.
Review Completion Date	1/28/2010
Established Name	Lamotrigine XR
(Proposed) Trade Name	Lamictal XR
Therapeutic Class	Anticonvulsant
Applicant	GlaxoSmithKline (GSK)
Formulation(s)	XR = extended release
Dosing Regimen	Oral, once daily
Indication(s)	Adjunctive treatment for primary generalized tonic clonic (PGTC) seizures
Intended Population(s)	Adults and Children age 13 and above

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT	10
1.1	Recommendation on Regulatory Action	10
1.2	Risk Benefit Assessment.....	10
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies .	10
1.4	Recommendations for Postmarket Requirements and Commitments	11
2	INTRODUCTION AND REGULATORY BACKGROUND	11
2.1	Product Information	11
2.2	Tables of Currently Available Treatments for Proposed Indications	13
2.3	Availability of Proposed Active Ingredient in the United States	16
2.4	Important Safety Issues With Consideration to Related Drugs.....	16
2.5	Summary of Presubmission Regulatory Activity Related to Submission	16
2.6	Other Relevant Background Information	18
3	ETHICS AND GOOD CLINICAL PRACTICES.....	18
3.1	Submission Quality and Integrity	18
3.2	Compliance with Good Clinical Practices	18
3.3	Financial Disclosures.....	18
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES	20
4.1	Chemistry Manufacturing and Controls	20
4.2	Clinical Microbiology.....	21
4.3	Preclinical Pharmacology/Toxicology	21
4.4	Clinical Pharmacology	21
4.4.1	Mechanism of Action.....	21
4.4.2	Pharmacodynamics.....	21
4.4.3	Pharmacokinetics.....	21
5	SOURCES OF CLINICAL DATA.....	22
5.1	Tables of Studies/Clinical Trials	22
5.2	Review Strategy	22
5.3	Discussion of Individual Studies/Clinical Trials.....	23
6	REVIEW OF EFFICACY	26
	Efficacy Summary.....	26
6.1.1	Methods	27
6.1.2	Demographics.....	30
6.1.3	Subject Disposition.....	33
6.1.4	Analysis of Primary Endpoint(s).....	35
6.1.5	Analysis of Secondary Endpoints(s)	37
6.1.6	Other Endpoints	41
6.1.7	Subpopulations	43

6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	47
6.1.10	Additional Efficacy Issues/Analyses.....	47
7	REVIEW OF SAFETY.....	52
	Safety Summary.....	52
7.1	Methods.....	52
7.1.1	Studies/Clinical Trials Used to Evaluate Safety.....	52
7.1.2	Categorization of Adverse Events.....	54
7.1.3	Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence.....	56
7.2	Adequacy of Safety Assessments.....	58
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations.....	58
7.2.2	Explorations for Dose Response.....	61
7.2.3	Special Animal and/or In Vitro Testing.....	61
7.2.4	Routine Clinical Testing.....	61
7.2.5	Metabolic, Clearance, and Interaction Workup.....	61
7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class..	61
7.3	Major Safety Results.....	62
7.3.1	Deaths.....	62
7.3.2	Nonfatal Serious Adverse Events.....	63
7.3.3	Dropouts and/or Discontinuations.....	72
7.3.4	Significant Adverse Events.....	79
7.3.5	Submission Specific Primary Safety Concerns.....	79
7.4	Supportive Safety Results.....	79
7.4.1	Common Adverse Events.....	79
7.4.2	Laboratory Findings.....	84
7.4.3	Vital Signs.....	89
7.4.4	Electrocardiograms (ECGs).....	89
7.4.5	Special Safety Studies/Clinical Trials.....	93
7.4.6	Immunogenicity.....	93
7.5	Other Safety Explorations.....	93
7.5.1	Dose Dependency for Adverse Events.....	93
7.5.2	Time Dependency for Adverse Events.....	93
7.5.3	Drug-Demographic Interactions.....	93
	Sex	94
7.5.4	Drug-Disease Interactions.....	94
7.5.5	Drug-Drug Interactions.....	97
7.6	Additional Safety Evaluations.....	97
7.6.1	Human Carcinogenicity.....	97
7.6.2	Human Reproduction and Pregnancy Data.....	97
7.6.3	Pediatrics and Assessment of Effects on Growth.....	97
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	98
7.7	Additional Submissions / Safety Issues.....	99

8	POSTMARKET EXPERIENCE.....	99
9	APPENDICES	117
9.1	Literature Review/References	119
9.2	Labeling Recommendations	119
9.3	Advisory Committee Meeting.....	119

Table of Tables

Table 2-1	Simplified synopsis of drug interactions properties of common AEDs
Table 2-2	Overview of adverse effects of AEDs
Table 2-3	Preferred first-line AEDs for new-onset and refractory epilepsy In adults
Table 2-4	Dosages and effective plasma concentrations of often used AEDs for adults
Table 3-1	Studies covered under the rule*
Table 6-1	Sample Size- Power
Table 6-2	Study Population Demographics
Table 6-3	Baseline Seizure Data (ITT Population: Study LAM100036)
Table 6-4	Most common (Incidence of Greater Than or Equal to 5% Of Subjects in Either Treatment Group) Previous AED Therapy (ITT Population: Study LAM100036)
Table 6-5	Number of AED Concomitant Medications and AED Group (ITT Population: Study LAM100036)
Table 6-6	Concurrent AED Therapy- US / Non-US sites
Table 6-7	Subject Accountability (Safety Population: Study LAM100036)
Table 6-8	Enrolment by Country
Table 6-9	Analysis of the Median Percent Reduction in PGTC Seizure Frequency during the Entire Treatment Phase (ITT Population: Study LAM100036)
Table 6-10	Summary of Analysis of Percent Change from Baseline in Weekly Seizure Frequency, ITT Population, All sites
Table 6-11	Summary of Analysis of Percent Change from Baseline in Weekly Seizure Frequency by US Sites, ITT Population
Table 6-12	Analysis of the Percent Reduction in PGTC Seizure Frequency during Escalation, Maintenance, and the Last 8 Weeks of Maintenance (ITT Population: Study LAM100036)
Table 6-13	Percent Reduction from Baseline in PGTC Seizure Frequency (ITT Population: Study LAM100036)
Table 6-14	Analysis of Time (in Weeks) to 50% Reduction in Seizure Frequency for PGTC Seizures (ITT Population: Study LAM100036)
Table 6-15	Summary of Analysis of Investigator's Global Assessment, ITT Population
Table 6-16	Investigator's Global Assessment and Subject Satisfaction at Study Conclusion (ITT Population: Study LAM100036)
Table 6-17	Summary of Analysis of Percent Change from Baseline in Weekly Seizure Frequency by Non-US Sites, ITT Population
Table 6-18	Summary of Percent Change from Baseline in Weekly Seizure Frequency by US Sites, ITT Population

Table 6-19	Summary of Percent Change from Baseline in Weekly Seizure Frequency by Non-US Sites, ITT Population
Table 6-20	Distribution of Lamictal XR dose during DB maintenance interval according to concomitant AED category
Table 7-1	Clinical Studies Providing Safety Information for Lamictal XR in the ISS
Table 7-2	Listing of Studies Included in the Current Submission and in NDA 22-115
Table 7-3	Definition of an Adverse Event
Table 7-4	ISS Study Groupings
Table 7-5	Exposure to 24 / 52 Weeks by Gender and Age
Table 7-6	Exposure to Study Drug by Modal Dose for All Clinical Studies.
Table 7-7	Demographic Characteristics – Controlled Adjunctive Studies (LAM100036 and LAM100034, Individual and Pooled Double-blind Treatment Phases)
Table 7-8	Demographics for the Single Dose Healthy Volunteer Studies (LAM102611, LAM10014, LAM10005 [Part A], LEP111102, and LAM105379)
Table 7-9	Time and Events Schedule- Studies LAM100034 and LAM100036
Table 7-10	Deaths reported in Lamictal XR development Program
Table 7-11	Summary of TESAEs for the Controlled Adjunctive Studies (LAM100036 and LAM100034, Individual and Pooled Double-blind Treatment Phases)
Table 7-12	Summary of TESAEs Reported by >1 Subject for All Clinical Studies (LAM100036, LAM100034, and LAM30055)
Table 7-13a	Previously Reported SAEs (NDA22115) from All phase III and ongoing studies
Table 7-13b	SAEs not previously reported to the NDA22509 safety database in NDA221215 from All phase III and ongoing studies
Table 7-14	Listing of All TESAEs for Ongoing Clinical Studies (LAM30055, LEP105972, and LEP108937)
Table 7-15	Summary of Treatment-Emergent Serious Adverse Events for All Clinical Studies
Table 7-16	Summary of All TEAEs Leading to Withdrawal for the Controlled Adjunctive Studies (LAM100036 and LAM100034, Individual and Pooled Double-blind Treatment Phases)
Table 7-17	Narratives All Phase III and Ongoing Study Subjects with Narratives for AEs Leading to Withdrawal- not including safety update (ISS)
Table 7-18	Summary of Treatment-Emergent Adverse Events Leading to Withdrawal in All Clinical Studies, Safety Update compared to ISS
Table 7-19	Summary of the Most Common TEAEs ($\geq 2\%$) with an Onset

	in Escalation Phase for the Controlled Adjunctive Studies (LAM100036 and LAM100034, Pooled Double-blind Treatment Phases)
Table 7-20	Summary of the Most Common TEAEs ($\geq 2\%$) with an Onset in Maintenance Phase for the Controlled Adjunctive Studies (LAM100036 and LAM100034, Pooled Double-blind Treatment Phases)
Table 7-21	Summary of the Most Common TEAEs ($\geq 5\%$) for the Controlled Adjunctive Studies (LAM100036 and LAM100034, Individual and Pooled Double-blind Treatment Phases)
Table 7-22	Summary of the Most Common TEAEs ($\geq 5\%$) for All Clinical Studies (LAM100036, LAM100034, and LAM30055)
Table 7-23	Summary of the Most Common Treatment-Emergent Adverse Events ($\geq 5\%$) in All Clinical Studies grouping (LAM100036, LAM100034 and LAM30055), 120 day Safety Update
Table 7-24	Clinical Laboratory Shift Tables for all Subjects- LAM100036 & LAM10034
Table 7-24a	Subjects with hepatic function values in range of clinical concern.
Table 7-24b	Hematology Changes from Baseline to Low or to High Relative to the Reference Range for the Controlled Adjunctive Studies (LAM100036 and LAM100034, Pooled Double-blind Treatment Phases)
Table 7-25	Outlier Criteria for Observed Values and Increases from Baseline for QTcB and QTcF
Table 7-26	Summary of Change from Screening to Endpoint in ECG Values for the Controlled Adjunctive Studies
Table 7-27	ECG Change from Baseline Outliers for QTc for the Controlled Adjunctive Studies (LAM100036 and LAM100034, Pooled Double-blind Treatment Phases)
Table 7-28	Summary of ECG Outliers for QTc by Visit for Controlled Adjunctive Studies
Table 7-29	Summary of Treatment Effect on Incidence: (LAMICTAL XR Dose Group - PLACEBO) for Treatment Emergent Adverse Events with Onset in Escalation Phase
Table 7-30	Summary of Treatment Effect on Incidence: (LAMICTAL XR Dose Group - PLACEBO) for Treatment Emergent Adverse Events with Onset in Escalation or Maintenance Phase
Table 7-31	Summary of Treatment Effect on Incidence: (LAMICTAL XR – PLACEBO) by AED Groups For Treatment Emergent Adverse Events with Onset in Escalation Phase
Table 7-32	Summary of Treatment Effect on Incidence: (LAMICTAL XR -PLACEBO) by AED Groups For Treatment Emergent Adverse Events with Onset in Escalation or Maintenance Phase
Table 8-1	Summary of the Cause of Death

Table 8-2	Incidence of Reports (per 10,000 Patient-years) of Serious Skin Rash
Table 8-3	Incidence Rate (per 10,000 Patient-years) of Hypersensitivity Reaction
Table 8-4	Incidence Rate (per 10,000 Patient-years) of Blood Dyscrasia
Table 8-5	Summary of the Number of Suicide and Suicide-related Reports
Table 8-6	EB05 Signal Scores for Suicide Related Events for lamotrigine from AERS
Table 8-7	Datamining run Trade Name (S), Lamictal, Lamictal CD

Table of Figures

Figure 1 (figure 2-1) Formulation Design Schematic of a Lamotrigine Extended Release Tablet	13
Figure 2 (figure 5-1) LAM100036 Study Design	24
Figure 3 (figure 6-1) Time to 50% Reduction in Seizure Frequency (ITT Population: Study LAM100036)	41
Figure 4 (figure 6-2) Lamotrigine Concentrations in LAM100034 & LAM100036 Adults vs Adolescents.....	46
Figure 5 (figure 8-1) Sponsor Analysis EB05 lamotrigine and Comparator AEDs to Quarter 1, 2005.....	102
Figure 6 (figure 8-2) Incidence of Reports (per 10,000 Patient years) of Serious Skin Rash for the US and the Rest of the World (ROW).....	103
Figure 7 (figure 8-3) Incidence of Reports (per 10,000 Patient Years) of Hypersensitivity Reactions for the US and the Rest of the World (ROW)	105
Figure 8 (figure 8-4) Incidence Rate (per 10,000 Patient-years) of Blood Dyscrasias for the US and Rest of World (ROW)	107
Figure 9 (figure 8-5) EB05 for sudden death, comparison of anticonvulsants.....	109
Figure 10 (figure 8-6) Lamictal Sudden Death / Year.....	110
Figure 11 (figure 8-7) EB05 value by year for serious rash.....	111
Figure 12 (figure 8-8) EB05 values by year for PTs related to Hypersensitivity Reaction	112
Figure 13 (figure 8-9) EB05 values by year for PTs related to Hepatic dysfunction	112
Figure 14 (figure 8-10) EB05 values by Year for Blood Dyscrasia Preferred terms	113
Figure 15 (figure 8-11) EB05 values by Year for Suicide Attempt.....	113

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Approval is recommended as follows: Lamictal XR for adjunctive therapy in treatment of PGTC seizures in patients ≥ 13 years of age.

Study LAM10036 revealed a positive result for the primary efficacy endpoint, the median percent change from Baseline in average weekly PGTC seizure frequency during the entire double-blind treatment phase. Analysis of the ITT population yielded an estimated difference of 31.6% in the median percent reduction between the placebo and lamotrigine XR cohort with a $p < 0.0001$, 95% CI (15.8, 48.1) [Table 6-9](#). The study results demonstrated that lamotrigine XR was statistically superior to placebo for the primary efficacy endpoint of median reduction of primary generalized tonic-clonic seizures from baseline.

1.2 Risk Benefit Assessment

Serious skin rash is the primary threat in the use of Lamictal. This risk is well defined and present in a boxed warning. The array of both serious and common adverse events seen with the use of Lamictal is similar to the community of other anticonvulsants in use. On the benefit side of the equation this product has proven to be an effective anticonvulsant agent and has an extensive established record of successful clinical use. The availability of this agent in the armamentarium for the treatment of epilepsy outweighs the risks of use.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

The Lamictal XR label will contain a comprehensive Medguide, including suicide risk labeling, the most recent safety signal of concern. In addition the sponsor defines a pharmacovigilance plan to capture new safety signals over time using disproportionality analysis. In addition the sponsor identifies ongoing programs to monitor congenital anomalies, hepatotoxicity and dispensing errors. The sponsor has initiated a program to work with dispensing pharmacies to prevent medication errors when drugs with LASA names are encountered (Look-alike, Sound-alike) This is called the RxSafety Advisor program. These measures in addition to labeling currently in place represent an acceptable status of risk evaluation and mitigation for this product.

1.4 Recommendations for Postmarket Requirements and Commitments

No programs recommended

2 Introduction and Regulatory Background

2.1 Product Information

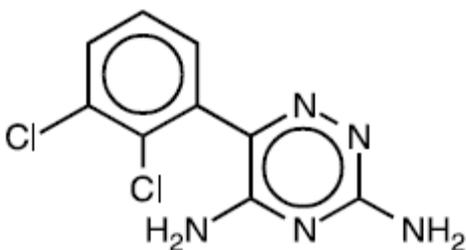
Generic Name: lamotrigine

Chemical name: 3,5-diamino-6-(2,3-dichlorophenyl)-s-triazine

Molecular formula: C₉H₇N₅Cl₂

Molecular Weight: 256.09

Structural Formula



LAMICTAL® (lamotrigine), a phenyltriazine anticonvulsant, was first approved internationally (Ireland) in 1990, and subsequently in the US in December 1994 (NDA 20-241) for adjunctive treatment of partial seizures in adults. Subsequent to this approval, LAMICTAL was approved in August 1998 for adjunctive treatment of the generalized seizures of Lennox-Gastaut syndrome in pediatric (2-16 years of age) and adult subjects (along with a chewable dispersible tablet formulation; NDA 20-764), in December 1998 for conversion to monotherapy in adults receiving therapy with a single enzyme-inducing antiepileptic drug (EIAED), and in January 2003 as adjunctive treatment for partial seizures in pediatric subjects (2-16 years of age). LAMICTAL was approved in June 2003 for long-term management of mood episodes in subjects with Bipolar I disorder and in January 2004 for conversion to monotherapy from valproate (VPA) in adult subjects with partial seizures. LAMICTAL was approved for primary generalized tonic-clonic (PGTC) seizures in September 2006 in adults and pediatric subjects (2-16 years of age). Most recently Lamictal XR was approved on May 29, 2009 for adjunctive treatment of partial onset seizures with or without secondary generalization in patients ≥13 years of age.

Lamotrigine is currently marketed as immediate-release (IR) compressed (LAMICTAL Tablets) or chewable dispersible tablets (LAMICTAL Chewable Dispersible Tablets). The current dosing recommendations in the US for these formulations are twice daily for concurrent administration with EIAEDs or as monotherapy and once or twice daily administration with valproic acid (VPA). The LAMICTAL XR Extended-Release Tablet is a new, enteric coated, [DiffCORE™](#) formulation that may allow subjects with seizures to be on a once daily dosing regimen. Lamictal XR has been marketed in the US since approval in May of 2009. This new formulation slows the dissolution rate of lamotrigine by releasing ^{(b) (4)} or more of drug over a period of 12-15 hours, compared to a 15 minute time period for the immediate-release formulations. This modification results in a slower rate of absorption, a reduction in the peak to trough fluctuations and fewer fluctuations in lamotrigine concentrations over a 24-hour interval for LAMICTAL XR, compared to the immediate-release formulations. Administration of LAMICTAL XR may improve compliance due to once a day as opposed to twice a day dosing.

Figure 2-1 Formulation Design Schematic of a Lamotrigine Extended Release Tablet



Figure 1

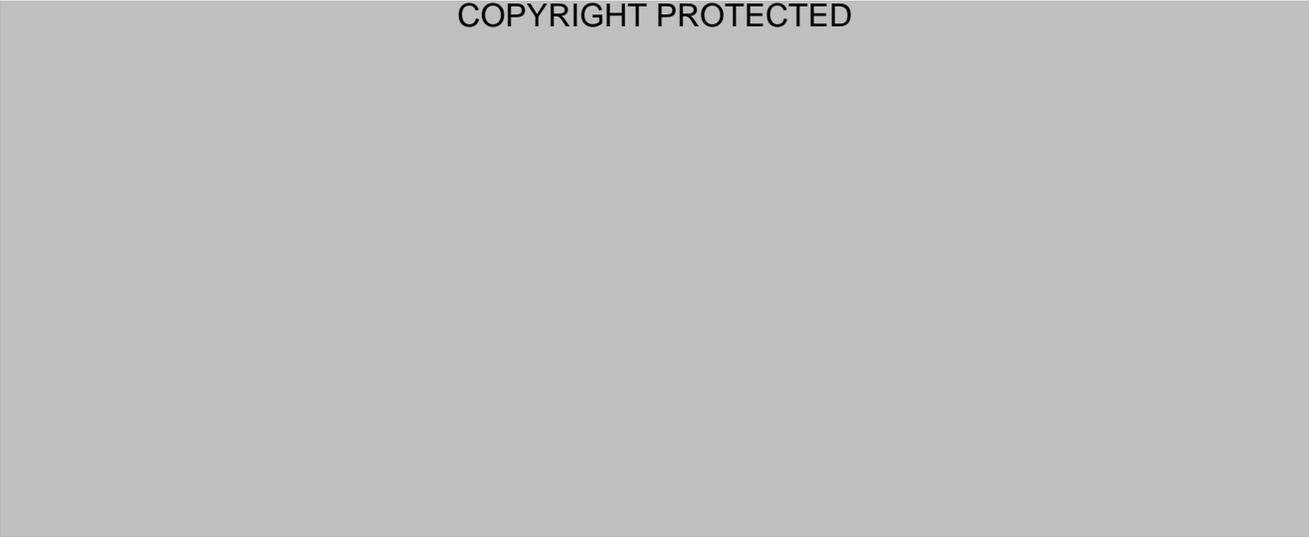
2.2 Tables of Currently Available Treatments for Proposed Indications

The following antiepileptic drugs (AEDs) have been approved by regulatory agencies in the United States and Europe: acetazolamide, carbamazepine, clonazepam, clorazepate, ethosuximide, ethotoin, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, mephenytoin, methsuximide, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, tiagabine, topiramate, trimethadione, valproate, vigabatrin, and zonisamide. The following additional agents are used mainly for the acute therapy of status epilepticus: diazepam, fosphenytoin, lorazepam, midazolam, and propofol.

Pragmatically, the choice of AED among first-line agents needs to be individualized mainly on the basis of the patient profile, including the efficacy for the seizure or the epilepsy syndrome, tolerability, safety, ease of use, pharmacokinetics (in consideration of the current or likely future need for concomitant medication for comorbidity), and finally cost. While AEDs provide satisfactory control of seizures for most patients with epilepsy a sizable proportion of patients continue to have some seizures. Thus, about 65% of patients with new-onset epilepsy initially respond with complete control (seizure recurrence occurs in 5%, of these) and 35% have uncontrolled epilepsy¹

The interactions and adverse effects profile of lamotrigine compared to other available anticonvulsants is illustrated in tables [2-1](#) and [2-2](#). Preferred first line AEDs for new onset and refractory epilepsy in adults as well as plasma and dosing characteristics are shown in tables [2-3](#) and [2-4](#)!

COPYRIGHT PROTECTED



¹ Schmidt D. Drug treatment of epilepsy: Options and limitations. *Epilepsy & Behavior* 2009;15:56-65.

Table 2-2

Overview of adverse effects of AEDs

COPYRIGHT MATERIAL

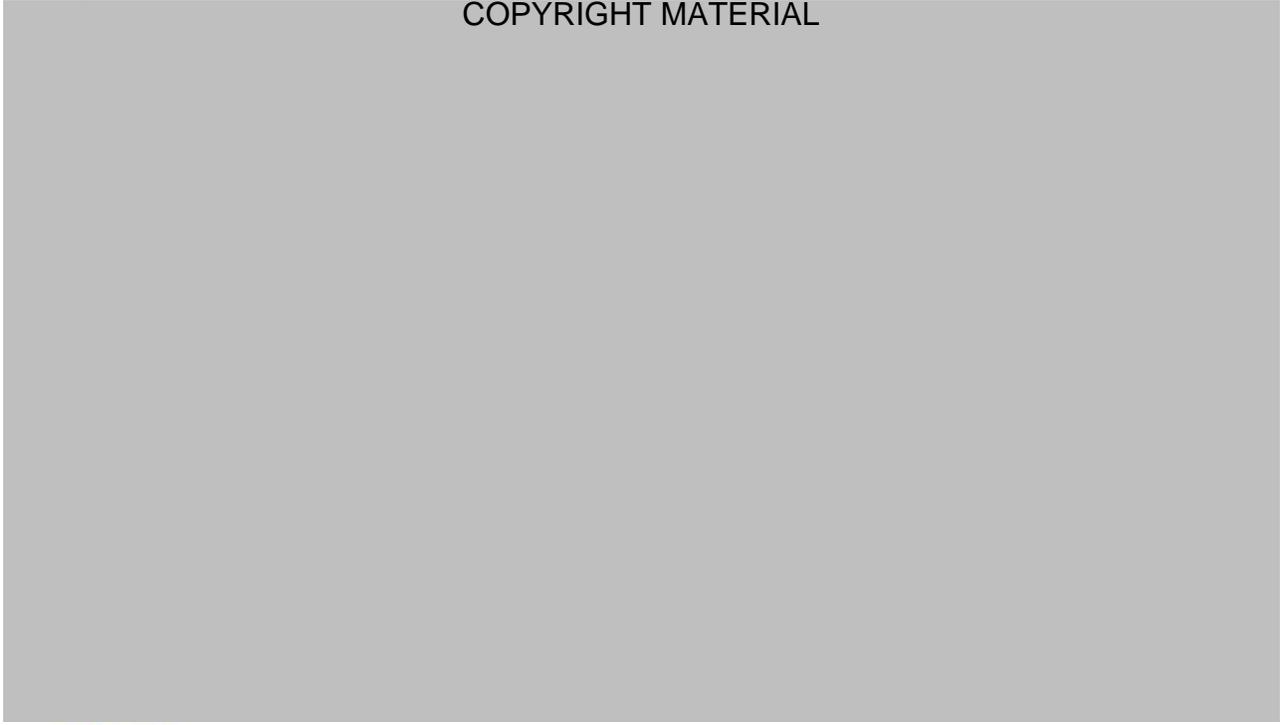


Table 2-3

Preferred first-line AEDs for new-onset and refractory epilepsy in adults

COPYRIGHT PROTECTED

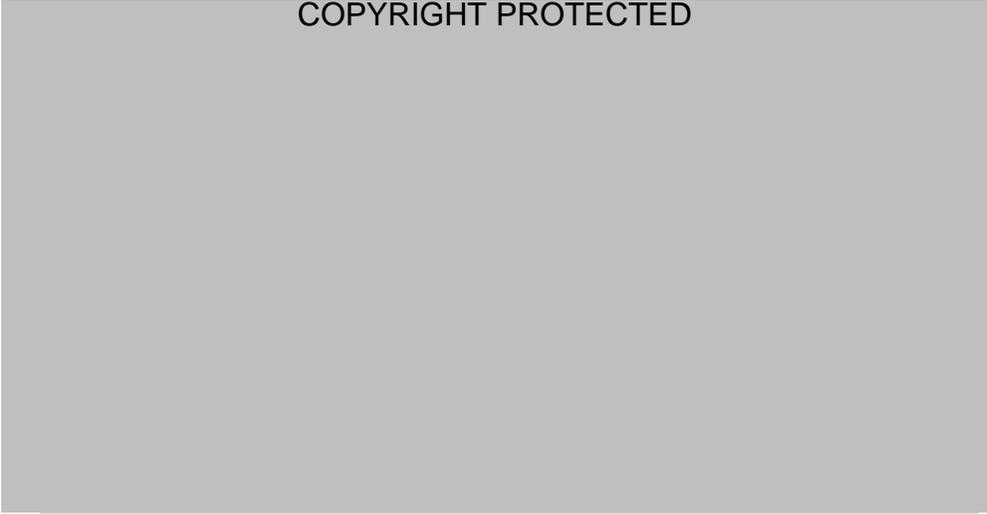
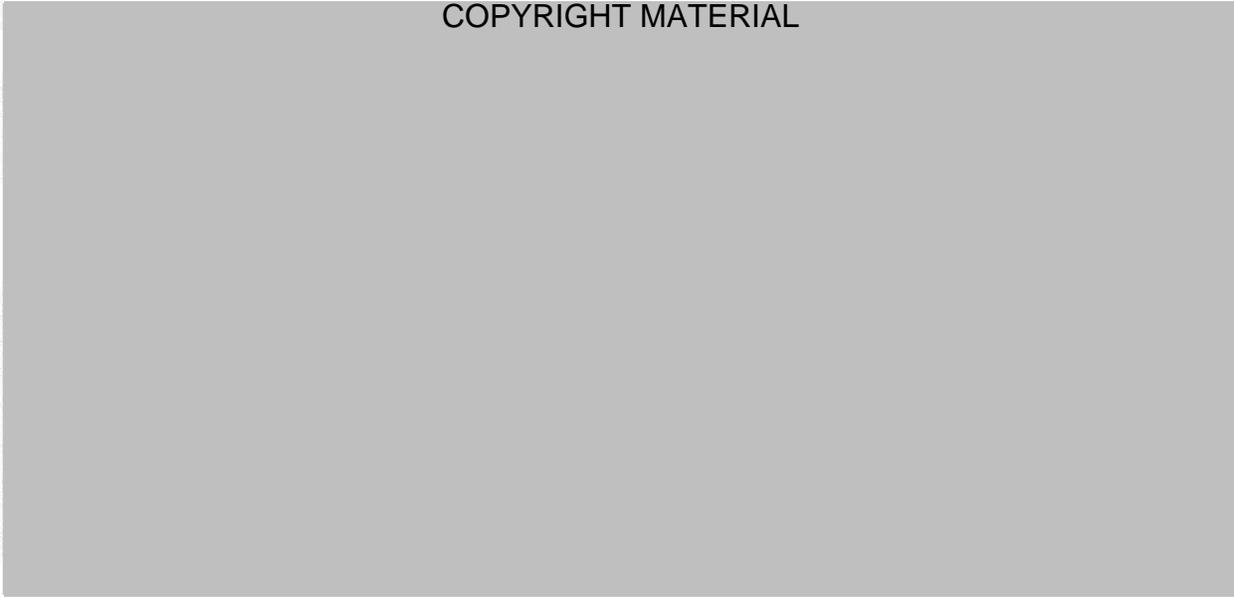


Table 2-4 Dosages and effective plasma concentrations of often used AEDs for adults

COPYRIGHT MATERIAL



2.3 Availability of Proposed Active Ingredient in the United States

Lamotrigine is approved in the US for several indications as noted in [section 2.1](#). The post marketing safety profile is extensively reviewed in [section 8](#).

2.4 Important Safety Issues With Consideration to Related Drugs

There are several drugs pharmacologically (chemically?) related to lamotrigine approved in the US, these are agents where the putative mechanism of action is through inhibition of voltage sensitive sodium channels,

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The submission of this application package for use of Lamictal XR as adjunctive therapy in treatment of PGTC seizures follows closely the related application seeking approval of Lamictal XR as adjunctive therapy of partial seizures.

The NDA seeking approval of LAMICTAL XR as adjunctive therapy of partial seizures in subjects ≥ 13 years of age was submitted to the Agency on 22 November 2006 (NDA 22-115; LAMICTAL® [lamotrigine] XR Extended-release Tablets). This application consisted of a single pivotal clinical trial (LAM100034), a supportive trial evaluating the pharmacokinetics (PK) of LAMICTAL Tablets and LAMICTAL XR in subjects with epilepsy (LEP103944), and 4 studies evaluating the PK and relative bioavailability of LTG XR (LAM10005, LAM10014, LAM10017, and LAM102611) in healthy volunteers. Also included was Chemistry, Manufacturing and Controls (CMC) information for 25mg, 50mg, 100mg, and 200mg tablets.

Safety information from the studies in the initial NDA (22115) was integrated into the current application with the exception of Study LEP103944, an open-label, double-conversion study to characterize the pharmacokinetics of lamotrigine when switching subjects with epilepsy from the LAMICTAL Tablets to LAMICTAL XR and vice-versa. This study was not included in the combined summaries due to the short duration of treatment (2 weeks on LAMICTAL XR), previous exposure to LAMICTAL Tablets, and study design compared with the other open-label studies. Study LAM100036 was ongoing at the time of 22-115 submission, only limited information was provided in that initial application and in the 120-day and Final Safety Updates. NDA 22-115 was under review by the Agency at the time of NDA 22509 submission on March 31, 2009.

A teleconference on August 23, 2007 between the Agency and GSK served to discuss and agree on the content and format of the application for adjunctive treatment of PGTC seizures. At that time FDA agreed that LAM100036 could support approval of Lamictal XR for adjunctive treatment of primary generalized tonic-clonic seizures in patients 13 years of age and older but stated that a claim for treatment of patients 13 to < 16 years old would depend upon the data supporting the efficacy and safety of this subgroup. While the Agency agreed with GSK's proposal to use the Clinical Overview for the primary summary of efficacy, it did not agree that the Clinical Overview could serve as the primary summary of safety. The Agency requested that GSK provide both a Summary of Safety (per CTD guidance) and an Integrated Summary of Safety (ISS; pursuant to 21 CFR 314.50(5)(vi)(a)) and that the ISS should be constructed in accordance with the reviewer template provided in the Agency's guidance entitled **"Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review (February 2005)"**. Additional safety and efficacy analyses were also requested. The Agency agreed that this application could be submitted as a New Drug Application in the event that the initial NDA for LAMICTAL XR (NDA 22-115) was still under review at the time GSK was ready to file. The application was subsequently filed on March 29, 2009 and NDA 22-115 was approved on May 29, 2009.

In a briefing document submitted to the Agency on November 13, 2008, GSK sought to obtain Agency agreement on updated proposals for safety analyses (due to completion of ongoing studies and additional studies being initiated since the August 23, 2007 pre-NDA meeting), agreement on GSK's proposal to construct the ISS similar to the Summary of Safety (m2.7.4), agreement on the content of the Chemistry, Manufacturing, and Controls section to support the (b) (4) 300 mg tablet strengths (specifically, provision of stability data and cross-referencing the CMC section of NDA 22-115), and agreement that the results of Study LEP111102 supports the approval of the (b) (4) tablet strength. In its February 10, 2009 correspondence, the Agency agreed with GSK's proposals for the content and format of the ISS as well as our proposals for provision of CMC information. However, the Agency did not agree that the results of LEP111102 established bioequivalence and recommended that the application include a justification and rationale for the adequacy of the existing data to

support the (b) (4) strength along with a discussion of the clinical significance of the lower AUC_{0-inf} . In addition, the Agency requested that individual release data from this study be included in the NDA. Subsequently the dosage forms for the (b) (4) 300mg strength were withdrawn from NDA22509 and submitted to NDA22115 as a prior approval CMC supplement.

2.6 Other Relevant Background Information

No additional information relevant to this section

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

Submission Quality was adequate for review. One additional data presentation was requested from the sponsor. In order to confirm that each category in the dose escalation regimen based on concomitant AED had balanced representation in the double blind maintenance phase of the study an additional table was requested from the sponsor. This issue was not addressed in the efficacy study report by a concise table.

3.2 Compliance with Good Clinical Practices

Three parameters were examined to determine the need for DSI audit, this included analysis of protocol violation by center, treatment change by center and enrolment by center. The examination did not reveal a disproportion of protocol violations or treatment change by center. There was however a disproportionately large number of enrollees from India and the Russian federation. Two sites in India accounted for 24% of study enrolment; these two sites were chosen for DSI audit.

An overview of the DSI audits reveal instances of discordance between entries in the medical record and entries in the case report forms. Similarly there are instances of discordance in the reverse direction. There do not appear to be systematic errors that result in compromise to the efficacy analysis or to patient safety. The results and conclusion will be presented fully in the DSI consult.

3.3 Financial Disclosures

The sponsor includes financial disclosure compliance statement concerning clinical investigators for the relevant studies. the documentation is provided to meet compliance

with the Final Rule on Financial Disclosure by Clinical Investigators published on February 2, 1998 (63 FR 5233), as subsequently revised by publication on December 31, 1998 (63 FR 72171). Financial interest information is provided for clinical investigators participating in studies covered by the rule included in the new drug application for NDA 22-509. The sponsor statement describes the methods used for the collection and reporting of the investigator financial disclosure information.

The financial disclosure statement indicates that the GlaxoSmithKline group of companies was formed by a merger completed on December 27, 2000 which joined together the Glaxo Wellcome and SmithKline Beecham groups. Subsequently a fully integrated process for collecting and reporting financial disclosure information across the entire GlaxoSmithKline group has been developed and implemented for prospective use. However in the transition to the new integrated process GlaxoSmithKline adopted certain working practices to guide compliance for previously initiated studies. Among these was the interim continuation of existing processes already in place within each heritage organization. The sponsor indicates conceivable limitations on information capture under the transitional arrangements. An interim basis solution, will have effectively addressed investigators' financial interests and arrangements relative to the heritage organization that sponsored the "covered" studies, and relative to those parts of the merged GlaxoSmithKline group that came from that heritage organization.

Table 3-1 Studies covered under the rule*			
Protocol No.	Protocol Title	Overall Study Start Date	Overall Study Completion Date
LEP111102	A pivotal single-dose, randomised, parallel-group, open-label study to demonstrate bioequivalence of 250 mg lamotrigine XR relative to 200 mg + 50 mg lamotrigine XR and to demonstrate lack of food effect on 250 mg lamotrigine XR in healthy male and female volunteers.	17 JAN 2008	06 MAR 2008
LAM105379	A pivotal single-dose randomised, parallel-group, open-label study to demonstrate bioequivalence of 300mg lamotrigine XR relative to 100mg + 200mg lamotrigine XR and to demonstrate lack of food effect on 300mg lamotrigine XR in healthy male and female volunteers	06 FEB 2007	17 APR 2007
LAM100036	A Multicenter, Double-Blind, Randomized, Parallel-Group Evaluation of LAMICTAL Extended-release Adjunctive Therapy in Subjects with Primary Generalized Tonic-Clonic Seizures	06 DEC 2004	27 DEC 2006
LAM30055	A Multicenter, Double-Blind, Randomized Conversion to Monotherapy Comparison of Two Doses of Lamotrigine for the Treatment of Partial Seizures	21 APR 2006	07 NOV 2008
LAM100034*	A Multicenter, Double Blind, Randomized, Parallel group Evaluation of LAMICTAL® Extended release Adjunctive Therapy in Subjects with Partial Seizures	15 OCT 2004	26 JUN 2006
LAM100034*	A Multicenter, Double-Blind, Randomized, Parallel-Group Evaluation of LAMICTAL® Extended-Release Adjunctive Therapy in Subjects with Partial Seizures: Open-Label Continuation Phase	30 MAR 2005	17 JULY 2007
*Final Rule on Financial Disclosure by Clinical Investigators revised by publication on December 31, 1998 (63 FR 72171)			

The financial disclosure statement continues to provide statements related to the following elements of the CFR: [21 CFR 54.4(a)(3)(ii), 54.2(f)], (21 CFR 54.4(a)(3)(iii), and 54.2(c)), (21 CFR 54.4(a)(3)(iv), 54.2(b)) as well as the sponsor's signed certification that there is no financial arrangement with listed investigators whereby the values of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). A list of the investigators with no disclosable financial interests/arrangements and certification of absence of clinical investigator financial interests/arrangements as to a GlaxoSmithKline-sponsored study is provided by study.

There is also a "**Certification of Unavailability of Required Information About Clinical Investigator Financial Interests/Arrangements**" for those investigators whose updated equity interest, proprietary interest information and/or information about payments of other sorts, could not be timely obtained from them. The sponsor indicates that available internal information indicates that none of the clinical investigators listed had disclosable interests of the type described in 21 CFR 54.2(a) (compensation potentially affected by the outcome of the study). In addition, based on whatever information may have been obtained at the threshold from some or all of the listed clinical investigators, no one listed had a disclosable interest of the type described in 21 CFR 54.2(b) (significant equity interest in the study sponsor) or 21 CFR 54.2(c) (proprietary interest in the tested product). This certification covered 13 participant investigators in study LAM30055, 21 investigators are listed under this certification for study LAM100034 and 14 investigators are listed under study LAM100036.

Overall the financial disclosure is complete and without conflict with the exception of the updated financial disclosures of 48 investigators listed under the Certification of Unavailability. This certification does imply these investigators were free of conflict at an early checkpoint.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The sponsor inserts the following cross reference into m3.2.S of the application:
Reference is made to LAMICTAL® (lamotrigine) Tablets (NDA 20-241) for all drug substance Chemistry, Manufacturing and Control information.

4.2 Clinical Microbiology

No applicable information in this submission

4.3 Preclinical Pharmacology/Toxicology

No applicable information in this submission

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

As noted in the current Lamictal XR label, *“The precise mechanism(s) by which lamotrigine exerts its anticonvulsant action are unknown.”*

The actions of this agent most relevant to anticonvulsant activity are blockade of sodium channels). LTG acts pre- and postsynaptically; presynaptically, it inhibits the release of neurotransmitters, among them the excitatory amino acids Glu and aspartate; postsynaptically, it diminishes the excitability of neurons like other anticonvulsive sodium channel blockers. Apart from inhibiting the sodium conductance LTG may reduce high-voltage activated calcium currents².

4.4.2 Pharmacodynamics

Lamotrigine pharmacodynamics is well known and described in the current label for Lamictal XR in section 12.2

4.4.3 Pharmacokinetics

The pharmacokinetics of Lamictal XR have been characterized for approval in NDA 22115 and are described in the current Lamictal XR label in section 12.3. Core points of discussion from the pharmacokinetics section of Dr. Kapcala’s review of NDA22115 are included below²-

The key ADME characteristics of lamotrigine are derived from the immediate release (IR) formulation. The pharmacokinetic (PK) parameters after the administration of XR lamotrigine are summarized in the following question. Absorption from the XR dosage form is slower as compared to the IR dosage form. Median peak concentrations are reached at 10-14 hours post dose from the XR dosage form at about 1-5 hours from the IR dosage form in healthy volunteers. In epilepsy patients, the median time to peak concentration (T_{max}) following administration of XR was 4 to 6 hours in patients taking carbamazepine, phenytoin, phenobarbital, or primidone, 9 to 11 hours in patients taking

² Stefan H, Feuerstein T. Novel anticonvulsant drugs. Pharmacology & Therapeutics. 2007;113:165-183

VPA, and 6 to 10 hours in patients taking AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or VPA.

The distribution, metabolism and elimination characteristics are similar to those of the IR dosage form, with the half-life also being similar with the two dosage forms. The mean half-life was about 37-44 hours in healthy subjects for the XR and about 38 hours for IR dosage form in a crossover study using the 25 mg strength (according the IR label, the mean half-life of the IR dosage form is 33 hours). The half-life of lamotrigine changes depending on the concomitant AED in patients. Although the sponsor has not characterized the half-life of the XR dosage with concomitant AEDs, it is reasonable to expect them to be similar to the IR dosage form.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

See [table 7-1](#).

5.2 Review Strategy

Efficacy: the approach to determination of efficacy was primarily analysis of the pivotal study LAM10036 contained in NDA 22509. Important characteristics of LAM10036 including study design, sample size, dropout rate, balance between treatment and control groups were all considered.

Safety: the safety review included pooled data from both NDA22115 and NDA22509. The safety review by Dr. Kapacala for NDA22115 was also referenced.

Post marketing: the post marking analysis was more extensive than in a less mature drug treatment due to the long post marketing history. This section of the review was an important extension of the safety review and included examination of the AERS database in addition to examination of the sponsor analysis of events of special interest per patient year exposure.

5.3 Discussion of Individual Studies/Clinical Trials

The current application seeks approval of LAMICTAL XR as an adjunctive treatment of PGTC seizures in subjects ≥ 13 years of age. This application consists of two completed clinical studies evaluating this formulation in patients with epilepsy: LAM100036, a study of adjunctive treatment of PGTC seizures in patients age 13 years or older and LAM30055, a study of conversion to lamotrigine XR monotherapy in patients 13 years of age and older with partial seizures. Study LAM30055 is submitted for safety information only. In addition limited safety information (deaths, SAEs, and withdraws due to adverse events) is provided for the ongoing continuation phase of LAM30055 and ongoing studies, LEP105972, an open label study of lamotrigine extended release in elderly patients with epilepsy and LEP108937, an open label study of the effect of lamotrigine and phenytoin on the pharmacokinetics of atorvastatin in healthy subjects.

LAM100036 study design

This was an international, multicenter, double-blind, randomized, placebo-controlled, parallel-group study. The trial comprised a Screen (≤ 2 weeks) and 4 Phases: Baseline (8 weeks); Double-Blind Treatment (19 weeks total, consisting of 7 weeks of Escalation and 12 weeks of Maintenance); Continuation (52 weeks total, consisting of 7 weeks of Blinded Transition and 45 weeks of Open-Label), and Taper/Follow-up (3 to 6 weeks).

Figure 5-1 LAM100036 Study Design

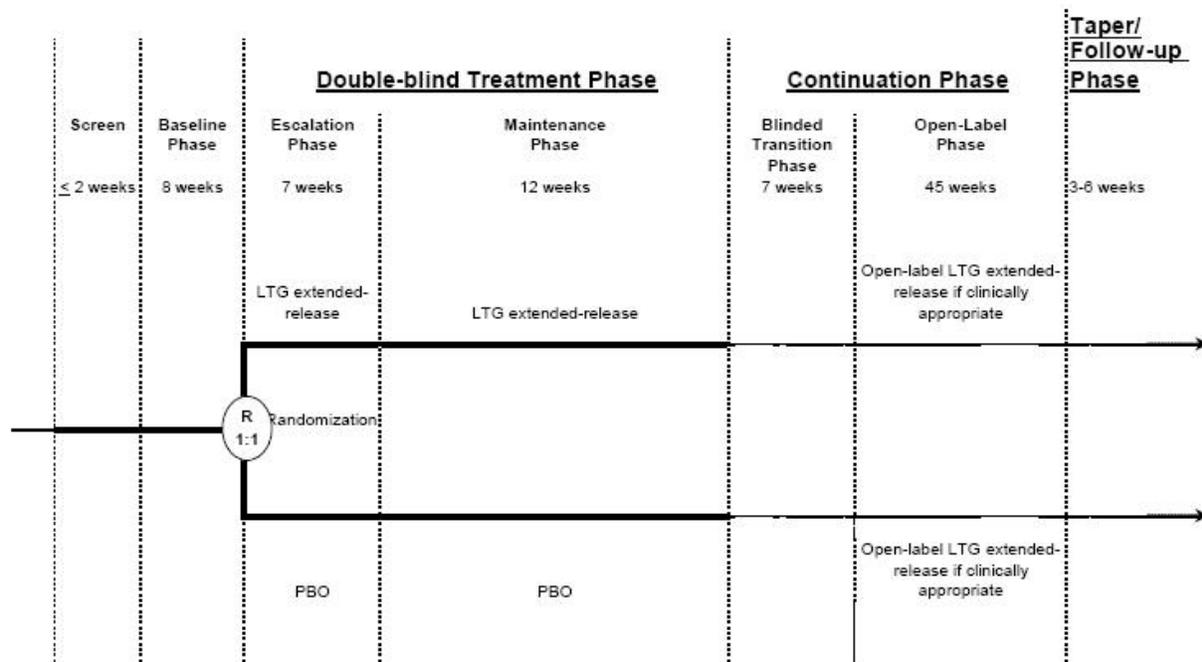


Figure 2

Diagnosis and Main Criteria for Inclusion: Male or female subjects ≥ 13 years of age with a confident diagnosis of epilepsy with PGTC seizures for more than 24 weeks prior to the Baseline Phase. Subjects must have had an EEG consistent with PGTC seizures inadequately controlled with a stable regimen of 1 or 2 antiepileptic drugs (AEDs) for at least 4 weeks prior to the Baseline Phase, with no evidence of interictal expression of partial seizures.

In addition, subjects must have had a documented history of PGTC seizures, with at least 1 PGTC seizure during the 8 consecutive weeks (i.e., 56 consecutive days) prior to starting the Baseline Phase, and at least 3 PGTC seizures occurring anytime during the 8-week Baseline Phase.

Treatment Administration: 19 weeks of LTG XR (25mg, 50mg, 100mg, or 200mg tablets) or placebo (matching tablets) during the double-blind Treatment Phase, including an escalating dose for 7 weeks and maintenance dose for 12 weeks. Subjects were assigned to 1 of 3 dosing schedules based on their concurrent AED(s).

Criteria for Evaluation: The primary efficacy endpoint was percent change from Baseline in weekly PGTC seizure frequency during the double-blind Treatment Phase.

Secondary efficacy endpoints were as follows: percent change from Baseline in PGTC seizure frequency during the Escalation Phase, the Maintenance Phase, and during the last 8 weeks of the Maintenance Phase; proportion of subjects with $\geq 25\%$, $\geq 50\%$, $\geq 75\%$, or 100% reduction in PGTC seizure frequency during the entire double-blind Treatment Phase, the Escalation Phase, the Maintenance Phase, and the last 8 weeks of the Maintenance Phase; time to $\geq 50\%$ reduction in seizure frequency; change from Baseline in body weight; and the proportion of subjects with improved clinical status on the investigator assessment of subject's clinical status questionnaire and subject's satisfaction with seizure control.

Safety assessments included treatment-emergent adverse events (AEs), clinical laboratory evaluations, physical and neurological examinations, vital signs, and electrocardiograms (ECGs).

For subjects ≥ 16 years of age, perception of their mood state and quality of life were to be assessed using 7 questionnaires at Screen and the end of double-blind Treatment Phase (i.e., Visit 8): Profile of Mood States (POMS); Center for Epidemiological Studies-Depression Scale (CES-D); Neurological Disorders Depression Inventory-Epilepsy (NDDI-E, 46-item research version); Quality of Life (QOLIE-31-P); Liverpool Adverse Experience Profile (AEP); Seizure Severity Questionnaire (SSQ); and Epworth Sleepiness Scale (ESS).

Safety: AEs were coded using the MedDRA coding dictionary, with incidences summarized by preferred term within system organ class for each treatment group. A composite term of "All Rash" was constructed from several potential preferred terms. Descriptive statistics were used to summarize AE reports, clinical laboratory assessments, vital signs, neurological examinations, and ECGs. All safety analyses were performed using the Safety Population, defined as all subjects who took at least one dose of the study drug.

For clinical laboratory assessments, the median changes from Screen and 2-sided 95% confidence intervals for within-group and between-group changes were computed based on the Wilcoxon signed rank test and rank sum tests, respectively.

For vital signs and ECGs, the mean change from Baseline and 2-sided 95% confidence intervals based on both the t-test (between-group changes) and the paired t-test within group changes) were computed.

6 Review of Efficacy

Efficacy Summary

Primary efficacy endpoint:

There is a single randomized, double blind, placebo-controlled study, LAM10036, to support the approval of lamotrigine XR. The study revealed a positive result for the primary efficacy endpoint, the median percent change from Baseline in average weekly PGTC seizure frequency during the entire double-blind treatment phase. Analysis of the ITT population yielded an estimated difference of 31.6% in the median percent reduction between the placebo and lamotrigine XR cohort with a $p < 0.0001$, 95% CI (15.8, 48.1) [Table 6-9](#). The study results demonstrated that lamotrigine XR was statistically superior to placebo for the primary efficacy endpoint of median reduction of primary generalized tonic-clonic seizures from baseline.

Secondary endpoints were also positive, in favor of lamotrigine XR treatment:

- The percentage of subjects who showed a $\geq 50\%$ reduction in PGTC seizure frequency over the entire double-blind Treatment Phase was greater in LTG XR group (69.6%) than the placebo group (31.9%, $p < 0.0001$) for the ITT Population.
- Time (in weeks) to 50% reduction in PGTC seizure frequency for the entire double blind Treatment Phase was shorter for the LTG XR group compared with the placebo group ($p < 0.0001$) for the ITT Population. Statistical separation of LTG XR from placebo was seen as early as Day 8 ($p < 0.05$) and was maintained for the remainder of treatment.
- There were differences in the ITT Population between the two treatment groups in the frequency distribution of the investigator's global assessment of subjects' overall clinical status in favor of LTG XR ($p = 0.0002$).

77 patients were randomized to placebo and 76 to lamotrigine XR with 73 placebo and 70 lamotrigine XR patients eligible for the ITT population. One subject each in the placebo and lamotrigine XR group did not have any PGTC seizures during the baseline phase, reducing the contributing ITT population to 72 placebo and 69 lamotrigine XR subjects, [Table 6-9](#).

Discussion of valproic acid treatment is a consideration in this study due to the increased AUC and C_{max} compared to the commonly used enzyme inducing AED's (EIAEDs, carbamazepine, phenytoin, phenobarbital and primidone) which may lower AUC and C_{max}. The distribution of valproic acid treatment and EIAEDs between placebo and lamotrigine XR groups is well matched, [Tables 6-4](#), [6-5](#).

There is a differential in effect size between the US and Non-US sites. This was a significant concern in study LAM100034, a very similarly designed study of lamotrigine XR in partial onset seizures where the Non-US effect size (median of differences in percent change from baseline seizure frequency) was 26.19% compared with the pooled US site effect size of 3.49%. In this study, LAM100036, the pooled non-US effect size was 34.5% and the US effect size was 22.2%. Although there is a gradient of 12.3% between the Non-US and US sites, the effect size is of sufficient size to have a plausible treatment effect.

The overwhelming majority of patients enrolled in study LAM10036 are in the age range of 16 years to 65 years of age, 90% of the placebo group and 93% of the lamotrigine XR treatment group. By study design patients were not recruited below the age of 13 years. Only 1% of patients in each treatment assignment were greater than age 65 years old and 8% of placebo treatment group and 6% of lamotrigine XR treated patients were less than 16 years of age. These small groups outside the range of 16 to 65 years old do not allow a meaningful subset analysis of efficacy. This deficiency however is mitigated by the robust experience with immediate release lamotrigine which has an indication for adjunctive therapy in patients as young as 2 years.

6.1 Indication

Adjunctive therapy for primary generalized tonic-clinic (PGTC) seizures and partial onset seizures with or without secondary generalization in patients \geq 13 years of age.

6.1.1 Methods

A single multicenter, double-blind, randomized, parallel group, placebo-controlled study ([LAM100036](#)) was submitted to demonstrate efficacy of Lamictal XR for the treatment of primary generalized tonic clonic seizures (PGTC), with no interim analysis planned.

Primary Comparisons of Interest

The study primary endpoint is the median percent change from baseline in average weekly PGTC seizure frequency during the entire double-blind treatment phase, compared between Lamictal XR and the placebo treated group. The primary comparison will be analyzed based upon the Intent-to-treat efficacy population. An additional analysis of the primary endpoint will be performed using the Per-Protocol efficacy population.

Secondary Comparisons

Comparisons of LTG and PBO will be made using a two-sided level of significance for each secondary endpoint. The ITT and Per Protocol efficacy populations will be used for all secondary comparisons.

Sample Size Considerations

Sample size assumption- The primary endpoint will be percent change in PGTC seizure frequency between the Baseline and Double-Blind Treatment Phase. Assuming

an estimated pooled standard deviation of 43%, 128 subjects will provide 90% power to detect a 25% difference in the seizure frequency at a two-sided 5% alpha level based on a ranked ANCOVA, controlling for ranked baseline weekly seizure frequency. Assuming a 35% drop-out rate, approximately 197 subjects will be enrolled in order to obtain 128 randomized subjects. Subjects will be centrally randomized in a 1:1 ratio to receive either lamotrigine or matching PBO.

Sample size sensitivity- The robustness and sensitivity of the above calculation is dependent upon the LTG/PBO response rate and standard deviation. Given a fixed standard deviation of 43% and a fixed sample size, the power to detect the given difference between treatment arms will vary significantly, as shown in table 6-1.

Table 6-1 Sample Size -Power		
Treatment Difference	Power	Number of patients needed for 90% power (per arm)
15%	49%	174
25%	90%	64
35%	99%	33

The rate of response and the pooled standard deviation was taken from an existing protocol (see protocol of study LAM40097, GKS Document Number RM2000/00370/03).

Analysis Populations

The following populations will be considered for analyzing the data:

- Intent to Treat (ITT) efficacy population: defined as all subjects who take at least one dose of study drug and have at least one post-baseline efficacy assessment in the Double-blind Treatment Phase.
- Per Protocol efficacy population: defined as all subjects who complete the double-blind treatment phase, excluding those with major protocol violations.
- Safety Population: defined as all subjects who take at least one dose of the study drug.

General Considerations for Data Analysis

Missing Data

Seizures that are impossible to count, as noted on the innumerable seizure activity CRF page will be imputed. The highest daily seizure count observed during a given phase (Baseline, Escalation, Maintenance) will be used as the seizure count on these days. For the change from baseline to end of study weight analysis only, LOCF will be used to impute missing weight data if at least one post baseline weight value is recorded. The

last missing weight value recorded prior to the visit with the missing data will be assigned to the missing weight value. Screening values will not be carried forward.

Derived and Transformed Data

Seizure frequency data recorded during the last 8 weeks of the Baseline Phase and during the first 19 weeks of the Double-Blind Treatment Phase will be determined for each subject. Average weekly seizure frequency, defined as the frequency of seizures divided by the number of study weeks in the Baseline or analyzed treatment time period contributing to the frequency counts, will be computed for each subject in order to derive the percent change from Baseline in seizure frequency value. Percent change from baseline will be computed as $((\text{Baseline} - \text{Treatment})/\text{Baseline}) * 100$, where a positive value indicates a reduction from Baseline in seizure frequency.

Time to $\geq 50\%$ reduction in seizure frequency (in days) will be calculated from the first day of study medication to the day at which a $\geq 50\%$ reduction from baseline in seizure frequency is observed. Only subjects who maintain the $\geq 50\%$ reduction in seizure frequency for the remainder of the Treatment Phase will meet this endpoint. Percent change (relative to baseline) will be calculated at each day, after completion of 1 week on study drug. The cumulative experience during the treatment phase will be compared to baseline to determine success. Subjects who fail to meet this endpoint will be censored at the date of last dose.

The proportion of subjects with improved clinical status on the Investigator assessment of subject's clinical status questionnaire and subject's satisfaction with seizure control will be defined as any improvement in clinical status (i.e. mild, moderate, or marked).

Change from baseline for each subject will be calculated as baseline value minus post-baseline value.

Treatment differences will be calculated as LTG minus PBO

Multiple Comparison Strategy

Since there are both primary and key secondary comparisons of interest, the overall Type I error will be controlled by employing sequential testing. The key secondary endpoints are shown below:

1. Time to $\geq 50\%$ reduction (based upon change from baseline in seizure frequency)
2. Change from baseline in weight

Health Outcomes Questionnaires: Seizure Severity Questionnaire (SSQ, Total Score), Epworth Sleepiness Scale (ESS, Total Score), Quality of Life in Epilepsy (QOLIE-31, Total Score), Profile of Mood States (POMS, Total Score)

Adjustments will only be made for the key secondary endpoints listed above. Testing of the key secondary endpoint comparisons will be conducted only if the test of the primary endpoint, change from baseline in seizure frequency during the entire double-blind treatment phase, is statistically significant. If this test is not significant, then no further testing will be conducted and no claims of significance can be made for the primary or any key secondary endpoints.

Time to Greater than or equal to 50% reduction in Seizure Frequency

Time to $\geq 50\%$ reduction in seizure frequency will be tested only if the primary endpoint is significant at the 0.05 level of significance. No adjustments to the Type I error will be made for this endpoint since it is highly correlated with the primary endpoint.

Health Outcomes Endpoints

If a significant difference is found for the primary comparison, then the step-up procedure derived by [Hochberg, 1988] will be used to test the Health Outcomes endpoints to control Type I error. Significance probabilities (p-values) will be ranked for each of the tests from the most significant (lowest p-value) to the least significant (highest p-value). If the highest p-value (P_K) is < 0.05 , then all remaining secondary endpoints are statistically significant as well. If $P_K > 0.05$, then the next test in the sequence (P_{K-1}) must be $< 0.05/2$ (0.025) in order to reject the null hypothesis for the remaining tests. This process will continue sequentially (P_{K-2} , 0.05/3; etc.) until either significance is reached or no additional endpoints exist.

Center

Center will not be included as a factor in any analysis because a central randomization scheme will be used in this study.

6.1.2 Demographics

The demographics of study 100036 reveal a minor 1 year difference in age, where the study drug treatment group (LTG XR) mean is one year greater in age than placebo. There are only a small number of patients less than 16 years of age, 8% in placebo, 6% in LTG XR group. There is a small majority of females in the placebo group, 52% compared to 46% in LTG XR treatment group. There is a small majority of males in the LTG XR treatment group, 54% compared to 48% in placebo. Racial composition reveals the two most prominent groups are Asian and Caucasian, together comprising 95% of the placebo group and 93% of the LTG XR group, [Table 6-2](#).

Table 6-2 Study Population Demographics		
Demographic Characteristic	PBO N=73	LTG XR N=70
Age, y		
Mean (SD)	28.4 (11.48)	29.4 (12.78)
Range	13-74	14-69
Age Group, y, n (%)		
<16	6 (8) 66 (90)	4 (6) 65 (93)

Table 6-2 Study Population Demographics		
Demographic Characteristic	PBO N=73	LTG XR N=70
16-65 >65	1 (1)	1 (1)
Sex, n (%)		
Female	38 (52)	32 (46)
Male	35 (48)	38 (54)
Ethnicity, n (%)		
Hispanic/Latino	14 (19)	8 (11)
Not Hispanic/Latino	59 (81)	62 (89)
Race, n (%)		
African American/African Heritage	1 (1)	2 (3)
American Indian or Alaskan Native	2 (3)	0
Asian - Central/South Asian Heritage	31 (42)	28 (40)
Asian - East Asian Heritage	0	1 (1)
Asian - Japanese Heritage	1 (1)	0
Asian - South East Asian Heritage	0	2 (3)
Native Hawaiian or Other Pacific Islander	0	0
White - Arabic/North African Heritage	0	0
White - White/Caucasian/European Heritage	41 (56)	37 (53)

Baseline Seizure Data- The distribution of Screening seizure types and Baseline medians (historical or prospective) were similar between the treatment groups, [Table 6-3](#).

Table 6-3 Baseline Seizure Data (ITT Population: Study LAM100036)		
	PBO N=73	LTG XR N=70
Baseline Data		
Screening Seizure Type1, n (%)		
Absence	10 (14)	10 (14)
Myoclonic	11 (15)	7 (10)
Clonic	1 (1)	0
Tonic	1 (1)	0
Tonic-Clonic	73 (100)	69 (99)2
Atonic	1 (1)	0
Baseline Seizure Frequency per Week – PGTC Seizures		
Entire Baseline, n	73	70
Median (Range)	0.6 (0.0, 7.4)	0.8 (0.0, 7.3)
Historical Baseline, n	17	19
Median (Range)	0.75 (0.3, 2.0)	0.75 (0.0, 7.3)
Mean (SD) Age at First Seizure, y	14.8 (9.83)	16.5 (11.29)
Mean (SD) Duration of Epilepsy, y	14.6 (8.77)	13.9 (9.88)
1. Some subjects had more than one type of seizure.		
2. One subject (#1259) did not have tonic-clonic seizures at Screening.		

Concurrent AED Therapy- A summary of the most common (incidence $\geq 5\%$ of subjects) concurrent AED therapy is presented in [table 6-4](#). Concurrent AED therapy was similar between the treatment groups.

Table 6-4	Most Common (Incidence of Greater Than or Equal to 5% of Subjects in Either Treatment Group) Previous AED Therapy (ITT Population: Study LAM100036)		Number (%) of Subjects	
			PBO	LTG XR
		N=73	N=70	
Previous AED Therapy				
Phenytoin		20 (27)	18 (26)	
Carbamazepine		13 (18)	18 (26)	
Phenobarbital		28 (23)	33 (28)	
Valproic Acid		11 (15)	9 (13)	
Clonazepam		6 (8)	2 (3)	
Clobazam		6 (8)	0	
Benzobarbital		4 (5)	5 (7)	
Topiramate		4 (5)	4 (6)	
Ethosuximide		4 (5)	3 (4)	

Number of Concomitant AED's- A summary of AED concomitant medications and number of concomitant AED's is presented in [table 6-5](#). The incidence of subjects taking 1 AED was higher in the Lamictal XR group (67%) compared with the placebo group (51%). An important consideration, the number of patients on valproic acid and enzyme inducing antiepilepsy drugs is identified in [table 6-5](#). Valproic acid may increase the lamotrigine level while enzyme inducing AEDs may reduce the level. The table reveals almost complete symmetry in this respect between the placebo treatment and lamotrigine XR treated cohorts. In those subjects taking any VPA there are 41% in both the placebo and lamotrigine treated groups. In those on EIAEDs the placebo group contains 48% and the lamotrigine group contains 47%.

Table 6-5	Number of AED Concomitant Medications and AED Group (ITT Population: Study LAM100036)		Number (%) of Subjects	
			PBO	LTG XR
		N=73	N=70	
Concurrent AED Therapy				
Number of AEDs				
1 AED		37 (51)	47 (67)	
2 AEDs		36 (49)	23 (33)	

Table 6-5	Number of AED Concomitant Medications and AED Group (ITT Population: Study LAM100036)	
	Number (%) of Subjects	
	PBO	LTG XR
Concurrent AED Therapy	N=73	N=70
AED Group		
Any VPA	30 (41)	29 (41)
Enzyme-Inducing AED	35 (48)	33 (47)
Other Regimens	8 (11)	8 (11)

AED group and number of concomitant AED's by US or Non-US sites- Overall, the non-US sites greater numbers of subjects in both treatment groups (52% placebo, 36% LTG XR) taking 2 concurrent AEDs than the US sites (38% placebo, 11% LTG XR). Also a high percentage of subjects (45% placebo, 43% LTG XR) at the non-US sites were in the “any VPA” group than at the US sites (23% placebo, 33% LTG XR), [Table 6-6](#). This increase proportion of VPA concurrent treatment in the Non-US group may bias toward increased efficacy due to the potential to increase Lamictal XR levels.

Table 6-6	Concurrent AED Therapy		Number (%) of Subjects	
			PBO N=73	LTG XR N=70
US Sites	n		13	9
	Number of AEDs	1 AED	8(62)	8(89)
		2AEDs	5(38)	1(11)
	AED group	Any VPA	3(23)	3(33)
		EIAED	6(46)	4(44)
		Other regimens	4(31)	2(22)
Non-US Sites	n		60	61
	Number of AEDs	1 AED	29(48)	39(64)
		2AEDs	31(52)	22(36)
	AED group	Any VPA	27(45)	26(43)
		EIAED	29(48)	29(48)
		Other regimens	4(7)	6(10)

6.1.3 Subject Disposition

A total of 153 subjects were randomized from 9 countries, 77 subjects were entered into the placebo group and 76 subjects into the LTG XR group. Study completion was very

close between placebo and LTG XR groups, 93% of placebo subjects completed study compared to 92% LTG XR patients. 7% of placebo subjects withdrew prematurely compared to 8% of 8% of LTG XR subjects [Table 6-7](#).

The small number of premature withdraws did not reveal a large differentiation of causes between the placebo and LTG XR groups. The largest strata was “subject decided to withdraw from the Study” comprised of 2 (3%) subjects in the placebo group and 3 (4%) in the LTG XR group. 2 subjects in the placebo group withdrew due to an adverse event and 1 in the LTG XR group. One subject in the placebo group withdrew due to pregnancy.

	Number (%) of Subjects	
	PBO N=74	LTG XR N=72
Completion Status		
Completed Study	69 (93)	66 (92)
Prematurely Withdrawn	5 (7)	6 (8)
Reason for Premature Withdrawal		
AE	2 (3)	1 (1)
Lost to Follow-Up	0	1 (1)
Protocol Violation	0	1 (1)
Subject Decided to Withdraw from the Study	2 (3)	3 (4)
Non-compliance	0	0
Other, Specify	1 (1) pregnancy	0

Randomization by country may be seen in table 6-4. Largest foreign site enrollment is from India, with Russian Federation second. India and Russian Federation added 54% of total placebo group enrollment and 65% of LTG XR enrollment. The US was the third largest country of recruitment comprising 19% of the placebo group and 12% of the LTG XR group [Table 6-8](#).

Country	Placebo		Lamictal XR	
Total Randomized	77		76	
Argentina	8	(10%)	2	(3%)
Brazil	2	(3%)	0	
Germany	2	(3%)	9	(12%)
India	31	(40%)	30	(39%)
Korea	0		1	(1%)
Malaysia	1	(1%)	2	(3%)

Table 6-8	Enrolment by Country			
Russian Federation	11	(14%)	18	(24%)
Ukraine	7	(9%)	5	(7%)
United States	15	(19%)	9	(12%)

6.1.4 Analysis of Primary Endpoint(s)

The analysis of the primary efficacy endpoint, percent change from Baseline in weekly PGTC seizure frequency during the double-blind Treatment Phase, was carried out using a ranked ANCOVA analysis, controlling for the ranked Baseline weekly seizure frequency. The ranked percent change and Baseline weekly seizure frequency were modeled to calculate the residuals from a linear regression. The residuals were used to calculate a Cochran-Mantel-Haenszel mean score statistic to compare the 2 treatment groups

In addition, the primary efficacy endpoint was summarized separately for US sites and non-US foreign sites for the ITT Population, the Per Protocol Population, and the subgroup of subjects completing the study were analyzed.

Primary Efficacy Results

The primary endpoint was the median percent change from Baseline in average weekly PGTC seizure frequency during the entire double-blind Treatment Phase.

The median percent reduction from Baseline in all PGTC seizure frequency during the entire Treatment Phase was greater in the LTG XR group (75.4%) than in the placebo group (32.1%; $p < 0.0001$)

Table 6-9 Analysis of the Median Percent Reduction in PGTC Seizure Frequency during the Entire Treatment Phase (ITT Population: Study LAM100036)		
PGTC Seizures	PBO	LTG XR
	N=73	N=70
n ¹	72	69
Median (Range)	32.1 (-427, 100)	75.4 (-100, 100)
Estimated Difference ²	31.6	
95% CI for Difference ²	15.8, 48.1	
p-value ²	<0.0001	
<p>1. One subject in the PBO group and one subject in the LTG XR group did not have any PGTC seizures during the Baseline Phase.</p> <p>2. Hodges Lehman estimates for the median treatment difference, 95% CI and p-value are based upon a Cochran-Mantel-Haenszel Rank Sum Test. All positive values indicate a reduction in seizure frequency in favor of LTG XR.</p>		

Percent Change from Baseline in Weekly Seizure Frequency, by study phase with significance level

Table 6-10		Summary of Analysis of Percent Change from Baseline in Weekly Seizure Frequency, ITT Population, All sites				
Tonic-Clonic Seizures						
Period	Treatment Group	N	n	Estimated Difference in Treatment Groups [1]	95% CI for Difference [1]	p-value for Difference in Treatment Groups [1]
Escalation	Placebo	73	72	25.7	(7.6, 43.4)	0.0016
	Lamictal XR	70	69			
Maintenance	Placebo	73	70	35.8	(22.2, 50.5)	<0.0001
	Lamictal XR	70	68			
Last 8 Weeks of Maintenance	Placebo	73	70	40.0	(17.9, 54.2)	<0.0001
	Lamictal XR	70	68			
Entire Treatment	Placebo	73	72	31.6	(15.8, 48.1)	<0.0001
	Lamictal XR	70	69			
<p>[1] Hodges Lehman estimates for the median treatment difference as well as 95% confidence interval and p-value are based upon a Cochran-Mantel-Haenszel Rank Sum Test. All positive values indicate a reduction in seizure frequency in favor of Lamictal.</p>						

Efficacy results, US compared to Non-US sites

The efficacy results for the subset of sites in the US are presented below. This was a source of concern in study LAM100034 due to very low treatment effect and absence of statistically significant difference between the treatment and placebo groups.

Table 6-11		Summary of Analysis of Percent Change from Baseline in Weekly Seizure Frequency by US Sites, ITT Population				
Tonic Clonic Seizures						
Period	Treatment Group	N	n	Estimated Difference in Treatment Groups [1]	95% CI for Difference [1]	p-value for Difference in Treatment Groups [1]
Escalation	Placebo	12	12	7.6	(-22.8, 61.9)	0.5179
	Lamictal XR	9	9			
Maintenance	Placebo	13	11	33.3	(0.0, 66.1)	0.0582
	Lamictal XR					
Last 8 Weeks of Maintenance	Placebo	13	11	27.3	(-2.7, 74.3)	0.1313
	Lamictal XR	9	8			
Entire Treatment	Placebo	13	12	22.2	(-8.0, 51.3)	0.1685
	Lamictal XR	9	9			

[1] Hodges Lehman estimates for the median treatment difference as well as 95% confidence interval and p-value are based upon a Cochran-Mantel-Haenszel Rank Sum Test. All positive values indicate a reduction in seizure frequency in favor of Lamictal.

6.1.5 Analysis of Secondary Endpoints(s)

The ITT and Per Protocol Populations were used to analyze secondary endpoints.

All of the secondary efficacy endpoints were summarized separately for US sites and non-US foreign sites for the ITT Population and the Per Protocol Population.

Secondary Endpoint Results

Median Percent Reduction from Baseline in PGTC seizure frequency

The median percent reduction from Baseline in PGTC seizure frequency was greater in the LTG XR group than the placebo group for the Escalation Phase (p=0.0016), the Maintenance Phase (p<0.0001), and the last 8 weeks of Maintenance Phase for the ITT Population (p<0.0001), [Table 6-10](#), [6-12](#). The percent change from Baseline in weekly PGTC seizure frequency during the Escalation Phase, the Maintenance Phase, and during the last 8 weeks of the Maintenance Phase was analyzed in the same manner as the primary endpoint.

Table 6-12	Analysis of the Percent Reduction in PGTC Seizure Frequency during Escalation, Maintenance, and the Last 8 Weeks of Maintenance (ITT Population: Study LAM100036)	
PGTC Seizures	PBO N=73	LTG XR N=70
Escalation Phase		
n	72	69
Median (Range)	30.6 (-319, 100)	61.9 (-197, 100)
Estimated Difference ¹	25.7	
95% CI for Difference ¹	7.6, 43.4	
p-value ¹	0.0016	
Maintenance Phase		
n	70	68
Median (Range)	33.3 (-492, 100)	89.7 (-142, 100)
Estimated Difference ¹	35.8	
95% CI for Difference ¹	22.2, 50.5	
p-value ¹	<0.0001	
Last 8 Weeks of Maintenance Phase		
n	70	68
Median (Range)	35.4 (-180, 100)	100.0 (-131, 100)
Estimated Difference ¹	40.0	
95% CI for Difference ¹	17.9, 54.2	
p-value ¹	<0.0001	
1. Hodges Lehman estimates for the median treatment difference, 95% CI and p-value are based upon a Cochran- Mantel-Haenszel Rank Sum Test. All positive values indicate a reduction in seizure frequency in favor of LTG XR.		

Reduction in Seizure Frequency from Baseline by Percentage intervals

The percent reduction from Baseline in PGTC seizure frequency by discrete categories ($\geq 25\%$, $\geq 50\%$, $\geq 75\%$ and 100% reduction) for the entire double-blind Treatment Phase, the Escalation Phase, the Maintenance Phase, and the last 8 weeks of Maintenance Phase is presented in [table 6-13](#) for the ITT Population.

The percentage of subjects who showed a $\geq 50\%$ reduction in PGTC seizure frequency over the entire double-blind Treatment Phase was greater in the LTG XR group (69.6%) compared with the placebo group (31.9%, $p < 0.0001$). Likewise, the percentages of subjects who showed a 50% reduction in PGTC seizure frequency during the Maintenance Phase and the last 8 weeks of Maintenance Phase were greater in the LTG XR group compared with the placebo group ($p < 0.0001$ for both Phases), [Table 6-13](#).

The proportion of subjects with $\geq 25\%$, $\geq 50\%$, $\geq 75\%$, and 100% reduction in weekly PGTC seizure frequency during the entire double-blind Treatment Phase, the Escalation Phase, the Maintenance Phase, and the last 8 weeks of the Maintenance Phase were analyzed using a Fisher's exact test.

Table 6-13		Percent Reduction from Baseline in PGTC Seizure Frequency (ITT Population: Study LAM100036)		
	PBO N=73 n (%)	LTG XR N=70 n (%)	p value¹	
Entire Treatment Phase				
n	72	69	-	
≥25% Reduction	43 (59.7)	56 (81.2)	0.0060	
≥50% Reduction	23 (31.9)	48 (69.6)	<0.0001	
≥75% Reduction	14 (19.9)	35 (50.7)	0.0001	
100% Reduction	7 (9.7)	14 (20.3)	0.0989	
≥50% Increase	8 (11.1)	5 (7.2)	0.5634	
Escalation Phase				
n	72	69	-	
≥25% Reduction	39 (54.2)	51 (73.9)	0.0222	
≥50% Reduction	23 (31.9)	38 (55.1)	0.0067	
≥75% Reduction	14 (19.4)	24 (34.8)	0.0570	
100% Reduction	9 (12.5)	15 (21.7)	0.1805	
≥50% Increase	11 (15.3)	5 (7.2)	0.1849	
Maintenance Phase				
n	70	68	-	
≥25% Reduction	46 (65.7)	60 (88.2)	0.0023	
≥50% Reduction	29 (41.4)	51 (75.0)	<0.0001	
≥75% Reduction	14 (20.0)	40 (58.8)	<0.0001	
100% Reduction	10 (14.3)	31 (45.6)	<0.0001	
≥50% Increase	9 (12.9)	5 (7.4)	0.3993	
Last 8 Weeks of Maintenance Phase				
n	70	68	-	
≥25% Reduction	47 (67.1)	61 (89.7)	0.0017	
≥50% Reduction	29 (41.4)	54 (79.4)	<0.0001	
≥75% Reduction	18 (25.7)	44 (64.7)	<0.0001	
100% Reduction	15 (21.4)	35 (51.5)	0.0004	
≥50% Increase	9 (12.9)	4 (5.9)	0.2438	
1. p-value using a Fisher's Exact test comparing the number of subjects with the given percent reduction in seizure frequency				

Time to Greater than or Equal to 50% Reduction in Seizure Frequency

An analysis of time to ≥50% reduction in PGTC seizure frequency is summarized in [table 6-14](#) for the ITT Population. The time (in weeks) to ≥50% reduction in seizure frequency for the entire double-blind Treatment Phase was statistically significant (p<0.0001).

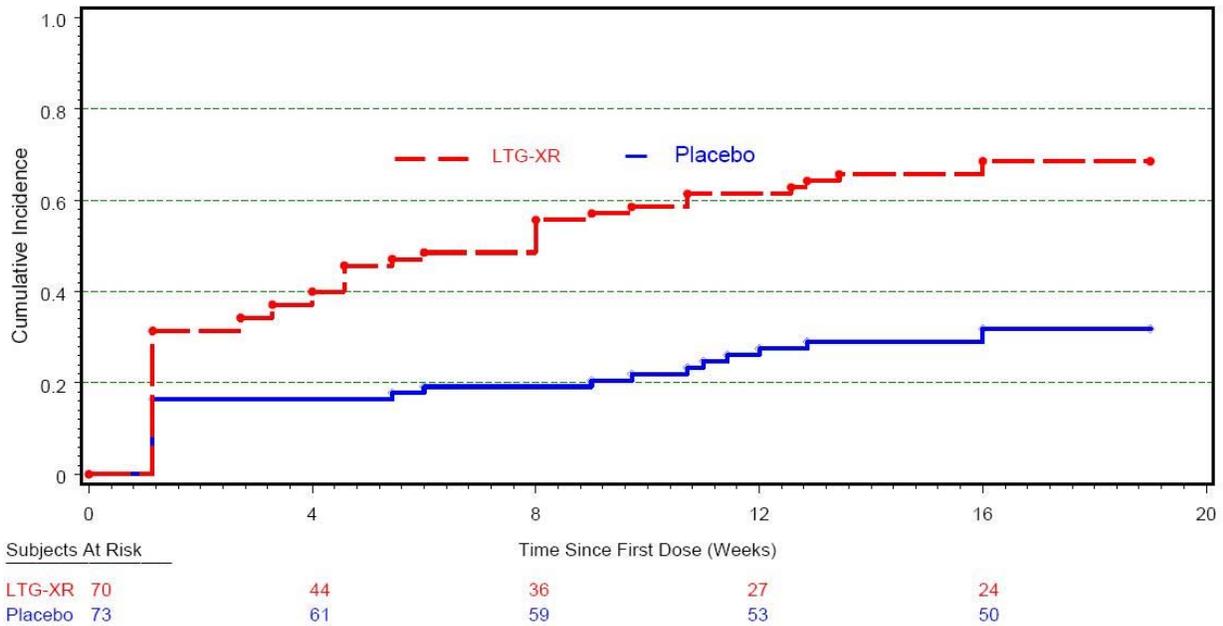
Table 6-14			Analysis of Time (in Weeks) to 50% Reduction in Seizure Frequency for PGTC Seizures (ITT Population: Study LAM100036)	
50% Reduction¹ Up to Time (in Weeks)	Number (%) of Subjects		PBO	LTG XR
			N=73	N=70
2	12	(16.4)	22	(31.4)
4	12	(16.4)	28	(40.0)
8	14	(19.2)	39	(55.7)
12	20	(27.4)	43	(61.4)
16	23	(31.5)	48	(68.6)
Treatment Comparison p-value		<0.0001		
<p>Note: The first eligible time to achieve the endpoint was Week 1. All observations were censored at the end of Week 19 [Day 133]; Active versus placebo treatment effect p-values based on log rank test.</p> <p>Note: Subjects 71 (Placebo) and 1259 (LTG XR) had no PGTC seizures during Baseline, which implies percent change from Baseline is incalculable. As a result, these two subjects are failures in this analysis.</p> <p>Note: The onset of efficacy was seen as early as Day 8 (p<0.05).</p> <p>1. 50% reduction in seizure frequency is defined as the time at which a subject first achieved and maintained a ≥50% reduction in seizure frequency following exposure to at least 1 week of study drug.</p>				

The treatment difference reached statistical significance as early as Day 8 of the Escalation Phase in the ITT Population (p<0.05 for time in weeks to ≥50% reduction in seizure frequency for the double-blind Treatment Phase) and was maintained the remainder of treatment ([figure 6-1](#)).

Time to Greater than or equal to 50% Reduction in Seizure Frequency

Time to ≥50% reduction in PGTC seizure frequency for the entire double-blind Treatment Phase was analyzed using a 2-sided log-rank statistic. Kaplan-Meier methodology was used to estimate and graph the time to ≥50% reduction curve for each treatment group see [figure 6-1](#).

Figure 6-1 Time to 50% Reduction in Seizure Frequency (ITT Population: Study LAM100036)



Note: Statistical significance was seen as early as Day 8. Data from the first week has been censored from the analysis.

Figure 3

6.1.6 Other Endpoints

Clinical Status

The proportion of subjects with improved clinical status on the investigator assessment of subject's clinical status questionnaire and subject's satisfaction questionnaire was analyzed using a chi-square test assessing improvement (mild, moderate or marked), deterioration (mild, moderate or marked), and no change.

There were significant differences in favor of LTG XR for the following individual factors: Seizure Frequency ($p=0.0420$), Seizure Duration ($p=0.0005$), Seizure Intensity ($p=0.0012$), Adverse Experiences ($p=0.0197$) and Overall Status ($p=0.0002$).

No differences were noted in the results of the subject's satisfaction questionnaire, [Table 6-15](#), [6-16](#).

Table 6-15

Protocol: LAM100036
Population: Intent-to-Treat
From Table 7.17, p162

Summary of Analysis of Investigator's Global Assessment, ITT Population

Clinical Factors	Treatment	n	Total Improvement	No Change	Total Deterioration	p-value [1]
Seizure Frequency	Placebo	71	49 (69%)	20 (28%)	2 (3%)	0.0420
	Lamictal XR	68	59 (87%)	8 (12%)	1 (1%)	
Seizure Duration	Placebo	71	38 (54%)	33 (46%)	0	0.0005
	Lamictal XR	68	56 (82%)	11 (16%)	1 (1%)	
Seizure Intensity	Placebo	71	41 (58%)	29 (41%)	1 (1%)	0.0012
	Lamictal XR	68	58 (85%)	9 (13%)	1 (1%)	
Adverse Experiences	Placebo	71	16 (23%)	50 (70%)	5 (7%)	0.0197
	Lamictal XR	68	28 (41%)	32 (47%)	8 (12%)	
Social Functioning	Placebo	71	22 (31%)	49 (69%)	0	0.0772
	Lamictal XR	68	32 (47%)	35 (51%)	1 (1%)	
Intellectual Functioning	Placebo	71	17 (24%)	53 (75%)	1 (1%)	0.7639
	Lamictal XR	68	20 (29%)	47 (69%)	1 (1%)	
Motor Functioning	Placebo	71	14 (20%)	57 (80%)	0	0.5489
	Lamictal XR	68	15 (22%)	52 (76%)	1 (1%)	
Overall Status	Placebo	71	36 (51%)	33 (46%)	2 (3%)	0.0002
	Lamictal XR	68	57 (84%)	10 (15%)	1 (1%)	

Table 6-16	Investigator's Global Assessment and Subject Satisfaction at Study Conclusion (ITT Population: Study LAM100036)		
	PBO N=73 n (%)	LTG XR N=70 n (%)	p value ¹
Investigator's Global Assessment			
Overall Status			
N	71	68	0.0002
Any Improvement	36 (51)	57 (84)	
No Change	33 (46)	10 (15)	
Any Deterioration	2 (3)	1 (1)	
Subject Satisfaction Questionnaire			
N	71	68	0.1203
Any Improvement	53 (74)	60 (88)	
No Change	13 (18)	6 (9)	
Any Deterioration	5 (7)	2 (3)	
1. p-value using a Chi Square Fisher's Exact test comparing total improvement versus no change versus total deterioration			

6.1.7 Subpopulations Country

Examination of the contribution to the overall study population reveals that India is the majority contributor by a large margin. India contributes 46.2% to the ITT population. The second largest contributor is the Russian Federation, contributing 19.2% to the ITT analysis. Together these countries are the majority contributors, adding to 61.7% of the total ITT population. The US cohort contributes 14.9% of the total subject population compared to the 61.7% of the combined Russian and Indian contribution, [Table 6-8](#).

The non-US population is driven largely by two countries outside of the sphere of nations which more confidently approximate the US standard of practice for epilepsy. The estimated difference in treatment groups (effect size) is 34.5% with a $p < 0.0001$ for the entire treatment interval in the non US sites ([Table 6-17](#)) and 22.2 with a $p < 0.1685$ in the US group, [Table 6-11](#). Although the effect size is 12.3% greater in the non-US sites, the 22.2% effect size of the US sites is within the expected range of effect size seen in AED studies. The US sample size of 21 subjects is not powered to generate a conclusive p value.

As noted in demographics, there was a higher percentage of subjects in the category of any VPA in the non-US sites compared to US sites which may produce a bias toward higher Lamictal treatment levels in the VPA treated non-US subject cohort, [Table 6-6](#). In the search for explanation of the larger treatment effect in the Non-US cohort this along with a larger US placebo response are factors to consider. It is noted that for the entire treatment period, the placebo group in the US study cohort had a placebo, median percent change from baseline of 53.6% ([Table 6-18](#)) compared to 28.4% in the non-US cohort ([Table 6-19](#)).

Table 6-17		Summary of Analysis of Percent Change from Baseline in Weekly Seizure Frequency by Non-US Sites, ITT Population				
Tonic Clonic Seizures						
Period	Treatment Group	N	n	Estimated Difference in Treatment Groups [1]	95% CI for Difference [1]	p-value for Difference in Treatment Groups [1]
Escalation	Placebo	60	60	28.6	(10.8, 47.6)	0.0013
	Lamictal XR	61	60			
Maintenance	Placebo	60	59	39.4	(22.2, 57.1)	<0.0001
	Lamictal XR	61	60			
Last 8 Weeks of Maintenance	Placebo	60	59	42.1	(20.0, 60.7)	<0.0001
	Lamictal XR	61	60			
Entire Treatment	Placebo	60	60	34.5	(16.4, 52.6)	<0.0001

Table 6-17	Summary of Analysis of Percent Change from Baseline in Weekly Seizure Frequency by Non-US Sites, ITT Population				
	Lamictal XR	61	60		

[1] Hodges Lehman estimates for the median treatment difference as well as 95% confidence interval and p-value are based upon a Cochran-Mantel-Haenszel Rank Sum Test. All positive values indicate a reduction in seizure frequency in favor of Lamictal.

Table 6-18

Summary of Percent Change from Baseline in Weekly Seizure Frequency by US or Non-US Sites, ITT Population

Site: US Sites	Seizure Type	Treatment Period	Treatment Group	n	Mean	SD	Median	Min.	Max.
Tonic-Clonic Seizures	Escalation	Placebo		12	41.1	66.42	43.9	-128.6	100.0
		Lamictal XR		9	61.3	45.10	85.7	-37.1	100.0
	Maintenance	Placebo		11	55.4	35.57	57.1	-8.6	100.0
		Lamictal XR		8	84.2	23.97	97.2	33.3	100.0
	Last 8 wks Maintenance	Placebo		11	55.6	43.74	62.7	-16.7	100.0
		Lamictal XR		8	85.1	20.24	96.6	50.0	100.0
	Entire Treatment	Placebo		12	52.2	42.25	53.6	-32.3	100.0
		Lamictal XR		9	75.9	30.27	92.0	7.4	100.0

Table 6-19

Summary of Percent Change from Baseline in Weekly Seizure Frequency by US or Non-US Sites, ITT Population

Site: Non-US Sites	Seizure Type	Treatment Period	Treatment Group	n	Mean	SD	Median	Min.	Max.
Tonic-Clonic Seizures	Escalation	Placebo		60	7.5	81.86	29.2	-319.0	100.0
		Lamictal XR		60	42.1	60.81	61.9	-197.1	100.0
	Maintenance	Placebo		59	17.1	91.27	33.3	-491.9	100.0
		Lamictal XR		60	62.3	57.53	86.1	-142.4	100.0
	Last 8 wks Maintenance	Placebo		59	24.3	66.77	33.3	-180.0	100.0
		Lamictal XR		60	65.7	54.65	100.0	-131.3	100.0
	Entire Treatment	Placebo		60	14.9	80.72	28.4	-427.2	100.0
		Lamictal XR		60	54.6	51.29	74.2	-100.0	100.0

Age

The sponsor has analyzed age in three strata, less than 16 years old, 16 to 65 years old and greater than 65 years old. The stratum under age 16 comprises 7% of the total enrollment. The stratum 16 years to 65 years old represents the overwhelming majority of the study participants at 91.4%. The representation over age 65 is only 1.4% of enrollment, [Table 6-2](#).

The age range less than 16 is not sufficiently represented to draw conclusions on efficacy. Only 4 patients less than 16 were randomized to LTG XR and 6 patients to placebo. In this age range the placebo had a greater mean reduction in seizure frequency from baseline than the LTG XR group.

Only one patient older than age 65 was present in each of the treatment assignments.

Sex

There is a minor predominance of females in the placebo group and a corresponding predominance of males in the treatment group. Overall however there is adequate balance, [Table 6-2](#).

Race / ethnic origin

The demographic profile is dominated by two racial groups, Asian and Caucasian in proportions where meaningful conclusion may be drawn concerning the efficacy of LTG XR in these populations, however the numbers of African-Americans have insufficient numbers for conclusions directly applicable to that group, [Table 6-2](#).

Pediatrics

As noted in demographics of study LAM100036 there are 6 (8%) subjects under the age of 16 enrolled in the placebo group and 4 (6%) of subjects in the lamotrigine XR treatment group. These small numbers do not allow a meaningful statistical analysis of the treatment effect. In the similarly designed study of lamotrigine XR for partial onset seizures (LAM10034) there were 4 subjects in the placebo group and 5 in the lamotrigine XR group which combined provide 10 placebo subjects and 9 lamotrigine XR treated patients. Pooling these two subject groups may provide a more valid analysis of the utility of lamotrigine XR in the pediatric population. This was presented to the statistical team who did not feel the total group size of 19 subjects would yield more meaningful statistical analysis.

A pooled analysis of the subjects age 13 to 18 years examining the relationship between dose and concentration at two time points was performed by the clinical pharmacology reviewer. This analysis found a nearly concordant overlap between values for adults and subjects ≤ 18 years old see [figure 6-2](#).

Figure 6-2

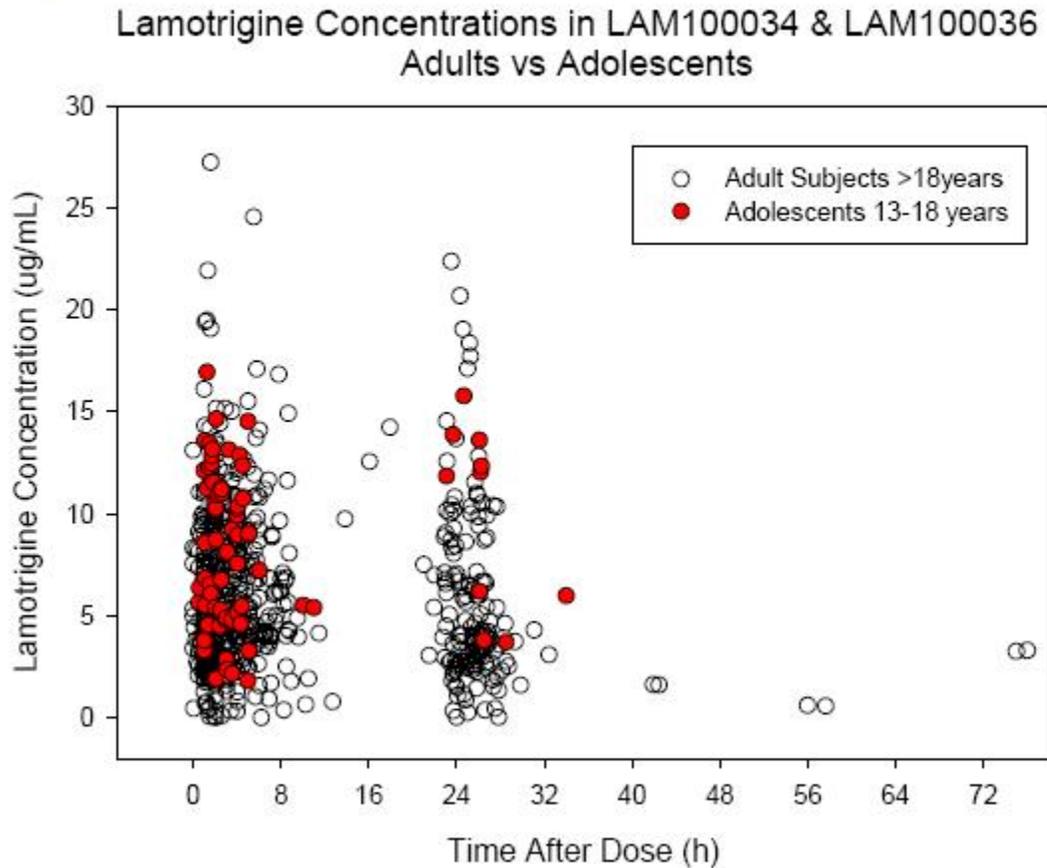


Figure 4

Reviewer Comment: although the study cohort age 18 years or less is too small for a meaningful statistical analysis, the alignment of dose – concentration between the below and above age 18 groups and the accepted efficacy of lamotrigine IR for PGTC seizures are strongly support labeling for Lamictal XR use in age 13 and above.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations
Dose response relationship of LTG XR has been evaluated in NDA 22115. This discussion may be found on pages 26 and 27, section 5.1 Pharmacokinetics in the NDA review by Dr. Kapcala, however the salient features of the discussion are captured in the following excerpts from Dr. Kapcala's review:

The increase in systemic exposure to lamotrigine was dose proportional between 50 and 200 mg XR. At doses between 25 mg and 50 mg, the increase in exposure was less than dose proportional, with a 2-fold increase in dose resulting in an approximate

1.6-fold increase in exposure. This observation is not likely to be considered of any significant clinical relevance as the doses are titrated up starting with 25 mg QD.

Assessment of dose proportionality of the dose range 50-200 mg XR lamotrigine showed dose proportionality for both C_{max} and AUC(0-24)_{ss}. The slope of the power model was close to unity and the 90% CI was completely contained within the pre-defined range of 0.8391- 1.1609.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Analysis of the last 8 weeks of maintenance does not reveal loss of significant treatment effect, [Table 6-10](#). This is some although modest indication that efficacy is not lost during the early phase of treatment. In addition, there is robust experience with lamotrigine XR to support long term efficacy.

6.1.10 Additional Efficacy Issues/Analyses

The target dose and dose escalation of Lamictal XR is stratified according to the type of concomitant anticonvulsant medications and their enzyme inducing or inhibiting properties or absence of effect on the metabolism of lamotrigine. This type of dose escalation and target dose table has been included in the approved label for Lamictal XR in partial seizures and Lamictal IR. A similar guide is present in labeling for Lamictal XR in PGTC seizures. In order to determine if the lamotrigine dosage in the treatment population of study LAM100036 corresponds to the labeling guideline an analysis of dose by AED treatment category is performed.

Labeling assigns three concomitant AED treatment categories, [table 6-20](#). Study LAM100036 is examined to determine the distribution of Lamictal XR dose among the concomitant AED category. The purpose of the examination is to determine if the spectrum of Lamictal XR dose within each category is commensurate with the proposed labeling guidelines based on concomitant AED treatment.

Table 6-20	Distribution of Lamictal XR dose during DB maintenance interval according to concomitant AED category		
	Any VPA	For Patients NOT TAKING Carbamazepine, Phenytoin, Phenobarbital, Primidone ^b , or Valproate ^a	For Patients TAKING Carbamazepine, Phenytoin, Phenobarbital, or Primidone ^b and NOT TAKING Valproate ^a
Maintenance Range (Week 8 and onward)	200 to 250 mg every day ^c	300 to 400 mg every day ^c	400 to 600 mg every day ^c
# assigned to each AED category	29	8	33
# with Dose during DB maintenance falling within category guidelines	22	6	33
# with dose not within category guideline	7 subjects with dose <200mg day	1 subject dose not provided, 1 subject <300mg / day	

Examination of the dose categories reveals that the “Any VPA” category had the largest number of subjects with a dose divergent from that expected value for the category. Seven subject doses fell below the 200mg floor of the guideline for the category. Four of the 7 or 57% of these subjects were within 8mg of the target 200mg dose. The median average maintenance interval dose for these seven subjects was 192mg with a mean of 182.9mg. The range was 150mg to 199.4mg. The most divergent of the 7 was an average maintenance interval dose of 150mg, however examination of the dataset reveals that there is no dose information entered after dose step number 4. Full analysis of these 7 subjects is presented in table 6-21 below. Overall analysis of the 29 patients of the Any VPA category (including the 7 with values below the 200mg category guideline) reveals a mean dose of 196.4mg Lamictal XR with a median of 200mg and a range of 150mg to 216.7mg. Full analysis of the combined groups of those below and above the 200mg a day dose threshold is presented in table 6-22.

There were 8 patients in the "other regimens" category. One subject had no dose recorded, of the 7 whose dose was recorded the mean was 298.6 mg with a range of 290mg to 300mg. 6/7 had a dose of 300mg which is within the guideline of 300mg to 400mg. A single patient had an average maintenance interval dose of 290.6mg Lamictal

XR. The median average maintenance interval dose of the 7 with a recorded data point was 300mg and a mean of 298.7mg with a range of 290.6 to 300mg.

Table 6-21 Category: Any VPA, dose <200mg. Graphic and Central Tendency Analysis

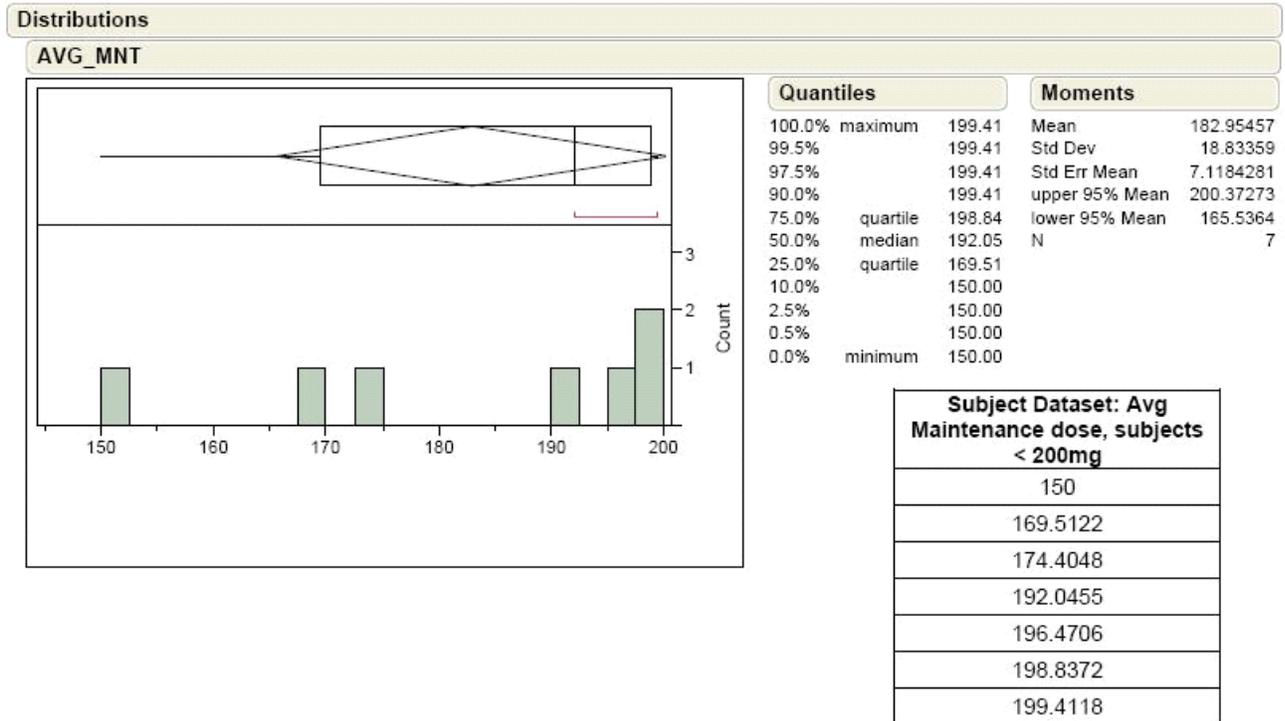
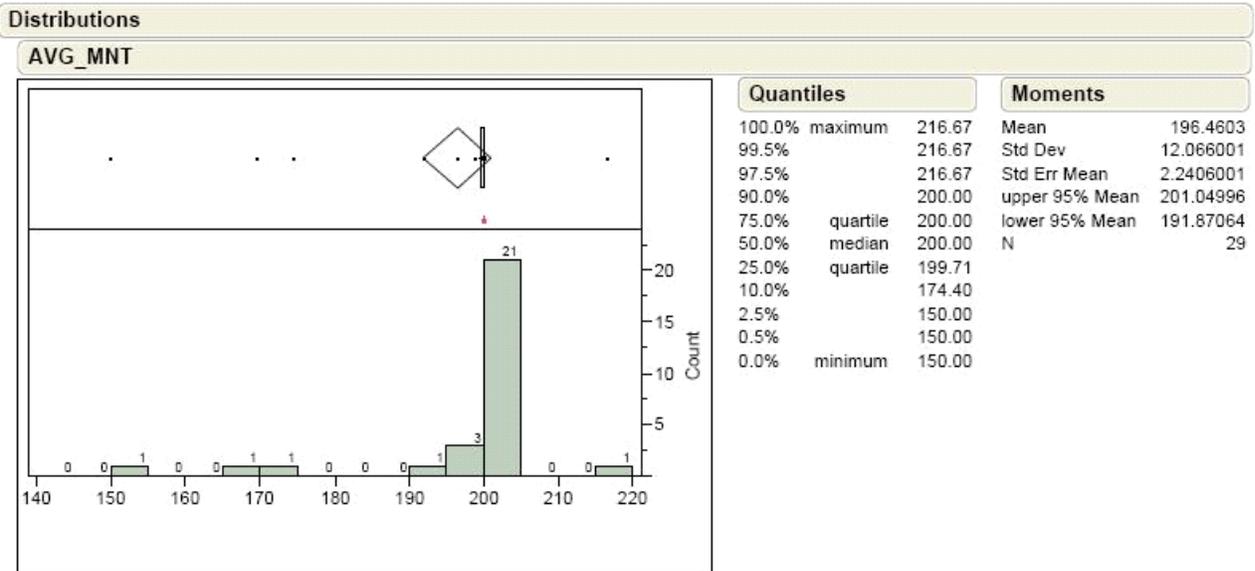


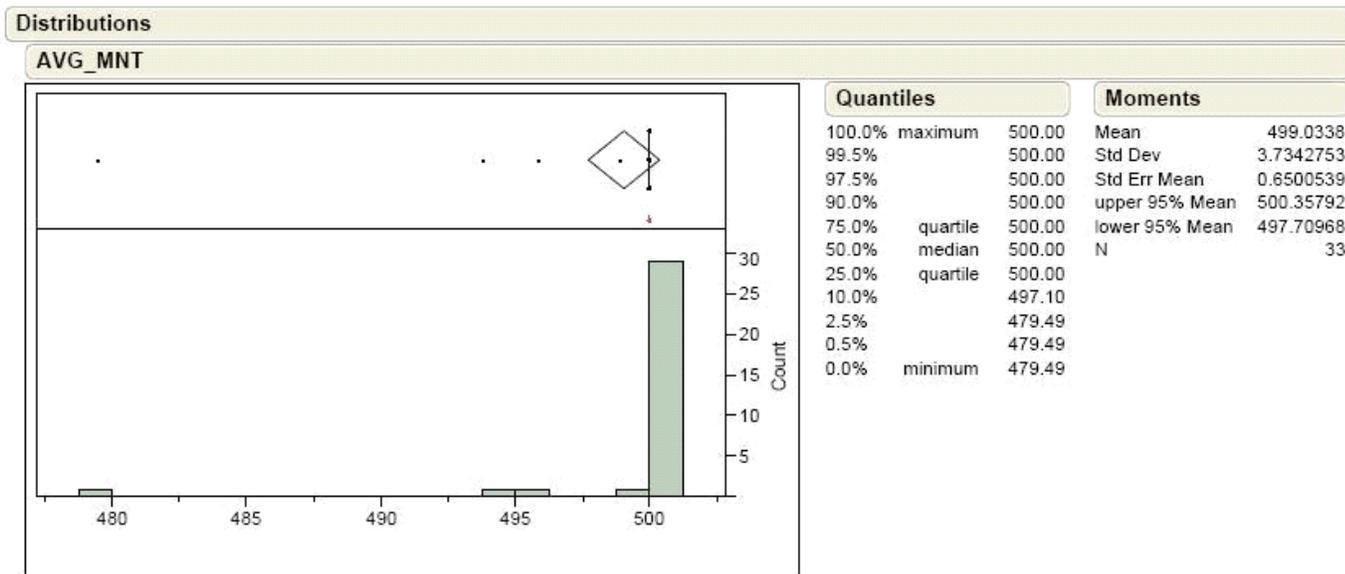
Table 6-22 Category Any VPA: Combined graphic and central tendency analysis of doseage above and below 200mg- (All)



In the category for those taking EIAEDs there were 33 patients and the dose of all subjects fell within the 400 to 600mg guideline, with a mean dose of 500mg. There were 29 subjects whose average maintenance interval dose was 500mg and 4 subjects whose average maintenance interval dose was below 500mg but above the lower limit of this concomitant AED category guideline of 400mg /day. The central tendency analysis of this concomitant AED group is seen in table 6-23.

Table 6-23

Category: Patients taking EIAED, graphic and central tendency analysis



Reviewer comment: There are three categories of concomitant AED with associated dose escalation and target dose guidelines. The distribution of LAM100036 Lamictal XR treated subjects is examined to determine if the actual delivered dose of Lamictal XR during maintenance phase corresponds to the associated labeling guidelines. The “Any VPA” concomitant AED category has the largest number of subjects whose dose is divergent from the category labeling guideline. 7 subjects have average maintenance interval dose that is lower than the floor of the labeling guideline of 200mg Lamictal XR daily. The most extreme divergence occurs in a subject who has incomplete entry of dose data. No dose entry is found after dose step number 4, in a dataset where dose steps are recorded to dose seven. This subject 1711 is not found in the list of patients who withdrew from the study, thus no explanation is available for this truncated dose timeline. In the absence of this outlier the remaining six subjects have a median average maintenance dose of 194.2mg and a mean of 188.4mg with a range of 169.5 to 199.4. When the entire cohort of 29 subjects of the “Any VPA” concomitant AED group is examined, the median of the group is 200mg and the mean is 196.4mg (table 6-22). This limited divergence from the lower limit, of the guideline (200mg daily) for “Any VPA” is not of sufficient magnitude to reduce the current dose escalation and target dose labeling.

The cohort of subjects falling into the “other regimen” group of concomitant AED use has only a single subject whose value falls 9.5mg below the lower range of the target dose guideline, with an additional subject where no dose is recorded. This cohort is

small for substantive conclusions to be extracted, although the current label is supported by 86% of the subjects with recorded dose.

In the final concomitant AED group, those taking EIAED's, there is no divergence from the labeled guideline for the category. 29 of 33 subjects have an average maintenance interval dose of 500mg Lamictal XR daily, with the remaining 4 subjects having an mean of 492mg daily with a range of 479.5 to 499mg. All of these values cluster tightly around the 500mg midrange of this concomitant AED category guideline.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data from 11 studies was submitted for this safety review. These include data from double blind and open label phase of three controlled clinical trials, LAM100036, LAM100034, LAM30055. At the initial submission of NDA 22509 the open label phase of LAM30055 was ongoing; at the submission of the 120 day safety update this open label phase is completed. Safety data cut off at initial submission was 9/28/08; safety data cut off for the 120 day safety update was on 3/31/2009.

At time of initial safety data cut off there were 5 completed clinical pharmacology studies and two ongoing clinical pharmacology studies contributing safety data. At the submission of the 120 day safety update the open label continuation phase of study LAM30055 was completed. The clinical pharmacology study LEP108937 was also completed. The remaining clinical study, LEP105972 is still ongoing. For this study, deaths, serious adverse events (SAE's) and withdraws due to AE's that occurred during the 120day Safety Update period (1 October2008 to March 2009) are included.

Table 7-1 Clinical Studies Providing Safety Information for Lamictal XR in the ISS					
Study Number	Status of study, initial submission 9/28/2008	Status of study 120 day safety update, 3/31/09	Type of study	Number of subjects in safety population	Information provided
Phase III studies					
LAM100036	Complete		Pivotal efficacy and safety (PGTC seizures), 19 weeks blinded, 52 weeks open-label	146	All Safety Data
LAM10034	Complete		Pivotal efficacy and safety (partial seizures), 19 weeks blinded, 52 weeks open-label	239	All Safety Data
LAM30055	Complete (DB only)	Complete (DB & open label)	Efficacy and safety (conversion to monotherapy, partial seizures), 22 to 23 weeks blinded, 24 weeks open-label	223	All Safety Data
Clinical Pharmacology Studies (Single Dose Healthy Volunteer)					
LAM102611	Complete		Single dose esomeprazole drug interaction, LTG XR formulation	61	All Safety Data
LAM10014	Complete		Single dose food effect, LTG XR formulation	95	All Safety Data
LAM10005	Complete		Single dose safety and PK (LTG XR formulation at different release rates), food effect	28	All Safety Data
LEP111102	Complete		Single dose relative bioequivalence (different LTG XR doses), food effect	209	All Safety Data
LAM105379	Complete		bioequivalence (different LTG XR doses), food	180	All Safety Data
LEP108937	Ongoing	Complete	Open-label study to assess the effect of LTG XR and phenytoin on the PK of atorvastatin	75 (LTG XR cohort)	All Safety Data
LEP105972	Ongoing	Ongoing	Safety and tolerability of adjunctive and monotherapy in elderly subjects with epilepsy	70	Pregnancies, deaths, withdrawals due to AEs, and SAEs

There is considerable overlap between the safety database for the review of NDA 21-115, which was submitted for approval for the use of lamotrigine XR in the treatment of partial onset seizures and NDA 22509, the application submitted for the use of lamotrigine XR in the treatment of primarily generalized tonic clonic seizures (PGTC). [Table 7-2](#) presents a listing of the studies included in the current submission and in NDA 22-115.

Table 7-2 Listing of Studies Included in the Current Submission and in NDA 22-115

Study	Included in CSS	Included in NDA 22-115	Reason for Exclusion from CSS
Phase II/III Studies			
LAM100036	✓	-	-
LAM100034	✓	✓	-
LAM30055	✓	-	-
LEP103944	-	✓	Excluded due to the short duration of treatment (2 weeks on LTG XR), previous exposure to LTG IR, and open-label study design
Clinical Pharmacology Studies			
LAM10005	✓	✓	LAM10005 Part B was not included because study was repeat-dose; repeat-dose integration was included in NDA 22-115
LAM10014	✓	✓	-
LAM10017	-	✓	Repeat-dose study
LAM102611	✓	✓	-
LAM105377	-	✓ (120-day update)	Pilot study for formulation selection
LAM105379	✓	-	-
LEP111102	✓	-	-
LAM10004	-	✓	Exploratory PK study which did not utilize LTG XR formulation
LAM10007	-	✓	Exploratory PK study which did not utilize LTG XR formulation

7.1.2 Categorization of Adverse Events

Reviewers Comment: following are the sponsor's categorization of Adverse Events.

Table 7-3 Definition of an Adverse Event

Study Number	Definition of an AE
LAM100036 LAM100034 LAM30055 LAM10014 LAM102611 LAM105379	An AE was defined as any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE could therefore have been any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, an AE could also include failure to produce expected benefits (i.e., lack of efficacy), abuse, or misuse.
LEP111102 LAM10005 [Part A]	An AE was defined as any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE could have therefore been any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Serious Adverse Event- Any Untoward medical occurrence that, at any dose:

- Resulted in death
- Was life-threatening
 - NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Required hospitalization or prolongation of existing hospitalization
 - NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE was considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline was not considered an AE.

- Resulted in disability/incapacity
 - NOTE: The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Was a congenital anomaly/birth defect

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The principal groupings discussed by the sponsor are based on the controlled clinical trials LAM100036 and LAM100034. [Table 7-4](#) indicates the pooling combinations of these trials which are examined.

Table 7-4 ISS study Groupings	
Study Grouping	Studies (Groupings refer to subjects exposed to LTG XR during a particular Phase of the study)
Controlled Adjunctive Studies	double-blind Treatment Phases of Study LAM100036 and Study LAM100034
Pivotal Adjunctive Study	double-blind Treatment Phase of Study LAM100036
Conversion to Monotherapy Study	double-blind Treatment Phase of Study LAM30055 (Completed)
Uncontrolled Adjunctive Studies	open-label Continuation Phases of Study LAM100036 and Study LAM100034
Controlled and Uncontrolled Adjunctive Studies	double-blind and open-label Continuation Phases of Study LAM100036 and Study LAM100034
LAM100036 open-label Continuation Phase Data	open-label Continuation Phase of Study LAM100036
All Clinical Studies	double-blind Treatment Phases of Study LAM100036, Study LAM100034, and Study LAM30055 (Completed) and open-label Continuation Phases of Study LAM100036 and Study LAM100034
Single Dose Healthy Volunteer Studies	Study LAM102611, Study LAM10014, Study LAM10005 (Part A), Study LEP111102, and Study LAM105379

Grouping Descriptions **Controlled Adjunctive Studies (LAM100036 and LAM100034, Pooled Double-blind Treatment Phases)**

The Controlled Adjunctive Studies grouping includes pooled data from subjects exposed to LTG XR during the double-blind Treatment Phases of Study LAM100036 or Study LAM100034. These 2 Phase III studies were of similar study design and duration, and provide the largest source of controlled safety data available. Selected safety data from individual studies are presented side-by-side with combined data from the Controlled Adjunctive Studies.

Pivotal Adjunctive Study in PGTC Seizures (LAM100036)

The Pivotal Adjunctive Study grouping includes data from subjects exposed to LTG XR during the double-blind Treatment Phase of Study LAM100036 only. These safety data are presented in their entirety in the CSR for Study LAM100036. A summary of safety data is presented in this CSS.

Uncontrolled Adjunctive Studies (LAM100036 and LAM100034 Open-label Continuation Phases)

The Uncontrolled Adjunctive Studies grouping includes pooled data from subjects exposed to LTG XR during the open-label Continuation Phases of Study LAM100036 or LAM100034.

Controlled and Uncontrolled Adjunctive Studies (LAM100036 and LAM100034)

The Controlled and Uncontrolled Adjunctive Studies grouping includes pooled data from subjects exposed to LTG XR at any time during Study LAM100036 or Study LAM100034 (double-blind Treatment and/or open-label Continuation Phases).

Open-label Continuation Phase Data (LAM100036)

The LAM100036 open-label Continuation Phase Data grouping includes data from subjects exposed to LTG XR during the open-label Continuation Phase of Study LAM100036.

All Clinical Studies (LAM100036, LAM100034, and LAM30055)

The All Clinical Studies grouping includes integrated data from subjects exposed to LTG XR at any time during the double-blind Treatment and/or open-label Continuation Phases of Study LAM100036 or Study LAM100034, or the double-blind Treatment Phase of Study LAM30055 (Completed). Although safety analyses are provided for the All Clinical Studies grouping, these combined summaries will be less comprehensive due to the different trial design for Study LAM30055 (historical control and different study design [withdrawal to monotherapy]).

Conversion to Monotherapy Study (LAM30055)

The Conversion to Monotherapy Study grouping includes data from subjects exposed to LTG XR during the double-blind Treatment Phase of Study LAM30055 (Completed) only. These safety data are presented in their entirety in the CSR for Study LAM30055. A summary of safety data is presented in this CSS.

Grouping of Clinical Pharmacology Studies (LAM102611, LAM10014, LAM10005 [Part A], LEP111102, and LAM105379)

The Single Dose Healthy Volunteer Studies grouping includes healthy volunteers exposed to LTG XR during Study LAM102611, Study LAM10014, Study LAM10005 (Part A), Study LEP111102, and Study LAM105379. The safety data from healthy volunteers who received the LTG XR formulation are integrated and summarized. Although the designs of these studies are different, all have pre-dose measurements and at least 1 post-dose measurement within 21 days of the last dose.

7.2 Adequacy of Safety Assessments

Description of Safety Populations: The Safety Population consists of all subjects who took at least 1 dose of study drug.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

At the time of the 120 day safety update a total of 662 subjects were treated with lamotrigine XR in All Clinical Studies Grouping. This represents an increase of 12 subjects since the initial NDA submission. A total of 558 subjects were exposed to lamotrigine XR for 24 weeks, and 270 subjects for 52 weeks. The distribution of this exposure by gender is balanced with 278 males and 280 females exposed for 24 weeks. 140 males and 130 females were exposed for 52 weeks. There is much less balance when exposure is examined by age. 35 subjects age <16 reached a 24 week exposure, 8 subjects >65 years old reached a 24 week exposure and 515 subjects between the ages of 16 to 65 reached a 24 week exposure. There were 14 subjects age <16 who reached a 52 week exposure, 6 subjects age >65 years and 251 between the ages of 16 to 65 who reached a duration of 52 weeks exposure. See [table 7-5](#) for 24 and 52 week exposure.

Exposure to at least week (t)	Total Subjects	Gender		Age at Screen		
		Male	Female	<16	16-65	>65
24	558	278	280	35	515	8
52	270	140	130	14	251	5

The exposure by dose mode is displayed in [table 7-6](#). In the clinical studies possible dosage modes were <300mg, ≥300mg to <500mg, ≥500mg.

Duration of exposure	<300mg (N=218)		≥300mg to <500mg (N=268)		≥500mg (N=176)		All lamotrigine XR (N=662)	
	N	% ^a	N	% ^a	N	% ^a	N	% ^b
≥26 weeks	143	26.2	245	44.9	158	29	546	82.5
≥52 weeks	94	34.8	59	21.9	117	43.3	270	40.8
Any Exposure	218		268		176		662	

^a percent of subjects exposed to duration indicated in row and total indicated in all lamotrigine

^b percent of subjects compared to any exposure (662)

[Table 7-6](#) shows exposure by modal dose group for both ≥26 weeks and ≥52 weeks. This profile reveals the mid dose mode, ≥300mg to <500mg for greater than or equal to 26 week exposure has the largest percent (44.9%), the high dose exposure group, ≥500mg contains 29% of subjects and the <300mg/day group contains 26.2% of subjects. The group with ≥52 weeks exposure has the largest number of participants in the high dose mode, ≥500mg containing 43.3% of participants. In the same ≥52 week cohort the mid dose exposure ≥300mg to <500mg a day, contains 21.9% of subjects and the low dose <300mg / day group contains 34.8% of subjects.

The demographic profile of study subjects in the pivotal trials LAM100034 and 100036 at time of NDA submission, safety data cut off, 9-28-2008 reveal a close balance in both studies in age distribution between placebo and lamotrigine XR treatment. The distribution of subjects between placebo and lamotrigine XR for both studies is balanced. In the age range encompassing the majority of subjects, 16 to 65 years old, both studies are balanced between placebo and lamotrigine XR subject enrollment. Gender enrollment reveals the greatest disparity in placebo compared to lamotrigine XR subject distribution both in males and females for both studies; however, the difference which reaches a maximum of 6% does not suggest an intrinsic bias and is within a range of random asymmetry see [table 7-7](#).

Demographic Characteristic	Study LAM100036		Study LAM100034		Study LAM100036 and Study LAM100034	
	PBO (N=73)	LTG XR (N=70)	PBO (N=120)	LTG XR (N=116)	PBO (N=195)	LTG XR (N=190)
	Age (yrs)					
Mean (SD)	28.4 (11.48)	29.4 (12.78)	37.6 (14.32)	35.8 (12.68)	34.0 (14.05)	33.5 (13.34)

Range	13-74	14-69	14-73	13-70	13-74	13-73
Age Group (yrs), n (%)						
<16	6 (8)	4 (6)	4 (3)	5 (4)	10 (5)	10 (5)
16-65	66 (90)	65 (93)	112 (93)	108 (93)	180 (92)	175 (92)
>65	1 (1)	1 (1)	4 (3)	3 (3)	5 (3)	5 (3)
Gender, n (%)						
Male	35 (48)	38 (54)	63 (53)	54 (47)	98 (50)	94 (50)
Female	38 (52)	32 (46)	57 (48)	62 (53)	97 (50)	96 (51)

The pooled demographic profile of the single dose healthy volunteer studies is composed of 573 subjects of mean age 33.6 years, range 18 to 55 years. There is a majority of male participants compared to female, 63% to 38% respectively see [table 7-8](#).

Table 7-8		Demographics for the Single Dose Healthy Volunteer Studies (LAM102611, LAM10014, LAM10005 [Part A], LEP111102, and LAM105379)	
Demographic Characteristic		LTG XR (N=573)^a	
Age (yrs)			
Mean (SD)		33.6 (9.92)	
Range		18-55	
Age Group (yrs), n (%)			
<16		0	
16-65		573 (100)	
>65		0	
Gender, n (%)			
Male		358 (63)	
Female		215 (38)	
^a One additional subject (Subject 16; Study LAM10005 [Part A]) received a dose of LTG XR and is not included in this summary			

Reviewer Comment:

The total number of subject exposed to durations of 6 months and 1 year meet the International Conference on Harmonization (ICH) requirements for assessing the clinical safety of drugs for the long term treatment of life threatening conditions. The modal dose exposures at 26 weeks reveal a majority in the mid range of exposure ≥300mg to <500mg. At 52 weeks there is a majority exposure at the high end of dose range, ≥500mg. This distribution is favorable; the skew toward a higher dose, 52 week exposure assures a more robust test of safety characteristics of the test drug. The demographic parameters of the study population are balanced between placebo and lamotrigine XR groups. The age distribution, as also noted in section 6.1.7 find few subjects in the age less than 16 years or older than 65 years.

7.2.2 Explorations for Dose Response

Dose response is examined in NDA 22115

7.2.3 Special Animal and/or In Vitro Testing

None

7.2.4 Routine Clinical Testing

Time and Events schedule; Controlled Adjunctive Studies

Table 7-9 Time and Events Schedule- Studies LAM100034 and LAM100036

Event	Screen	Baseline Phase		Double-blind Treatment Phase					Continuation Phase ^{1,2}					Taper/Follow-up Phase ³	
		V2	V3	Escalation		Maintenance			Transition		Open-label				F/U visit ⁴
Visits	V1	V2	V3	V4	V5	V6	V7	V8 ⁵	V9	V10	V11	V12	V13	V14	V15
Week (i.e., end of specified week)	≤2 Wks	Base Wk 4	Base Wk 8	Treat Wk 3	Treat Wk 7	Treat Wk 11	Treat Wk 15	Treat Wk 19 /End	Con Wk 3	Con Wk 7	Con Wk 19	Con Wk 31	Con Wk 43	Con Wk 52 /End	3 wks after last dose
Eligibility															
Informed Consent	X														
Inclusion/Exclusion Criteria	X														
Demography	X														
Safety															
Vital Signs	X-----X														
Body weight/height	X			X		X		X							
Medical & Seizure history	X														
EEG	X														
Physical Exam	X							X							
Full Neurological Exam	X							X							
Brief Neurological Exam				X		X									
Urine Pregnancy Test ^{6,7}	X		X	X		X		X							X
Hematology/Clin Chemistry	X			X		X		X							
Adverse Events		X-----X							X-----X						
ECGs and Urinalysis	X							X							

7.2.5 Metabolic, Clearance, and Interaction Workup

This is addressed by the Clinical Pharmacology review of Lamictal XR in NDA 22115

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The observation interval for lamotrigine has been 15 years since first approval in the US, allowing adequate time for the emergence of post clinical trial adverse events. Therefore no large magnitude unexpected events are anticipated with a long acting

form. No additional examination of similar drugs in class is performed to seek insight into the potential for new adverse effects with use of Lamictal XR.

7.3 Major Safety Results

7.3.1 Deaths

There were 6 deaths in the lamotrigine XR clinical development program. Four of these deaths were reported in NDA 22-115. These four occurred in the open label phase, 3 in study LAM100034 and 1 in study LAM100036. The subject number, study and demographics are presented in [table 7-10](#). There is limited data and a complex array of medical complications noted for subject 1578, with the true nature of the catastrophic medical event unclear. Subject 2152 is noted to have died of drug toxicity, however no drug level is available only the presence of lamotrigine in multiple tissues. This may have been a SUDEP or more unlikely a suicide, again the true etiology of the death is obscure. A full review of these 4 deaths is present in the initial NDA 22115 reviewed by Dr. Kapcala³

Two additional deaths are reported in the 120 day Safety Update. One of these occurred in study LAM30055 (Efficacy and safety (conversion to monotherapy, partial seizures), 24 weeks open-label.) In this case the subject had hepatitis B and alcoholic hepatic cirrhosis. The subject developed hepatocellular carcinoma during the study. The subject case report narrative is provided in [appendix 1](#). The second of these occurred in study LEP105972 (Safety and tolerability of adjunctive and monotherapy in elderly subjects with Epilepsy). In this case subject 14 suffered a left hip fracture complicated by small bowel obstruction and myocardial infarction, see [appendix 2](#).

Table 7-10 Deaths reported in Lamictal XR development Program						
Study	Subject	Age/Race/sex	Medical event	Treatment related	Dose of lamotrigine XR at death (mg/day)	Previously reported in NDA 22-115 (yes/no)
LAM100036	1578	14F/Asian	Hydrocephalus	No	350	Yes
LAM100034	1546	38F/Asian	Aspiration/cardiac arrest/Grand mal convulsion	No	500	Yes
LAM100034	2094	35F/white	Cardiac Failure acute	Yes	500	Yes
LAM100034	2152	22F/white	Drug toxicity	Yes	500	Yes

³ Kapcala L. Medical Officer, Review of NDA 22115 Lamictal XR (lamotrigine XR), PDUFA date 9/14/07, p77. and Kapcala L. Medical Officer, Review of NDA 22115 Lamictal XR (lamotrigine XR), completion date 5/3/09, PDUFA date 5/31/09, p71.

Table 7-10 Deaths reported in Lamictal XR development Program						
Study	Subject	Age/Race/sex	Medical event	Treatment related	Dose of lamotrigine XR at death (mg/day)	Previously reported in NDA 22-115 (yes/no)
LAM30055	254	57M/Asian	Hepatocellular carcinoma	No	Not provided	No
LEP105972	14	85F/	Left hip fracture, small bowel obstruction, myocardial infarction	No	Uncertain, possibly 200mg but date not matching	No

Reviewer comment: The timeframe of the past medical history of subject 254 in study LAM30055 is not well defined. There is an entry of alcoholic cirrhosis and viral cirrhosis. It is unclear from the case report if this is concurrent or precedes the hepatocellular carcinoma. It is unlikely that chronic medical disorders such as alcoholic cirrhosis or viral cirrhosis developed during the course of the 105 day drug exposure. Both of these chronic medical conditions predispose to hepatocellular carcinoma. Although it is very unlikely that the hepatocellular carcinoma is related to study drug, it is likely that disqualifying medical conditions⁴ were present at the time of eligibility screening. The death of subject 14 in study LEP105972 is most consistent with the chain of events seen in the medically frail elderly, this death is also not likely related to lamotrigine XR treatment.

7.3.2 Nonfatal Serious Adverse Events

Controlled Adjunctive Studies (ISS)

In the Controlled Adjunctive Studies, a similar percentage of subjects in the placebo and LTG XR groups reported TESAEs (6 [3%] subjects in both groups) ([Table 7-11](#)). There were no TESAEs reported by more than 1 subject in either group. All subjects who reported TESAEs were reported to be recovered except for 1 event of diabetes mellitus and 1 event of pancreatitis. Treatment-emergent SAEs led to withdrawal of 3 subjects, all in Study LAM100034 (1 subject in the placebo group [Subject 1809 who reported TESAEs of cough, drop attack, and vomiting] and 2 subjects in the LTG XR group [Subject 1534 who reported a TESA of pancreatitis and Subject 1840 who reported TESAEs of dizziness, headache, and nystagmus]). All of these subjects were presented in NDA22115.

⁴ Protocol LAM30055. A Multicenter, Double-Blind, Randomized Conversion to Monotherapy Comparison of Two Doses of Lamotrigine for the Treatment of Partial Seizures; Exclusion criteria # 15. *Has any clinically significant cardiac, renal, hepatic condition, or a condition that affects the absorption, distribution, metabolism or excretion of drugs.*

Table 7-11	Summary of TESAEs for the Controlled Adjunctive Studies (LAM100036 and LAM100034, Individual and Pooled Double-blind Treatment Phases)					
	Number (%) of Subjects					
	Preferred Term	Study LAM100036		Study LAM100034		Study LAM100036 and Study LAM100034
	PBO (N=74)	LTG XR (N=72)	PBO (N=121)	LTG XR (N=118)	PBO (N=195)	LTG XR (N=190)
Any Event	0	1 (1)	6 (5)	5 (4)	6 (3)	6 (3)
Confusional state	0	1 (1)	0	0	0	1 (<1)
Dizziness	0	0	0	1 (<1)	0	1 (<1)
Headache	0	0	0	1 (<1)	0	1 (<1)
Intentional overdose	0	0	0	1 (<1)	0	1 (<1)
Myocardial infarction	0	0	0	1 (<1)	0	1 (<1)
Nystagmus	0	0	0	1 (<1)	0	1 (<1)
Pancreatitis	0	0	0	1 (<1)	0	1 (<1)
Partial seizures	0	0	0	1 (<1)	0	1 (<1)
Tibia fracture	0	0	0	1 (<1)	0	1 (<1)
Cough	0	0	1 (<1)	0	1 (<1)	0
Diabetes mellitus	0	0	1 (<1)	0	1 (<1)	0
Drop attacks	0	0	1 (<1)	0	1 (<1)	0
Gastritis erosive	0	0	1 (<1)	0	1 (<1)	0
Hypokalaemia	0	0	1 (<1)	0	1 (<1)	0
Hypomagnesaemia	0	0	1 (<1)	0	1 (<1)	0
Radius fracture	0	0	1 (<1)	0	1 (<1)	0
Sepsis	0	0	1 (<1)	0	1 (<1)	0
Urinary retention	0	0	1 (<1)	0	1 (<1)	0
Urinary tract infection	0	0	1 (<1)	0	1 (<1)	0
Urosepsis	0	0	1 (<1)	0	1 (<1)	0
Uterine leiomyoma	0	0	1 (<1)	0	1 (<1)	0
Vomiting	0	0	1 (<1)	0	1 (<1)	0

All Clinical Studies (ISS)

In the [All Clinical Studies](#) grouping, (LAM100036, LAM100034, and LAM30055), a total of 40 (6%) subjects reported TESAEs. Ataxia, dizziness, grand mal convulsion, nystagmus, partial seizures with secondary generalization, and vomiting were each reported by 2 (<1%) subjects; no other TESAEs were reported by more than 1 subject ([Table 7-12](#)).

Table 7-12 Summary of TESAEs Reported by >1 Subject for All Clinical Studies (LAM100036, LAM100034, and LAM30055)	
Preferred Term	Number (%) of Subjects
	All LTG XR (N=650)
Any Event	40 (6)
Ataxia	2 (<1)
Dizziness	2 (<1)

Preferred Term	Number (%) of Subjects
	All LTG XR (N=650)
Grand mal convulsion	2 (<1)
Nystagmus	2 (<1)
Partial seizures with secondary generalization	2 (<1)
Vomiting	2 (<1)

The NDA22509 safety database is primarily a continuation of the NDA22115 safety database with the addition of completed studies. There are 21 new TESAEs derived from the open label phases of studies LAM100034, LAM100036, LAM30055 and LEP105972 as well as the completed component of LAM30055. [Table 7-13a](#) represents the TESAEs occurring in all phase III and ongoing studies which were reported in NDA22115 while table 7-13b represent 21 new TESAEs which have occurred since the last safety submission relevant to NDA22115.

Subject	Age/ Gender	Serious Adverse Event (Preferred Term)	Dose of LTG XR at Onset (mg/day)
Study LAM100034 (Double-Blind)			
LTG			
12	31/F	Intentional overdose	N/A a
131	70/F	Tibia fracture, myocardial infarction	300
312	37/F	Partial seizures	300
1534	13/M	Pancreatitis	500
1840	30/F	Dizziness, headache, nystagmus	600
Study LAM100034 (Open-Label)			
Baseline Failure			
1845	48/F	Partial seizures with secondary generalization	N/A a
PBO-LTG			
35	57/F	Infection	300
218	63/M	Ataxia	450
		Vomiting	300
		Dysarthria	200
1363	32/F	Astrocytoma	200
1551	25/F	Multiple fractures	N/A a
1554	60/M	Abasia, dizziness	500
2063	39/F	Food poisoning	200
LTG-LTG			
148	46/F	Cholecystitis acute, cholelithiasis	500
172	56/F	Intervertebral disc protrusion	300
332	68/F	Cervical spinal stenosis	450
421	48/F	Diabetic ketoacidosis	175
1546	38/F	Gastritis	600

		Aspiration, cardiac arrest, grand mal convulsion	500
2094	35/F	Cardiac failure acute	500
2121	17/M	Brain contusion, contusion, skin laceration, skull fracture, traumatic brain injury	200
2152	22/F	Drug toxicity	200
Study LAM100036 (Double-Blind)			
LTG			
1558	22/M	Confusional state	50
Study LAM100036 (Open-Label)			
Baseline Failure			
1441	21/F	Abdominal pain, nausea, vomiting	150
		Ataxia, nystagmus	150
		Suicide attempt	N/A a
PBO-LTG			
1310	74/M	Bile duct cancer	200
LTG-LTG			
274	39/F	Uterine leiomyoma	250
1251	41/M	Syncope vasovagal	300
1641	20/F	Abortion spontaneous	N/A a
Study LAM30055 (Double-blind Treatment Phase - Completed)			
LTG XR 300 mg/day			
62	25/M	Head injury	25
LTG XR 250 mg/day			
Study LAM30055 (Open-label Continuation Phase - Ongoing)			
62	25/M	Head injury	300
233	25/F	Back injury	300
		Joint sprain	300
521	15/M	Status epilepticus	300
Study LEP105972 (Open-label- Ongoing)			
11	73/M	Congestive heart failure	400
<p>a. Adverse event was reported after the last dose of study drug was administered. The last administered dose for Subject 1845 was 500 mg/day . The last administered dose for Subject 1551 was 50 mg/day . The last administered dose for Subject 12 was 500 mg/day . The last administered dose for Subject 1441 was 150 mg/day. The last administered dose for Subject 1641 was 200 mg/day.</p>			

Table 7-13b		SAEs not previously reported to the NDA22509 safety database in NDA221215 from All phase III and ongoing studies	
Subject	Age/ Gender	Serious Adverse Event (Preferred Term)	Dose of LTG XR at Onset (mg/day)
Study LAM100034 (Open-Label)			
Baseline Failure			
147	42/F	Malignant hypertension	N/A a
213	62/F	Gastroenteritis viral	500
PBO-LTG			
305	56/F	Ankle fracture	700
		Pneumonia viral	500
		Pyelonephritis	500

411	55/F	Status epilepticus	325
LTG-LTG			
131	70/F	Pelvic fracture	300
312	37/F	Complex partial seizures	450
Study LAM100036 (Open-Label)			
PBO-LTG			
1578	14/F	Altered state of consciousness, hemiparesis, hydrocephalus* previously reported to study LAM100034 as death.	350
1579	18/M	Conversion disorder	200
Study LAM30055 (Double-blind Treatment Phase - Completed)			
LTG XR 300 mg/day			
522	14/M	Grand mal convulsion, respiratory failure	300
807	24/F	Brain neoplasm	50
LTG XR 250 mg/day			
223	33/F	Pyrexia, rash	25
254	56/M	Hepatic neoplasm	250
255	52/M	Partial seizures with secondary generalization	250
810	29/M	Concussion	250
821	42/F	Upper gastrointestinal hemorrhage	250
Study LAM30055 (Open-label Continuation Phase - Ongoing)			
331	62/F	Periorbital hematoma	300
Study LEP105972 (Open-label- Ongoing)			
42	81/F	Fractured right hip	400
		Ataxia	400
289	71/M	Acute pancreatitis	500
318	76/F	Ataxia	300
346	69/M	Lethargy	500
		Right femoral thrombosis	500
386	75/M	Stroke	25
a. Adverse event was reported after the last dose of study drug was administered. The last administered dose for Subject 147 was 500 mg/day .			

Study LAM100034 and LAM100036 ongoing open label studies

LAM100034

Subject 147: 43 yo female developed malignant htn- non compliant with antihypertensive medications. This event is unrelated to the study medication.
Subject 213: 63 yo female, weakness & nausea, - viral gastroenteritis , unrelated to study medication.
Subject 305: 56 yo f developed in sequence over a period of a year , a left ankle fracture, viral pneumonia and pyelonephritis. Unrelated to study medication
Subject 411: 56 yo f status epilepticus, 138 days after start of Lamictal XR. Treatment discontinued. Relationship to study medication possible but uncertain.

Subject 131: 70 yo f, had fall (uses background walker) 78 days after beginning product, MI 92 days after beginning product. These events have no compelling relationship to study medication.

Subject 312: 37 yo f flurry of seizures 55 days after beginning product- also had low grade fever. Remained in study on treatment. Breakthrough of seizures not likely related to study medication.

LAM100036

Subject 1579: 19 yo female developed pseudoseizures mimicking worsening epilepsy 8 months after beginning therapy. Unrelated to study medication

Completed Monotherapy with historic control study LAM30055

Subject 331 Lam30055, 63 yo female had fall, most consistent with syncope 260 days after start of lamotrigine. No seizure activity seen. Sinus bradycardia identified in the hospital. Relationship uncertain, confounded by potential for primary hemodynamic / cardiac cause.

Ongoing open label phase of study LAM30055

Subject 807 a 24 yo female developed a cerebral neoplasm approximately four months after beginning lamotrigine. The neoplasm developed 3 years after onset of seizures. Although it is unlikely that the tumor was the initiating cause of epilepsy three years before discovery it is also unlikely that tumor induction occurred due to lamotrigine in just four month. A search of the AERS database reveals no post marketing signal for cerebral neoplasm. No PT's under the HLGTT "Nervous system neoplasms malignant and unspecified NEC" have an EB05 >1. This case does not indicate a new safety signal of cerebral neoplasm.

Subject 522 a 14 yo M suffered severe seizure/ status epilepticus with respiratory failure. In an epilepsy patient this isolated case of seizure exacerbation is of uncertain relationship to lamotrigine treatment. There are too many additional variables to allow a conclusion of causality.

Subject 62 a 25 yo male suffered head trauma during a seizure, a consideration is insufficient efficacy of the anticonvulsant, however the ingredient in this investigational product has a robust history of utility in the treatment of epilepsy.

Subject 810 a 29 yo male suffered a concussion due to a seizure while driving. The subject was on Lamictal XR monotherapy at the time of this event. The relation to the study drug is unclear.

Subject 821 a 42 yo female suffered upper gastrointestinal bleeding approximately four months after beginning the study drug. Relationship to the treatment is unclear, many background variables which may not be apparent in the case may contribute to this disorder. Stomach ulcer is present in section 6.2 in the label as an “other” event seen in clinical trials.

Subject 223 a 33 yo f developed a significant rash and fever which needed treatment with corticosteroids beginning approximately 8 days after beginning Lamictal XR. The rash resolved in five days after Lamictal XR was withdrawn. This event is likely to be due to Lamictal XR treatment but is also at maximum prominence in labeling.

Subject 254 a 56 yo male developed hepatic neoplasm while on Lamictal XR but also has a background of ETOH cirrhosis which is also a risk factor for hepatic neoplasm. This severely confounded case does not allow a conclusion of causality.

Subject 255 a 52 yo male developed breakthrough of seizures while tapering off of his concomitant oxcarbazepine. The change in anticonvulsant program confounds a conclusion of causality with this seizure breakthrough.

Reviewer Comment; the most frequent of the serious adverse events is seizure in 4 of 8 cases of TESAE, however the relationship to Lamictal XR treatment is unclear due to confounding features in one case, a background risk of seizure in all cases and no clinically meaningful increase in seizure in the treatment group in the controlled adjunctive studies (1/190).

Study LEP105972 - adjunctive and monotherapy in elderly subjects with epilepsy

Subject 42: 81 yo who fell and suffered fx hip 56 days after beginning lamotrigine. Although AED may have destabilized axial stability the patient advanced age is confounding.

Subject 289; 71 yo male developed acute pancreatitis 143 days after beginning lamotrigine. No alternate cause identified. Causality is possible however pancreatitis is in current labeling under postmarketing experience.

Subject 318: 76 yo female developed moderate ataxia which resolved after lamotrigine reduced by 100mg. Causality is likely.

Subject 346: 69 yo male with pvd developed lethargy and femoral artery thrombosis. Causality not supported.

Subject 386: 75 yo male developed ataxia thought to be a stroke, but neuroimaging data not provided. Also UTI. Causality doubtful.

Reviewer comment: Six TESAEs in study of tolerability in elderly population. Two cases have qualities of causality, these are a case of pancreatitis and a case of ataxia. The pancreatitis is more serious but is currently in labeling. The remainder of the cases are events that are more common on the background of age related cardiovascular and cerebrovascular disorders. No new safety signal or change in labeling is directed by these findings.

Reviewer Summary Comment: Taken in summary the serious adverse events from completed study LAM30055 and the ongoing open label studies do not identify a new safety signal. There was a predominance of seizure as adverse events in monotherapy study LAM30055 which raises a question of efficacy as monotherapy, however seizure occurrence in the epilepsy population is reasonably expected to occur as a background event.

120 Day Safety Update

Narrative of Study Update

At the safety cut-off date for NDA submission (30 September 2008), one clinical pharmacology study and two clinical studies were ongoing. These studies were:

- An open-label, historic-controlled study (LAM30055) evaluating conversion to monotherapy with LTG XR in adult (≥ 13 years old) subjects with partial seizures receiving therapy with a single anti-epileptic drug (AED). Only the open-label Continuation Phase was ongoing at the time of NDA submission.
- LEP105972 (a clinical study in elderly subjects ≥ 65 years of age with epilepsy).
- LEP108937 (a clinical pharmacology study exploring the interaction between atorvastatin and AEDs in healthy volunteers).

As of the 31 March 2009 cut-off date for this 120-day Safety Update, the clinical pharmacology Study LEP108937 has been completed. The open-label Continuation Phase of Study LAM30055 was also completed as of the cut-off date for this 120-Day Safety Report. Safety data from this portion of the study have been integrated into the All Clinical Studies grouping that was presented as part of the Integrated Summary of Safety for this application. The remaining clinical study (LEP105972) that was ongoing at the time of the NDA submission is still ongoing as of the cut-off date for this 120-Day Safety Update.

The number of subjects who reported TESAEs in the updated All Clinical Studies grouping ([Table7-15](#)) is slightly higher than that presented in the ISS but the percentages of subjects with TESAEs remain the same. In the updated All Clinical

Studies grouping, 43 (6%) subjects reported TESAEs compared to 40 (6%) presented in the ISS. This slight change is due to the integration of the LAM30005 open-label Continuation Phase in the updated All Clinical Studies grouping.

Reviewer Comment: Overall this incremental addition to NDA22509 safety database does not reveal evidence of a new safety signal.

Table 7-15 Summary of Treatment-Emergent Serious Adverse Events for All Clinical Studies	
System Organ Class Preferred Term	All lamotrigine XR N= 662
Any Event	43 (6%)
Nervous system disorders	
Any event	13 (2%)
Ataxia	2 (<1%)
Dizziness	2 (<1%)
Grand mal convulsion	2 (<1%)
Nystagmus	2 (<1%)
Partial seizures with secondary generalization	2 (<1%)
Status epilepticus	2 (<1%)
Altered state of consciousness	1 (<1%)
Complex partial seizures	1 (<1%)
Dysarthria	1 (<1%)
Headache	1 (<1%)
Hemiparesis	1 (<1%)
Hydrocephalus	1 (<1%)
Partial seizures	1 (<1%)
Syncope vasovagal	1 (<1%)
Injury, poisoning and procedural complications	
Any event	10 (2%)
Ankle fracture	1 (<1%)
Back injury	1 (<1%)
Brain contusion	1 (<1%)
Concussion	1 (<1%)
Contusion	1 (<1%)
Drug toxicity	1 (<1%)
Head injury	1 (<1%)
Intentional overdose	1 (<1%)
Joint sprain	1 (<1%)
Multiple fractures	1 (<1%)
Pelvic fracture	1 (<1%)
Periorbital haematoma	1 (<1%)

Table 7-15 Summary of Treatment-Emergent Serious Adverse Events for All Clinical Studies	
System Organ Class Preferred Term	All lamotrigine XR N= 662
Skin laceration	1 (<1%)
Skull fracture	1 (<1%)
Tibia fracture	1 (<1%)
Traumatic brain injury	1 (<1%)
Gastrointestinal disorders	
Any event	6 (<1%)
Vomiting	2 (<1%)
Abdominal pain	1 (<1%)
Food poisoning	1 (<1%)
Gastritis	1 (<1%)
Nausea	1 (<1%)
Pancreatitis	1 (<1%)
Upper gastrointestinal haemorrhage	1 (<1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	
Any event	5 (<1%)
Astrocytoma	1 (<1%)
Bile duct cancer	1 (<1%)
Brain neoplasm	1 (<1%)
Hepatic neoplasm malignant	1 (<1%)
Uterine leiomyoma	1 (<1%)
Cardiac disorders	
Any event	3 (<1%)
Cardiac arrest	1 (<1%)
Cardiac failure acute	1 (<1%)
Myocardial infarction	1 (<1%)
Infections and infestations	
Any event	3 (<1%)
Gastroenteritis viral	1 (<1%)
Infection	1 (<1%)
Pneumonia viral	1 (<1%)
Pyelonephritis acute	1 (<1%)

Table 7-15 Summary of Treatment-Emergent Serious Adverse Events for All Clinical Studies	
System Organ Class Preferred Term	All lamotrigine XR N= 662
Psychiatric disorders	
Any event	3 (<1%)
Confusional state	1 (<1%)
Conversion disorder	1 (<1%)
Suicide attempt	1 (<1%)
General disorders and administration site conditions	
Any event	2 (<1%)
Abasia	1 (<1%)
Pyrexia	1 (<1%)
Musculoskeletal and connective tissue disorders	
Any event	2 (<1%)
Cervical spinal stenosis	1 (<1%)
Intervertebral disc protrusion	1 (<1%)
Respiratory, thoracic and mediastinal disorders	
Any event	2 (<1%)
Aspiration	1 (<1%)
Respiratory failure	1 (<1%)

Table 7-15 Summary of Treatment-Emergent Serious Adverse Events for All Clinical Studies	
System Organ Class Preferred Term	All lamotrigine XR N= 662
Hepatobiliary disorders	
Any event	1 (<1%)
Cholecystitis acute	1 (<1%)
Cholelithiasis	1 (<1%)
Metabolism and nutrition disorders	
Any event	1 (<1%)
Diabetic ketoacidosis	1 (<1%)
Pregnancy, puerperium and perinatal conditions	
Any event	1 (<1%)
Abortion spontaneous	1 (<1%)
Skin and subcutaneous tissue disorders	
Any event	1 (<1%)
All Rash	1 (<1%)
Vascular disorders	
Any event	1 (<1%)
Malignant hypertension	1 (<1%)

7.3.3 Dropouts and/or Discontinuations

Controlled Adjunctive Studies (ISS)

In the [Controlled Adjunctive Studies](#), TEAEs led to withdrawal of 4 (2%) subjects in the placebo group and 10 (5%) subjects in the LTG XR group ([Table 7-16](#)). No single TEAE led to withdrawal of more than 1 subject in the placebo group. In the LTG XR group, dizziness (5 [3%] subjects), and all rash, headache, nausea, and nystagmus (2 [1%] subjects for each) each led to withdrawal of more than 1 subject. In study LAM10036 there was only one withdraw due to TEAE in the study drug group, this was due to rash. There were two withdraws in placebo, one due to depressed level of consciousness and one due to hallucination. In the “Controlled Adjunctive Studies” group with TESAEs leading to withdrawal there are only two subjects that were not presented in NDA22115. These subjects were 000259 who suffered a rash 40 days after beginning treatment with Lamictal XR and subject 001253 who developed altered mental status and

hallucinations 3 days after beginning placebo. The skin rash is characterized as moderate intensity.

Preferred Term	Summary of All TEAEs Leading to Withdrawal for the Controlled Adjunctive Studies (LAM100036 and LAM100034, Individual and Pooled Double-blind Treatment Phases)					
	Number (%) of Subjects					
	Study LAM100036		Study LAM100034		Study LAM100036 and Study LAM100034	
	PBO (N=74)	LTG XR (N=72)	PBO (N=121)	LTG XR (N=118)	PBO (N=195)	LTG XR (N=190)
Any Event	2 (3)	1 (1)	2 (2)	9 (8)	4 (2)	10 (5)
Dizziness	0	0	0	5 (4)	0	5 (3)
All Rash	1 (1)	1 (1)	0	1 (<1)	1 (<1)	2 (1)
Headache	0	0	1 (<1)	2 (2)	1 (<1)	2 (1)
Nausea	0	0	0	2 (2)	0	2 (1)
Nystagmus	0	0	0	2 (2)	0	2 (1)
Anxiety	0	0	0	1 (<1)	0	1 (<1)
Asthenia	0	0	0	1 (<1)	0	1 (<1)
Ataxia	0	0	0	1 (<1)	0	1 (<1)
Depression	0	0	0	1 (<1)	0	1 (<1)
Diplopia	0	0	0	1 (<1)	0	1 (<1)
Gait Disturbance	0	0	0	1 (<1)	0	1 (<1)
Hot flush	0	0	0	1 (<1)	0	1 (<1)
Pancreatitis	0	0	0	1 (<1)	0	1 (<1)
Psychomotor retardation	0	0	0	1 (<1)	0	1 (<1)
Stomach discomfort	0	0	0	1 (<1)	0	1 (<1)
Somnolence	0	0	0	1 (<1)	0	1 (<1)
Tremor	0	0	0	1 (<1)	0	1 (<1)
Cough	0	0	1 (<1)	0	1 (<1)	0
Depressed level of consciousness	1 (1)	0	0	0	1 (<1)	0
Drop attacks	0	0	1 (<1)	0	1 (<1)	0
Hallucination	1 (1)	0	0	0	1 (<1)	0
Oral pruritus	0	0	1 (<1)	0	1 (<1)	0
Pruritus	0	0	1 (<1)	0	1 (<1)	0
Vomiting	0	0	1 (<1)	0	1 (<1)	0

Note: Subjects may have been discontinued for more than 1 TEAE

All Phase III and Ongoing Studies

In the grouping of all phase 3 and ongoing studies the tabular case reports provided in the ISS reveal 60 adverse events leading to withdraw, [table 7-17](#). The most serious of these not present in current labeling are cardiac failure, 2 neoplasms including a brain and hepatic neoplasm. Review of the individual case reports reveals the hepatic neoplasm occurred in an individual at high risk of hepatocellular carcinoma (the identified neoplasm) due to underlying alcoholic cirrhosis and hepatitis B virus. The

brain neoplasm is of unknown origin, no pathologic data is provided, and the lesion was discovered 137 days after start of the study drug. This is a very short latency for induction of a malignancy from study drug and is very unlikely due to study drug treatment. Examination of the case of acute cardiac failure is more consisted with a sudden unexpected death in epilepsy. The patient had gone to use the toilet, and suddenly fell. The patient son subsequently found the patient dead (case has been reported in NDA 22115).

Serious medical events of concern, although currently in the Lamictal XR label include 2 cases of pancreatitis, 19 cases of rash, one case of angioedema, 1 case of status epilepticus, 3 cases of worsening seizures and one case of a grand mal seizure with aspiration and death.

Pancreatitis: the first case of pancreatitis is reported to be moderate pancreatitis occurring 50 days after the start of lamotrigine. Amylase increased to 209U/L (normal range not provided). The symptoms subsided after temporary reduction of oxcarbazepine. Patient also reported similar symptom of abdominal pain at baseline. Etiology of the syndrome not fully elucidated because of patient refusal for further evaluation. The second patient suffered acute pancreatitis, considered severe in intensity 143 days after beginning study drug. There was resolution of the pancreatitis. Laboratory data not provided.

Status epilepticus: a subject developed status epileptics during the blinded transition phase to from placebo to open label lamotrigine XR. The event required 10mg diazepam and a loading dose of phenytoin for control in addition to a 4 day hospitalization. Causality from the study medication is a possibility due to temporal relationship to new drug introduction. Status epileptics is present in the warnings and precautions section of labeling, this single case does not provide evidence for strengthening of this current labeling.

Worsening seizures: there were three cases of worsening seizures. In the first subject there was a worsening of simple partial seizures which resolved upon discontinuation of study drug. There was no hospitalization. In a second case there was a transition from simple partial to complex partial seizures. The patient was treated with 250mg of lamotrigine XR for 2 months at the time. The transition is unlikely, due to study drug (but cannot be completely excluded) because the patient was on a course of increasing lamotrigine XR treatment. The third case of epilepsy worsening occurred in a subject who developed myoclonic seizures 5 days after titration to a plateau of 400mg of lamotrigine XR dose. Due to the association with dose escalation, the emergence of this new seizure variety may be due to study drug. The potential for worsening of seizures is currently presented in the information for patient section of labeling. These cases do not indicate a need for strengthening the current labeling.

Rash: there were 19 withdrawals due to rash; these cases will be discussed in section [7.3.4](#)

Table 7-17		Narratives All Phase III and Ongoing Study Subjects with Narratives for AEs Leading to Withdrawal- not including safety update (ISS)	
Subject	Age/ Gender	AE Leading to Withdrawal (Preferred Term)	Dose of LTG XR at Onset (mg/day)
Study LAM100034 (Double-Blind)			
PBO			
796	18/F	Headache, oral pruritus, pruritus	-
1809	15/M	Cough, drop attacks, vomiting	-
LTG			
142	42/M	Anxiety, hot flush, nausea, stomach discomfort	100
416	49/F	Rash generalized	50
1209	73/F	Depression	12.50
1501	34/F	Ataxia, gait disturbance, nystagmus, psychomotor retardation	50
1534	13/M	Diplopia, dizziness, somnolence	200
		Pancreatitis	500
1814	53/F	Dizziness	200
1830	42/M	Dizziness	500
1840	30/F	Dizziness, headache, nystagmus	600
2092	28/F	Dizziness, headache, nausea, tremor	200
		Asthenia	N/A
Study LAM100034 (Open-Label)			
PBO-LTG			
21	27/M	Rash	325
126	51/F	Rash	225
218	63/M	Ataxia	450
		Dysarthria	200
411	55/F	Status epilepticus	325
1514	28/M	Nystagmus, oscillopsia	350
1827	22/M	Vomiting	200
1833	21/F	Dizziness	600
1835	43/F	Rash	650
2067	28/M	Simple partial seizures	212.5
2075	46/F	Abdominal pain	1000
2164	73/M	Asthenia	700
		Somnolence, vertigo	800
LTG-LTG			
1546	38/F	Aspiration, grand mal convulsion	500
2094	35/F	Cardiac failure acute	500
2152	22/F	Drug toxicity	250
Study LAM100036 (Double-Blind)			
PBO			
259	34/M	Rash	-
1253	46/M	Depressed level of consciousness	-
		Hallucination	-
LTG			
1622	24/F	Rash	N/A
Subject	Age/ Gender	AE Leading to Withdrawal (Preferred Term)	Dose of LTG XR at Onset (mg/day)
Study LAM100036 (Open-Label)			

Table 7-17		Narratives All Phase III and Ongoing Study Subjects with Narratives for AEs Leading to Withdrawal- not including safety update (ISS)	
Subject	Age/ Gender	AE Leading to Withdrawal (Preferred Term)	Dose of LTG XR at Onset (mg/day)
Baseline Failure			
1299	69/M	Vertigo	12.50
		Malaise	12.50
1806	34/F	Dizziness	200
PBO-LTG			
1564	45/M	Rash	500
1578	14/F	Hydrocephalus	350
Study LAM30055 (Double-blind Treatment Phase - Completed)			
LTG-XR 300 mg/day			
8	34/F	Anxiety	300
318	36/M	Arthralgia, joint swelling	50
633	45/F	Rash	150
807	24/F	Brain neoplasm	50
LTG-XR 250 mg/day			
9	49/M	Dizziness, nausea	12.50
16	19/F	Rash	25
71	51/F	Rash	150
112	24/M	Rash	250
153	22/F	Rash	100
154	43/F	Rash	100
220	36/F	Rash	25
223	33/F	Pyrexia, rash	25
254	56/M	Hepatic neoplasm malignant	250
301	27/M	Simple partial seizures	250
805	39/F	Hand-foot-and-mouth disease	250
Study LAM30055 (Open-label Continuation Phase - Ongoing)			
13	53/M	Headache	300
		Chest pain	300
		Chest pain	300
		Headache	300
176	27/M	Myoclonic epilepsy	400
803	47/M	Rash	100
Study LEP105972 (Open-label- Ongoing)			
71	82/F	Weakness of lower extremities	150
116	72/F	Rash	100
267	73/M	Rash	150
289	71/M	Acute pancreatitis	500
290	72/M	Nausea	400
		Lethargy	400
		Nausea	500
		Nausea	300
293	65/F	Rash	200
		Itchy skin	200
		Periorbital edema	200
350	74/F	Allergic reaction	200
		Tired	-
Subject	Age/ Gender	AE Leading to Withdrawal (Preferred Term)	Dose of LTG XR at Onset (mg/day)

Table 7-17		Narratives All Phase III and Ongoing Study Subjects with Narratives for AEs Leading to Withdrawal- not including safety update (ISS)	
Subject	Age/ Gender	AE Leading to Withdrawal (Preferred Term)	Dose of LTG XR at Onset (mg/day)
367	69/F	Dizziness	50
		Sleepiness	50
		Loss of appetite	50
436	67/F	Rash	100
527	69/F	Headache	300
		Muscle cramps	300
		Constipation	300
		Stomach cramps	300
566	82/F	Loss of appetite	50
		Nausea	50
		Malaise	50
		Unsteadiness	50
Study LEP108937 (Open-label- Ongoing)			
142	41/F	Lip swelling	300
157	35/F	Pruritus	50
		Rash	50
167	24/M	Angioedema	25

Reviewer Comment: There were 3 adverse events of concern leading to withdraw which were serious medical events not currently in labeling. These included an event of cardiac failure and two malignancies. As noted in the discussion above, the malignancies are not likely associated with the study drug treatment. The cardiac failure is most consistent with SUDEP. Those events currently in labeling do not rise to a level of concern that warrants a strengthening of labeling. The remaining events are medical issues currently in labeling and do not warrant strengthening of current labeling. In summary, aside from these three events, the profile of events leading to withdrawal is contained within the list of adverse events reported in the clinical trials section of immediate release Lamictal.

All Clinical Studies (120 day safety report)

The number of subjects who experienced TEAEs leading to withdrawal in the updated All Clinical Studies is slightly higher than that presented in the ISS (ISS Table 63 and ISS Table 2.81) but the percentages of subjects remain the same. In the updated All Clinical Studies grouping 46 (7%) subjects had AEs leading to withdrawal compared to 43 (7%) presented in the ISS. This change is due to the integration of the LAM30005 open-label Continuation Phase in the updated All Clinical Studies grouping

Table 7-18 Summary of Treatment-Emergent Adverse Events Leading to Withdrawal in All Clinical Studies, Safety Update compared to ISS		
120 Day Safety Submission		ISS
	All lamotrigine XR (N= 662)	All lamotrigine XR (N= 650)
Any Event	46 (7%)	43 (7%)

Table 7-18 Summary of Treatment-Emergent Adverse Events Leading to Withdrawal in All Clinical Studies, Safety Update compared to ISS				
120 Day Safety Submission			ISS	
	All lamotrigine XR (N= 662)		All lamotrigine XR (N= 650)	
Any Event	46 (7%)		43 (7%)	
120 day safety	N	%	N	%
All rash	15	2	14	2
Dizziness	8	1	8	1
Headache	3	<1	2	<1
Nausea	3	<1	3	<1
Nystagmus	3	<1	3	<1
Anxiety	2	<1	2	<1
Asthenia	2	<1	2	<1
Ataxia	2	<1	2	<1
Simple partial seizures	2	<1	2	<1
Somnolence	2	<1	2	<1
Vertigo	2	<1	2	<1
Abdominal pain	1	<1	2	<1
Arthralgia	1	<1	1	<1
Aspiration	1	<1	1	<1
Brain neoplasm	1	<1	1	<1
Cardiac failure, acute	1	<1	1	<1
Chest pain	1	<1	0	0
Depression	1	<1	1	<1
Diplopia	1	<1	1	<1
Drug toxicity	1	<1	1	<1
Dysarthria	1	<1	1	<1
Gait disturbance	1	<1	1	<1
Grand mal convulsion	1	<1	1	<1
Hand-foot-and mouth disease	1	<1	1	<1
Hepatic neoplasm, malignant	1	<1	1	<1
Hot flash	1	<1	1	<1
Hydrocephalus	1	<1	1	<1
Joint swelling	1	<1	1	<1
Malaise	1	<1	1	<1
Myoclonic Epilepsy	1	<1	0	0
Oscillopsia	1	<1	1	<1
Pancreatitis	1	<1	1	<1
Psychomotor retardation	1	<1	1	<1
Pyrexia	1	<1	1	<1
Status epilepticus	1	<1	1	<1
Stomach discomfort	1	<1	1	<1
Tremor	1	<1	1	<1
Vomiting	1	<1	1	<1

Reviewer Comment: there are 3 additional adverse events leading to withdraw contained in the 120 day safety update. There is one withdraw due to rash, an additional withdraw due to headache and a withdrawal due to chest pain. All of these adverse events are in current labeling. Rash is presently in boxed warning, headache is

located in the adverse reaction section of labeling and chest pain is present in clinical trial experience.

7.3.4 Significant Adverse Events

Rash: In all phase 3 trials and ongoing studies, there were 19 occurrences of rash with one additional withdrawal due to rash in the 120 day safety update. The 19 case reports from the ISS are reviewed. None of the cases developed into Steven’s Johnsons syndrome or toxic epidermal necrolysis. One was serious enough to require hospitalization for four days and receipt of intravenous corticosteroids, 18 of 19 resolved after discontinuation of lamotrigine XR, in one of 19 the outcome was not provided. There was no case report form for review of the additional case in the 120 day safety report, thus the level of intensity cannot be determined.

Reviewer comment: The current labeling is at maximal with boxed warning and no modification is indicated based on the 20 cases of rash identified in this development program.

7.3.5 Submission Specific Primary Safety Concerns

No submission specific primary safety concerns are identified

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Controlled Clinical Trials

LAM100036 Escalation Phase

Treatment emergent adverse events occurring in $\geq 2\%$ of subjects were compared between placebo and lamotrigine XR groups. During escalation phase the top five adverse events noted, comparing any dose lamotrigine XR to placebo, were headache, nausea, diarrhea, dizziness, and somnolence. The rate of headache was greater in placebo than the treatment group. Nausea in the treatment group exceeded placebo by 3%. Diarrhea in the treatment group exceeded placebo by 3%. Dizziness was equal in placebo and treatment groups. Somnolence in the treatment group exceed placebo by 2%. The top four adverse effects ranked by the gradient of difference between placebo and treatment group, to a minimum of 2%, were nausea (3%), diarrhea (3⁺%), dizziness (2%), and somnolence (2%) see [table 7-19](#).

Table 7-19	Summary of the Most Common TEAEs ($\geq 2\%$) with an Onset in Escalation Phase for the Controlled Adjunctive Studies (LAM100036 and LAM100034, Pooled Double-blind Treatment Phases)				
	PBO (N=195)		Any Dose of LTG XR (N=190)		% Difference
Preferred Term	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	% Treatment subjects - % Placebo

					subjects
Any Event	93 (48)	179	81 (43)	235	-5
Headache	22 (11)	27	19 (10)	47	-1
Nausea	2 (1)	2	8 (4)	16	3
Diarrhea	1 (<1)	1	8 (4)	9	3 ⁺
Dizziness	4 (2)	5	7 (4)	7	2
Somnolence	3 (2)	3	7 (4)	7	2
Vomiting	2 (1)	2	7 (4)	7	3
Fatigue	3 (2)	4	4 (2)	4	0
Pyrexia	6 (3)	6	4 (2)	4	-1
Upper respiratory tract infection	5 (3)	5	4 (2)	4	-1
Vertigo	1 (<1)	1	4 (2)	4	1 ⁺
Nasopharyngitis	9 (5)	10	3 (2)	3	-3
Pruritus	4 (2)	5	1 (<1)	1	-1 ⁺

LAM100036 Maintenance Phase

Treatment emergent adverse events occurring in $\geq 2\%$ of subjects were compared between placebo and lamotrigine XR groups. During escalation phase the top five adverse events noted, were dizziness, headache, tremor, nausea and vomiting. Dizziness in the treatment group exceeded that in the placebo group by 6%, headache in the placebo group exceeded that present in the treatment group by 3%. Tremor in the treatment group exceeded placebo by 5% (no tremor was present in placebo group). Nausea in the treatment group exceeded the placebo group by 1%. Vomiting in the treatment group exceeded placebo by 2%. The top 4 adverse events ranked by percent of subjects affected in treatment minus placebo, to a minimum of 2% were dizziness (6%), tremor (5%), and vomiting (2%). In maintenance phase only dizziness, tremor, nausea, vomiting, pyrexia, and influenza had positive values for treatment over placebo. The remaining adverse effect terms had greater occurrence in placebo than treatment, see [table 7-20](#).

Preferred Term	Summary of the Most Common TEAEs ($\geq 2\%$) with an Onset in Maintenance Phase for the Controlled Adjunctive Studies (LAM100036 and LAM100034, Pooled Double-blind Treatment Phases)				
	PBO (N=187)		Any Dose of LTG XR(N=190)		% Difference
	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	% Treatment subjects - % Placebo subjects
Any Event	87 (47)	234	89 (50)	250	3
Dizziness	9 (5)	11	20 (11)	21	6
Headache	22 (12)	43	16 (9)	44	-3
Tremor	0	0	8 (5)	9	5
Nausea	5 (3)	6	7 (4)	9	1
Vomiting	4 (2)	4	7 (4)	9	2
Diplopia	1 (<1)	1	7 (4)	7	3 ⁺
Pyrexia	4 (2)	5	5 (3)	7	1

Preferred Term	Summary of the Most Common TEAEs (>=2%) with an Onset in Maintenance Phase for the Controlled Adjunctive Studies (LAM100036 and LAM100034, Pooled Double-blind Treatment Phases)				
	PBO (N=187)		Any Dose of LTG XR(N=190)		% Difference
	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	% Treatment subjects - % Placebo subjects
Asthenia	3 (2)	4	4 (2)	5	0
Influenza	2 (1)	2	4 (2)	4	1
Nasopharyngitis	6 (3)	6	3 (2)	3	-1
Abdominal pain	4 (2)	4	2 (1)	2	-1
Back pain	4 (2)	4	2 (1)	2	-1
Diarrhea	5 (3)	6	2 (1)	2	-2
Insomnia	4 (2)	4	1 (<1)	1	-1 ⁺
Pain in extremity	5 (3)	5	0	0	-3

Studies LAM100034 and LAM100036 individually and pooled- Double Blind Treatment Phase

Treatment emergent adverse events occurring in ≥5% of subjects were compared between placebo and lamotrigine XR groups for studies LAM100034, LAM100036 and both of these studies combined. The common adverse event occurrence, including headache, dizziness, nausea, vomiting, diarrhea, diplopia, somnolence and asthenia, were greater in LAM100034 compared to LAM100036. In LAM100036 the occurrence of headache was greater in placebo than lamotrigine treatment.

The pooled TEAE profile of LAM100036 + LAM100034 reveals the top 8 TEAEs to a minimum of 5% were: headache, dizziness, nausea, vomiting, diarrhea, tremor, diplopia, and somnolence, [table 7-21](#). Headache in the pooled placebo group exceeded the treatment group by 2% (of subjects affected), dizziness in the treatment group exceeded the placebo group by 8%, nausea in the treatment group exceeded the placebo group by 3%, vomiting in the treatment group exceeded the placebo group by 3%, diarrhea in the treatment group exceeded the placebo group by 2%, tremor in the treatment group exceeded the placebo group by 4%, diplopia in the treatment group exceeded the placebo group by 4%, somnolence in the treatment group exceeded the placebo group by 2%.

Preferred Term	Summary of the Most Common TEAEs (>=5%) for the Controlled Adjunctive Studies (LAM100036 and LAM100034, Individual and Pooled Double-blind Treatment Phases)					
	Number (%) of Subjects					
	Study LAM100036		Study LAM100034		Study LAM100036 and Study LAM100034	
	PBO (N=74)	LTG XR (N=72)	PBO (N=121)	LTG XR (N=118)	PBO (N=195)	LTG XR (N=190)
Any Event	42 (57)	39 (54)	83 (69)	86 (73)	125 (64)	125 (66)
Headache	12 (16)	10 (14)	22 (18)	19 (16)	34 (17)	29 (15)
Dizziness	5 (7)	4 (6)	6 (5)	23 (20)	11 (6)	27 (14)

Table 7-21	Summary of the Most Common TEAEs (>=5%) for the Controlled Adjunctive Studies (LAM100036 and LAM100034, Individual and Pooled Double-blind Treatment Phases)					
	Number (%) of Subjects					
	Study LAM100036		Study LAM100034		Study LAM100036 and Study LAM100034	
Preferred Term	PBO (N=74)	LTG XR (N=72)	PBO (N=121)	LTG XR (N=118)	PBO (N=195)	LTG XR (N=190)
Nausea	4 (5)	5 (7)	3 (3)	8 (7)	7 (4)	13 (7)
Vomiting	3 (4)	7 (10)	2 (2)	5 (4)	5 (3)	12 (6)
Diarrhea	0	1 (1)	6 (5)	9 (8)	6 (3)	10 (5)
Tremor	0	4 (6)	1 (<1)	6 (5)	1 (<1)	10 (5)
Diplopia	1 (1)	4 (6)	0	5 (4)	1 (<1)	9 (5)
Somnolence	0	1 (1)	6 (5)	8 (7)	6 (3)	9 (5)
Pyrexia	4 (5)	5 (7)	5 (4)	3 (3)	9 (5)	8 (4)
Asthenia	0	0	3 (3)	6 (5)	3 (2)	6 (3)
Nasopharyngitis	1 (1)	2 (3)	15 (12)	4 (3)	16 (8)	6 (3)
All Rash	4 (5)	2 (3)	1 (<1)	2 (2)	5 (3)	4 (2)

All Clinical Studies

438 (67%) of lamotrigine XR treatment patients in the All Clinical Studies group experience TEAEs. The top 4 TEAEs to a minimum of 7% were headache (24%), dizziness(16%), nausea (8%) and vomiting (7%), see [table 7-22](#).

Table 7-22	Summary of the Most Common TEAEs (>=5%) for All Clinical Studies (LAM100036, LAM100034, and LAM30055)	
	Number (%) of Subjects	
Preferred Term	All LTG XR (N=650)	
Any Event	438 (67)	
Headache	155 (24)	
Dizziness	102 (16)	
Nausea	50 (8)	
Vomiting	44 (7)	
All Rash ^a	37 (6)	
Nasopharyngitis	42 (6)	
Tremor	38 (6)	
Diplopia	30 (5)	
Somnolence	32 (5)	

^a "All Rash" was defined using a composite of multiple related search terms to capture AEs potentially related to rash.

120 Day Safety Update- All Clinical Studies

The overall safety profile for the updated All Clinical Studies is similar to the one presented in the ISS (ISS [Table 7-22](#)). The most frequently reported TEAEs (≥5%) for the updated All Clinical Studies grouping are summarized in [table 7-23](#). The number of

subjects who reported at least 1 TEAE in the updated All Clinical Studies grouping (455 or 69%) is comparable to that presented in the ISS (438 or 67%, ISS [Table 7-22](#)). There were no substantial changes in the number or percent of subjects who experienced the TEAEs.

Table 7-23	Summary of the Most Common Treatment-Emergent Adverse Events (≥5%) in All Clinical Studies grouping (LAM100036, LAM100034 and LAM30055), 120 day Safety Update
Preferred Term	Number (%) of Subjects All LTG XR
	(N=662)
Any Event	455 (69)
Headache	167 (25)
Dizziness	109 (16)
Nausea	56 (8)
Vomiting	47 (7)
Nasopharyngitis	47 (7)
Tremor	39 (6)
All Rash ^a	39 (6)
Somnolence	36 (5)
Pyrexia	34 (5)
Diarrhea	31 (5)
Diplopia	31 (5)
^a “All Rash” was defined using a composite of multiple related search terms to capture AEs potentially related to rash.	

Reviewer Comment: The profile of treatment emergent adverse events (TEAE) is characteristic of the adverse effects seen with the use of other anticonvulsant agents. In the controlled adjunctive studies group dizziness was more common in study LAM100036, vomiting more common in study LAM100034 and headache was more common in the placebo group of both studies. In the remainder of the common TEAEs the frequency was similar, see [table 7-21](#).

The controlled adjunctive studies are pooled and examined for TEAEs by study phase. This examination reveals in the escalation phase that nausea, vomiting, diarrhea, and somnolence are more frequent than in the maintenance phase. During the maintenance phase dizziness is more frequent, diarrhea and somnolence are not present (at $\geq 2\%$ occurrence) and two new adverse events emerge, tremor and diplopia which were not present during the escalation phase, see [tables 7-19](#) and [7-20](#). This is likely due to a degree of accommodation to the gastrointestinal effect of lamotrigine XR with development of more prominent central nervous system effect due to sustained exposure.

TEAEs are examined in all clinical studies which reveal a profile and frequency of adverse events very similar to that seen in the double blind treatment phase of the pooled events of studies LAM100034 and LAM100036. The only exception is the category of "all rash" which is more frequent in the all clinical studies examination which likely reflects the longer exposure to lamotrigine XR.

The 120 safety update does not reveal a change in the pattern of TEAEs. The total number of event increases by 2% but there is little difference between the categories and frequency of events, this can be seen by comparing [table 7-22](#) and [table 7-23](#).

The Adverse Reactions section, clinical trials experience of the current Lamictal XR label, sections 6.0 and 6.1 respectively, contains all of those TEAEs with reasonable grounds for causality that are identified in tables 7-19 to 7-23. The observations of common TEAE in this study do not necessitate labeling change.

7.4.2 Laboratory Findings

Clinical Chemistry:

Clinical chemistry studies were collected at screening, during the double blind treatment period, visit 4 (week 3), visit 6 (week 11), and visit 8 (week 19). Clinical laboratory data are presented in the NDA22509 application for Controlled Adjunctive Studies and Single Dose Healthy Volunteer Studies. The safety profile of the drug substance has been well characterized in the approval applications for Lamictal IR (NDA20241), Lamictal CD (NDA20764), and Lamictal ODT (NDA22251) in addition to post marketing experience from approval of Lamictal IR in December 1994, therefore the focus of this review will be on the results of the Controlled Adjunctive Studies where there is the greatest

likelihood of identifying a new or unexpected safety signal (in contrast to single dose healthy volunteer studies).

Clinical Chemistry Evaluation Strategy

From the available clinical chemistry data the examinations chosen for presentation and analysis in this review will include; a statement concerning reference ranges compared to accepted standards. High interest clinical laboratory parameters will be evaluated for change from screening through double blind period exposure, change according to modal dose group, capture of values outside of the reference range by visit and modal dose group, and shift table analysis- change (to high or low) from baseline.

Clinical Laboratory Shift table for all subjects LAM100036 & LAM100034			
Table 7-24	Reference Range Change Category	Number (%) of Subjects	
Parameter		PBO a (N=195)	LTG XR b (N=190)
AST (IU/L)	To High	2 (1)	3 (2)
ALT (IU/L)	To High	4 (2)	1 (<1)
Albumin (g/L)	To Low	1 (<1)	0
	To High	6 (3)	8 (5)
Alkaline Phosphatase (IU/L)	To Low	1 (<1)	0
	To High	9 (5)	7 (4)
Creatinine (µmol/L)	To Low	0	1 (<1)
	To High	2 (1)	1 (<1)
Glucose (mmol/L)	To Low	8 (4)	7 (4)
	To High	10 (6)	11 (7)
Potassium (mmol/L)	To Low	2 (1)	0
	To High	2 (1)	2 (1)
Sodium (mmol/L)	To Low	5 (3)	3 (2)
	To High	2 (1)	0
Total Bilirubin (µmol/L)	To High	1 (<1)	1 (<1)
Total Protein (g/L)	To Low	1 (<1)	1 (<1)
Urea (mmol/L)	To Low	5 (3)	9 (5)
	To High	3 (2)	0

Review of modal dose (controlled adjunctive studies, to high) shift tables for clinical chemistry reveals shift to high by 2 % at <300, and 6% 300 to 500 for albumin over placebo. Also 2% over placebo for alk phos at >500. Also 2% over placebo for AST at >500. glucose 3% over placebo at <300 to low. 12% over placebo at 300 to 500 in to high shift. Urea had a to low shift of 5% over placebo for <300 group.

Subjects with hepatic function parameters in the range of clinical concern are examined. Five subjects are identified. Three subjects had elevated ALT, however all three had elevated ALT at screening. In the first case the ALT increased from 139 (2.9 ULN- upper limit of normal) at screen to 223 (4.6 ULN) at maximum and remained at that level. In the same case AST was elevated to a maximum of 122 (2.9 ULN) and mildly elevated at screen. Total Bilirubin is was not elevated. In the second case the screening

ALT was 165 (3.4 ULN) which improved (decreased) to 142 (3.0 ULN) with no subsequent value provided. In the third case the ALT value was 302 (6.3 ULN) at day -268 which then improved, while remaining abnormal to 225 (4.7 ULN). AST in this same subject AST was elevated pre-study day -268 to 192 (4.6 ULN) and improved to 129 (3.1 ULN). The fourth case had a notation of a single value of elevated AST to 173 (4.1ULN) with no preceding or subsequent data point given. The fifth case had no transaminases value of clinical concern but a mildly elevated total bilirubin at 28umol/L (1.3 ULN). These cases may be seen in tabular form in table 7-24a. The column Max/mid study represents the treatment interval study visit with the maximum value. The best recovery column represents the subsequent study visit or end of study value.

Table 7-24a									
Subjects with hepatic function values in range of clinical concern.									
Subject #	ALT Ref. Range U/L (0-48) * 0-96			AST Ref. Range U/L (0-42) *0-84			Total Bilirubin Ref. Range umol/L (0-22) *0-27		
	Screen	Max/mid study	Best recovery	Screen	Max	Best recovery	Screen	Max	Best recovery
8565	139	223	223	87	122	122			
1832	165	142							
1557	302 (day -268)	225	225	192 (day -268)	129	129			
1422					173				
1309							28	28	

* Sponsor define, Clinically Acceptable Range

Reviewer Comment: All subjects with significantly elevated ALT also had evidence of hepatic dysfunction pre-treatment with elevations in the three ranging from 2.9 to 6.3 ULN. In two of three cases the value improved during treatment and in one the value rose by 1.3 ULN. None of these three subjects had elevations of total bilirubin in range of clinical concern. The study entry with ALT elevation is consistent with hepatic dysfunction that was pre existing rather than caused by lamotrigine. Subject 1422 noted in the table had a listing of AST with a value 4.1 ULN but no associated value of ALT or total bilirubin in a range of clinical concern. This isolated value is of uncertain significance. The fifth case had a mild elevation of total bilirubin with no transaminases values in a range of clinical concern, this is not consistent with a bilirubin elevation due to hepatocellular injury. These observations are not consistent with a new safety signal for hepatic dysfunction.

Hematology

Hematology parameters studied in the following analyses include: basophils, eosinophils, lymphocytes, monocytes, total neutrophils, WBC count, hematocrit, hemoglobin, MCH, MCHC, MCV, RBC count, and platelet count,

Controlled Adjunctive Studies

Analysis focused on measures of central tendency

The means, and medians of hematology parameters are examine comparing placebo to lamotrigine treatment at study visits from screening to end of study. Little change is seen across all hematology parameters.

Marked outliers for laboratory abnormalities (values of potential clinical concern)

Group outlier analysis reveals no trends over time of clinically important differences between the placebo and Lamictal XR groups

Individual listings of hematology parameters of potential clinical concern are examined. The most prominent outliers from reference range are seen in WBC count, neutrophil and eosinophil count. The observation of note for WBC and neutrophil count are in a direction of depressed cell count while the eosinophil count is observed to be increased.

Analyses focused on change from baseline relative to the reference range (shifts from normal to abnormal)

The maximum change from reference range in the treatment group in excess of the placebo group is seen in the MCH (mean corpuscular hemoglobin), MCV (mean corpuscular volume) and WBC counts, at 4% , 3% and 3% respectively. The remainder of changes in excess of placebo are 2% or less. These results may be seen in the tabular form in table 7-24b

Table 7-24b

Hematology Changes from Baseline to Low or to High Relative to the Reference Range for the Controlled Adjunctive Studies (LAM100036 and LAM100034, Pooled Double-blind Treatment Phases)

Parameter	Reference Range Change Category	PBO (N=195)		LTG XR (N=190)	
		n	n (%)	n	n (%)
Eosinophils (%)	To High	168	16 (10)	166	10 (6)
Eosinophils (gl/L)	To Low	166	9 (5)	166	11 (7)
	To High	166	7 (4)	166	8 (5)
Hematocrit (%)	To Low	167	18 (11)	168	9 (5)
	To High	167	0	168	4 (2)
Hemoglobin (g/L)	To Low	167	16 (10)	168	14 (8)
	To High	167	0	168	1 (<1)
Lymphocytes (%)	To Low	168	5 (3)	166	5 (3)
	To High	168	6 (4)	166	7 (4)
Lymphocytes (gl/L)	To Low	166	4 (2)	166	1 (<1)
	To High	166	1 (<1)	166	0
Mean Corpuscle Hg (PG)	To Low	167	0	168	6 (4)
	To High	167	9 (5)	168	5 (3)
Mean Corpuscle Hg Concentration (g/L)	To Low	160	4 (3)	163	3 (2)
Mean Corpuscle Volume (fL)	To Low	167	0	168	5 (3)
	To High	167	6 (4)	168	6 (4)
Monocytes (%)	To High	168	6 (4)	166	4 (2)
Monocytes (gl/L)	To Low	166	11 (7)	166	10 (6)
Platelet Count (gl/L)	To Low	165	1 (<1)	167	4 (2)
	To High	165	1 (<1)	167	3 (2)
RBC (TI/L)	To Low	167	12 (7)	168	10 (6)
Segmented Neutrophils (%)	To Low	168	5 (3)	166	6 (4)
	To High	168	5 (3)	166	7 (4)
Segmented Neutrophils (gl/L)	To Low	166	3 (2)	166	6 (4)
	To High	166	3 (2)	166	2 (1)
Total Neutrophils (%)	To Low	168	5 (3)	166	6 (4)
	To High	168	5 (3)	166	7 (4)
Total Neutrophils (gl/L)	To Low	166	3 (2)	166	6 (4)
	To High	166	3 (2)	166	2 (1)
WBC (gl/L)	To Low	166	2 (1)	166	6 (4)
	To High	166	4 (2)	166	2 (1)

Reviewer Comment: The most prominent abnormalities are seen when examining the individual line listings of subjects with values in the range of potential clinical concern. The majority of these abnormalities are in low neutrophil counts and elevated eosinophil counts. In multiple cases the study values were preceded by abnormal values at screening visit. No study dropout or discontinuation was associated primarily with a hematologic term. Examination of change from baseline (shift table) reveals the largest change in WBC, MCH and MCV. Abnormalities in hematologic parameters are observed with use of Lamictal and are currently present in labeling under warnings and precautions thus the current strength of labeling is appropriate.

7.4.3 Vital Signs

Shift tables by visit are examined for diastolic and systolic blood pressure and do not reveal greater than 2% divergence from placebo except for the strata diastolic blood pressure increase ≥ 10 . In this strata there is a treatment effect of 7%, where there are 7% greater number of subjects with this shift in the LTG treated group compared to placebo treated. One other VS parameter revealed a divergence between placebo and treatment greater than 2% , this was observed in the strata of shift to pulse increase ≥ 15 , where there was a 5% greater occurrence of this shift in lamotrigine treatment compared to placebo (p4018 ISS, table 4.5, also of interest Table 4.4 for summary). Weight (table 4.6 p4023) shows a mean increase of .17 kg for LTG and .49 for pcb at end of study (EOS), Median chg is .05 for LTG and .4 for pcb at EOS. Tables of vital sign trend over time show no clinically meaningful change between visit 1 and 8.

7.4.4 Electrocardiograms (ECGs)

Background / previous contributory studies:

A QT study SCA104648, was submitted with NDA application 22115. Subsequently a consult was performed by the cardio-renal QT review team. The team concluded that “it unlikely that lamotrigine XR administration is associated with QT interval prolongation or serious ventricular arrhythmias. However we acknowledge that a different observer might reasonably come to a different conclusion given the flaws in study SCA104648” The medical review also concluded that QTc prolongation was unlikely⁵.

Controlled Adjunctive Studies

Sponsor defined outlier criteria for increase from baseline for QTc intervals, see [table 7-25](#).

Table 7-25	Outlier Criteria for Observed Values and Increases from Baseline for QTcB and QTcF
	QTcB or QTcF value (msec)
Observed Value	≥ 450
	≥ 480

⁵ Kapcala L. Medical Officer, Review of NDA 22115 Lamictal XR (lamotrigine XR), PDUFA date 9/14/07, p123.

Table 7-25	Outlier Criteria for Observed Values and Increases from Baseline for QTcB and QTcF
	≥500
Change from Screening	≥30
	≥60

ECGs were obtained at screening and Visit 8 (end of double blind treatment phase). Examination of change from screening to visit 8 for ECG parameters does not reveal significant changes for heart rate, PR interval, QTcB and QTcF, and QRS duration. The confidence intervals when comparing baseline to Visit 8 for all parameters in the treatment group contained zero. The confidence interval for all parameters when comparing placebo group to treatment also contained zero. Although not designed for hypothesis testing these data suggest no significant change in ECG parameters between screening and visit 8 and between treatment and placebo groups, see [table 7-26](#).

Table 7-26		Summary of Change from Screening to Endpoint in ECG Values for the Controlled Adjunctive Studies		
		PBO (N=195)	LTG-XR (N=190)	95% CI
Heart Rate (bpm)	n	180	176	(-4.0,0.8)
	Mean	-0.133	1.477	
	SD	11.2996	11.8880	
	Median	0.000	2.000	
	Min.	-27.00	-34.00	
	Max.	32.00	49.00	
PR Interval (msec)	95% CI#	(-1.8,1.5)	(-0.3,3.2)	
	n	179	173	(-13.2,2.4)
	Mean	-1.447	3.965	
	SD	49.9750	15.5245	
	Median	0.000	0.000	
	Min.	-593.00	-68.00	
QTc (Bazett) (msec)	Max.	140.00	100.00	
	95% CI#	(-8.8,5.9)	(1.6,6.3)	
	n	178	170	(-6.9,5.2)
	Mean	-3.120	-2.262	
	SD	29.1496	28.5853	
	Median	-2.362	-0.540	
QTc (Fridericia) (msec)	Min.	-81.26	-135.42	
	Max.	96.04	64.39	
	95% CI#	(-7.4,1.2)	(-6.6,2.1)	
	n	178	170	(-5.1,5.7)
	Mean	-3.188	-3.511	
	SD	25.4817	25.4815	
	Median	-3.111	-0.565	
	Min.	-73.05	-157.07	
	Max.	93.29	55.81	

Table 7-26		Summary of Change from Screening to Endpoint in ECG Values for the Controlled Adjunctive Studies		
		PBO (N=195)	LTG-XR (N=190)	95% CI
	95% CI#	(-7.0,0.6)	(-7.4,0.3)	
QRS Duration (msec)	n	180	176	(-2.3,4.0)
	Mean	0.222	-0.631	
	SD	11.7238	18.2038	
	Median	0.000	0.000	
	Min.	-69.00	-200.00	
	Max.	46.00	38.00	
	95% CI#	(-1.5,1.9)	(-3.3,2.1)	

QT interval changes of magnitude ≥ 30 msec and ≥ 60 msec between screening and visit 8 for both QTcB (Bazett) and QTcF (Fridericia) were examined. For prolongation greater than 30 msec by Bazett's method there were 15 subjects in the placebo group and 17 subjects in the lamotrigine XR group representing 8% and 10% respectively. Prolongation greater than 60 msec by Bazett's method was seen in 5 (3%) of placebo subjects and 2 (1%) of lamotrigine XR treated subjects. Using Frederica's method there were 13 (7%) subjects in the placebo group with ≥ 30 msec prolongation and 11(6%) in the lamotrigine XR treatment group. Again, using Frederica's method there were 4(2%) subjects with ≥ 60 msec and no subjects in the lamotrigine XR treatment group, see [table 7-27](#).

Table 7-27	ECG Change from Baseline Outliers for QTc for the Controlled Adjunctive Studies (LAM100036 and LAM100034, Pooled Double-blind Treatment Phases)		
	Number (%) of Subjects		Treatment Effect (%)
	PBO (N=178)	LTG XR (N=170)	
QTcB			
≥ 30 msec	15 (8)	17 (10)	2
≥ 60 msec	5 (3)	2 (1)	-2
QTcF			
≥ 30 msec	13 (7)	11 (6)	-1
≥ 60 msec	4 (2)	0	-2

When QTc interval is examined by modal dose group the largest mean change is seen in the lamotrigine XR 300mg to 500mg a day treatment group. This change is in a negative (QT shortening direction) and represents a magnitude of change that is maximum when using Fridericia's method. The mean change is -7.5 msec, approximately -1.7% of a normal QTc defined as 440 msec. The mean change found when using Bazett's method is -5.5 msec, representing approximately -1.25% of a normal corrected QTc defined as 440 msec. The confidence intervals for all modal dose

groups when screening is compared to visit 8 contain the zero point. The zero point is also contained for confidence intervals comparing treatment to placebo for both QTcB and QTcF.

Controlled adjunctive study treatment groups are examined for QTc outliers by both Bazett's and Fridericia's methods. This analysis reveals that at visit 8 the frequency of subjects exceeding 3 predefined QTc intervals of 450 msec, 480 msec and 500 msec is greater in each group for placebo than with lamotrigine XR treatment, see [table 7-28](#).

Table 7-28 Summary of ECG Outliers for QTc by Visit for Controlled Adjunctive Studies

Parameter	Treatment	Visit 1	Visit 8
QTc (Bazett) >=450	LTG-XR	14 / 184 (8%)	5 / 172 (3%)
	PBO	9 / 193 (5%)	11 / 179 (6%)
QTc (Bazett) >=480	LTG-XR	1 / 184 (1%)	0 / 172 (0%)
	PBO	3 / 193 (2%)	2 / 179 (1%)
QTc (Bazett) >=500	LTG-XR	0 / 184 (0%)	0 / 172 (0%)
	PBO	1 / 193 (1%)	1 / 179 (1%)
QTc (Fridericia) >=450	LTG-XR	8 / 184 (4%)	1 / 172 (1%)
	PBO	4 / 193 (2%)	2 / 179 (1%)
QTc (Fridericia) >=480	LTG-XR	0 / 184 (0%)	0 / 172 (0%)
	PBO	1 / 193 (1%)	2 / 179 (1%)
QTc (Fridericia) >=500	LTG-XR	0 / 184 (0%)	0 / 172 (0%)
	PBO	0 / 193 (0%)	0 / 179 (0%)

Reviewer Comment: Examination of mean changes in heart rate, QRS duration and PR interval reveal no clinically significant mean changes between screening and end of double blind treatment phase. There is also no indication of significant difference between placebo and treatment groups between screening and visit 8 (end of double blind phase).

QT intervals are examined for changes greater than or equal to 30 msec or 60 msec for both QTcB and QTcF. Only the strata of ≥ 30 msec showed an increased frequency of occurrence in lamotrigine XR compared to placebo. This margin was small, 17 (10%) of lamotrigine XR treated subjects compared to 15 (8%) of placebo treated subjects. In the remainder of the strata, including ≥ 60 msec for QTcB and ≥ 30 msec and ≥ 60 msec using QTcF, the frequencies of these changes were greater in the placebo group. At the highest dose range there was a small mean increase in QT by both Bazett's and Fridericia's method; however there was no indication by the confidence intervals that these small increases were significant. Examination for QTcB and QTcF in three strata, >450 msec, >480 msec and >500 msec reveal that the frequency of occurrence is greater in the placebo group in 4 strata and equal between placebo and lamotrigine XR treatment in 2 strata. In addition there was a thorough QT study submitted with NDA 22115 for Lamictal XR in which the review team found no evidence of QT prolongation.

Overall the ECG studies and analysis for Controlled Adjunctive Studies do not indicate an electrophysiologic safety signal.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies submitted in this application.

7.4.6 Immunogenicity

The immunogenicity of lamotrigine has manifested in the occurrence of serious rash. This has been well characterized in lamotrigine IR which was approved in 1994. The threat of this immunologic response currently has a boxed warning in labeling. In all phase III and ongoing studies there were 19 withdrawals due to rash, review of the cases reveals only 1 event which required hospitalization, however none developed into Steven's Johnsons syndrome or toxic epidermal necrolysis.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In the uncontrolled adjunctive (open label) studies headache appears to have a dose dependent onset. There were 18(8%) subjects with headache reported at dose <300mg a day, 13(7%) subjects reported headache in the dose interval ≥ 300 mg/day to <500 mg/day, 20(10%) subjects reported headache in the ≥ 500 mg/day dose group. The clinical significance of this data is uncertain in light of the observation that in escalation and maintenance of the controlled clinical trials headache was more frequent in the placebo group.

7.5.2 Time Dependency for Adverse Events

In Controlled Adjunctive Studies headache was the most prominent adverse event but greater in placebo than the any dose lamotrigine XR group. In maintenance phase of the Controlled Adjunctive Studies dizziness, headache and tremor were the top three TEAEs, again the frequency of headache was greater in the placebo group. Dizziness was greater in the lamotrigine XR group by 6% and tremor by 5% (none in placebo). This suggests a time dependent relationship to the occurrence of dizziness and tremor, with dizziness increasing from escalation to maintenance and tremor first appearing in the maintenance phase. Headache is prominent in both phases but greater in placebo than lamotrigine treatment. Dizziness and tremor are not unexpected in central nervous system active agents such as anti-epilepsy drugs. They are also both present in current labeling in adverse reactions under Clinical Trial Experience (section 6.1).

7.5.3 Drug-Demographic Interactions

Age

Meaningful differentiation of adverse effects by age is not possible due to the small number of subjects in the under 16 year old and over 65 year old age group

Sex

Differentiation of adverse effects by sex reveals dizziness as the most common adverse reaction more common in females (17%) than males (12%). Nausea is also more common in females than males with a frequency of 9% and 4% respectively. Tremor is the remaining adverse reaction with a gender difference >2%. Tremor occurs in 7% of females and 3% of males.

Race

Only Asian and Caucasian subjects are present in sufficient numbers for comparison of adverse effects. The sponsor breaks out subjects into Asian subsets, however only those of South Asian heritage are present in large enough number for comparison. The reviewer examined lamotrigine XR treated subjects and has grouped Asian subsets into all Asian for comparison to Caucasian. The TEAEs with an occurrence greater than 4% between the Asian and Caucasian groups are dizziness at 25% in the all Asian compared to 8% in Caucasian, headache, occurring in 18% of all Asians and 13% of Caucasians, vomiting, occurring in 9.5% of all Asian and 4% of Caucasians. These data point to a greater frequency of TEAEs in Asians than Caucasians. In both Asians and Caucasians the frequency of these TEAEs was greater in lamotrigine XR treatment than placebo. As noted above, each of these TEAEs is present in current Lamictal XR labeling.

7.5.4 Drug-Disease Interactions

The safety submission is examined to determine if there is any increase in myoclonus or myoclonic epilepsy as an adverse effect of lamotrigine XR treatment. Several references have pointed to a possible negative interaction between myoclonic epilepsies and lamotrigine treatment^{6,7}. One withdrawal due to emergence of myoclonic epilepsy in the withdrawal program, this occurred in study LAM30055 in a 27 year old male.

Adverse event data tables are examined for seizure related MedDRA terms vs lamotrigine XR dose and concomitant AED treatment profile. The tables examining AE incidence in treatment – placebo for seizure related terms in escalation phase and escalation or maintenance phase, according to Lamictal XR dosing strata, reveals only small increases of incidence over placebo for the terms seizures (including subtypes) 1.43%, absence seizures 1.39%, petit mal epilepsy 1.39%, simple partial seizures 1.39%, and negative values, indicating placebo larger than treatment for the terms seizures and seizure disorders NEC, and convulsion, [table 7-29](#) and [table 7-30](#).

6 Genton P, Gelisse P, Crespel A. Lack of efficacy and potential Aggravation of Myoclonus with Lamotrigine in Unverricht-Lundborg Disease. *Epilepsia* 2006;47:2083-2085.

7 Crespel A, Genton P, Berramane M, et. al. Lamotrigine associated with exacerbation or de novo myoclonus in idiopathic generalized epilepsies. *Neurology* 2005;65:762-764.

Table 7-29	Summary of Treatment Effect on Incidence: (LAMICTAL XR Dose Group - PLACEBO) for Treatment Emergent Adverse Events with Onset in Escalation Phase			
	Lamictal XR dose Group - Placebo			
System Organ Class Higher Level Group Term Higher Level Term Preferred Term	<300	≥300 to <500	≥500	Any Dose
Seizures (incl subtypes)	1.43%	-1.35%	-1.35%	1.43%
Absence seizures	1.39%	0.00%	0.00%	1.39%
Petit mal epilepsy	1.39%	0.00%	0.00%	1.39%
Partial simple seizures NEC	1.39%	0.00%	0.00%	1.39%
Simple partial seizures	1.39%	0.00%	0.00%	1.39%
Seizures and seizure disorders NE	-1.35%	-1.35%	-1.35%	-1.35%
Convulsion	-1.35%	-1.35%	-1.35%	-1.35%

Table 7-30	Summary of Treatment Effect on Incidence: (LAMICTAL XR Dose Group - PLACEBO) for Treatment Emergent Adverse Events with Onset in Escalation or Maintenance Phase			
	Lamictal XR dose Group - Placebo			
System Organ Class Higher Level Group Term Higher Level Term Preferred Term	<300	≥300 to <500	≥500	Any Dose
Seizures (incl subtypes)	1.43%	-1.35%	-1.35%	1.43%
Absence seizures	1.39%	0	0	1.39%
Petit mal epilepsy	1.39%	0	0	1.39%
Partial simple seizures NEC	1.39%	0	0	1.39%
Simple partial seizures	1.39%	0	0	1.39%
Seizures and seizure disorders NE	-1.35%	-1.35%	-1.35%	-1.35%
Convulsion	-1.35%	-1.35%	-1.35%	-1.35%

The tables examining AE incidence in treatment – placebo for seizure related terms according to concomitant AED treatment in escalation phase and escalation or maintenance phase reveal a small increase 3.33% over placebo for treatment with any VPA for the terms seizures (including subtypes), absence seizures, and petit mal epilepsy. Also a small increase of 2.94% over placebo for treatment with EIAEDs for the terms partial simple seizures NEC and simple partial seizures. There are only negative associations, meaning placebo incidence of the AE is greater than Lamictal XR treatment for the terms seizure and seizure disorders NEC and the term convulsion. There is small positivity for all regimens pooled for the terms partial simple seizures NEC, simple partial seizures, seizures (including subtypes), absence seizures, and petit mal epilepsy, see [table 7-31](#) and [table 7-32](#).

Table 7-31		Summary of Treatment Effect on Incidence: (LAMICTAL XR - PLACEBO) by AED Groups For Treatment Emergent Adverse Events with Onset in Escalation Phase			
		Lamictal XR - Placebo			
System Organ Class Higher Level Group term Higher Level Term Preferred term	Any VPA %	EIAED %	Other regimens %	All regimens %	
Seizures (incl subtypes)	3.33%	0.08%	0.00%	1.43%	
Absence seizures	3.33%	0.00%	0.00%	1.39%	
Petit mal epilepsy	3.33%	0.00%	0.00%	1.39%	
Partial simple seizures NEC	0.00%	2.94%	0.00%	1.39%	
Simple partial seizures	0.00%	2.94%	0.00%	1.39%	
Seizures and seizure disorders NEC	0.00%	-2.86%	0.00%	-1.35%	
Convulsion	0.00%	-2.86%	0.00%	-1.35%	

Table 7-32		Summary of Treatment Effect on Incidence: (LAMICTAL XR - PLACEBO) by AED Groups For Treatment Emergent Adverse Events with Onset in Escalation or Maintenance Phase			
		Lamictal XR - Placebo			
System Organ Class Higher Level Group term Higher Level Term Preferred term	Any VPA %	EIAED %	Other regimens %	All regimens %	
Seizures (incl subtypes)	3.33%	0.08%	0.00%	1.43%	
Absence seizures	3.33%	0.00%	0.00%	1.39%	
Petit mal epilepsy	3.33%	0.00%	0.00%	1.39%	
Partial simple seizures NEC	0.00%	2.94%	0.00%	1.39%	
Simple partial seizures	0.00%	2.94%	0.00%	1.39%	
Seizures and seizure disorders NEC	0.00%	-2.86%	0.00%	-1.35%	
Convulsion	0.00%	-2.86%	0.00%	-1.35%	

Reviewer Comment: Examination of the adverse event tables of study LAM100036 does not reveal any clinically meaningful increase in the frequency of any seizure types captured as MedDRA preferred terms from the study. The available MedDRA preferred terms which capture myoclonus are myoclonus and myoclonic epilepsy. These terms do not appear in the ISS adverse event tables of study LAM100036 or the adverse event dataset of LAM100034. The only occurrence of myoclonus or related epileptiform activity is found in one study withdraw from LAM30055 for myoclonic epilepsy. This subject (176) developed myoclonic seizures 5 days after dose escalation to 400mg a day in the open label study.

The pivotal controlled trials reveal no evidence of lamotrigine treatment association with seizure exacerbation or myoclonus generation. One case of withdraw caused by emergence of myoclonic seizures is identified in study LAM30055, with a reasonable

suspicion of causality. To further explore this association an analysis of the post marketing AERS database is performed using [MGPS](#) methodology. This reveals an EB05 for myoclonic epilepsy and myoclonus, 1.26 and 1.01 respectively, well below 2.0. Overall there is insufficient evidence for strengthening the label beyond the current statement on exacerbation of seizures present in section 5.9 of warnings and worsening of seizures in section 17.3 of patient counseling.

7.5.5 Drug-Drug Interactions

Major drug-drug interactions between lamotrigine IR and concomitant AEDs are well characterized. A study was submitted to NDA 22115 to evaluate potential interaction between lamotrigine XR and the proton pump inhibitor esomeprazole. These results and implications of the study are presented by Dr. Kapcala⁸ in his medical review of NDA 22115. Esomeprazole is also noted in the drug interactions section of Pharmacokinetics (section 12.3) of currently approved labeling for Lamictal XR.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Non-clinical studies are not submitted with this application; however the currently approved label for Lamictal XR (section 13.1) cites previously performed carcinogenicity studies. One mouse and two rat studies following oral administration of lamotrigine for up to two years at maximum tolerated doses were performed; no evidence of carcinogenicity was seen.

7.6.2 Human Reproduction and Pregnancy Data

In the LTG XR clinical development program, there were 6 pregnancies that occurred: 4 in Study LAM100036, 1 in Study LAM30055, and 1 in Study LAM10005. One of the pregnancies resulted in a spontaneous abortion, which was considered reasonably attributable to study drug. The outcome for the other pregnancies included 2 healthy normal neonates, 2 elective terminations of pregnancy, and 1 unknown outcome.

7.6.3 Pediatrics and Assessment of Effects on Growth

No study examining effect of lamotrigine XR on growth is submitted in this application.

Safety- Controlled and Uncontrolled Adjunctive Studies

Study LAM100036 of the current application included patients ≥ 13 year old, however only 19 subjects < 18 years old were recruited into the study. One pediatric subject

⁸ Kapcala L. Medical Officer, Review of NDA 22115 Lamictal XR (lamotrigine XR), PDUFA date 9/14/07, p150, section 8.2.

LAM100036 suffered a TESA, in this case a 14 year old who developed communicating hydrocephalus and left hemiparesis. The case report characterizes both these events as acute. No past medical history is provided except for the underlying epilepsy. The patient suffered aspiration pneumonia and succumbed due to a sudden cardiopulmonary arrest. Within both controlled and open label studies performed in support of the approval of Lamictal XR, two pediatric patients suffered TESAs, one as noted above in study LAM100036 and a second, 17 year old subject in study LAM100034 who suffered moderate closed cranial injury and cranial fracture due to a motorcycle accident.

The occurrence of one medical death in the pediatric population is disproportionately high compared to the size of the adult population in the pivotal studies. This event is likely an outlier, the small number of pediatric patients does not allow for any generalization from this event.

The occurrence of one TESA in the 39 pediatric patients who were recruited results in a disproportionately low frequency of overall adverse events compared to the frequency of TESAs in the adult population. This is favorable and does not point to a trend of increased propensity to SAs in the pediatric population, however due to the small numbers there can be no generalization or conclusion concerning the outlook for SAs in a larger population.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

A possible overdose resulting in a fatal SA is reported in study LAM10034, however overdose is not well supported in the case report.

The sponsor indicates that acute ingestion in excess of 10 to 20 times the maximum therapeutic dose of lamotrigine IR has been reported. This has resulted in symptoms including nystagmus, ataxia, impaired consciousness and coma.

Drug Abuse

The abuse and dependence potential of Lamictal have not been evaluated in human studies.

Withdrawal and Rebound

The possibility of withdrawal and rebound were not assessed for LTG XR during this clinical development program.

The current Lamictal XR label indicates in section 5.8, Withdrawal Seizures; “*As with other AEDs, LAMICTAL XR should not be abruptly discontinued. In patients with epilepsy there is a possibility of increasing seizure frequency. Unless safety concerns require a more rapid withdrawal, the dose of LAMICTAL XR should be tapered over a period of at least 2 weeks (approximately 50% reduction per week) [see Dosage and Administration (2.1)].*”

7.7 Additional Submissions / Safety Issues

No additional submissions

8 Postmarket Experience

Lamotrigine (LAMICTAL) IR was first approved on 05 November 1990 in Ireland for use as add-on therapy in adult patients with partial seizures and generalized tonic-clonic seizures and is now available in over 100 countries. In the US, LAMICTAL was initially approved in December 1994 and launched in February 1995 for adjunctive use in adults with partial seizures. Subsequently, LTG was also approved for the prevention of mood episodes in patients with bipolar disorder, and is now available in over 50 countries for this indication with a cumulative world-wide exposure to lamotrigine for all indications, of 9.3 million patient-years (up to May 2008).

The sponsor searched the GSK clinical safety database with a data-lock point from November 1, 1997 to September 30, 2008 to identify all post-marketing reports, both spontaneous and post marketing surveillance, where lamotrigine was reported as a suspect drug. These reports were then further limited to those that met the regulatory seriousness criteria and where the patients were >12 years of age or where their age was unknown.

The above described search retrieved a total of 7527 reports. Eighty-six percent of the reports had been verified/received from a healthcare professional, and the remaining reports were from non-healthcare professional (i.e. consumers, lawyers, other manufacturers) or directly from regulatory authorities. The majority of reports were received from the US (47%), United Kingdom (UK, 11%), Germany (9%), and France (8%). No other single country contributed to more than 3% of the reports. The indication for the use of LTG was epilepsy in 42% of the reports, mood disorders in 29%, unknown indication in 22%, and other off-label use (i.e. pain, schizophrenia) accounted for 7% of the reports. There were 5678 reports where the exact age of the patients was specified (minimum 13 years, maximum 101 years, and median 36 years). A further 530 patients specified an approximate age group, and the remaining 1319 patients were of unknown age. The sex of the patients was specified in 7029 reports, of which 4956 were female

and 2073 were male. Of these 7527 serious reports, 418 reported a fatal outcome and 7109 did not.

The 7109 SAE reports where the patients had a non-fatal outcome documented a total of 28,567 events; SAE reports all document at least 1 SAE, but in some cases non-serious events are also reported within the same case. These events fell mostly into the MedDRA SOC of Skin and subcutaneous tissue disorders (5553 events); Nervous system disorders (4143); General disorders and administration site conditions (3236); Psychiatric disorders (2628); Investigations (2160); Gastrointestinal disorders (1996); Injury, poisoning and procedural complications (1221); and Blood and lymphatic system disorders (1209), and all the other SOCs contained less than 1000 events.

Fatal Reports

Of the 418 fatal reports, the majority of these reports were received from the US (198 reports), UK (48), France (33), and Germany (19); no other single country reported more than 15 deaths. There were 344 reports where the exact age of the patients was specified (minimum 13 years, maximum 94 years, and median 34 years). A further 21 patients specified an approximate age group, and the remaining 53 patients were of unknown age. The sex of the patients was specified in 369 reports, of which 212 were female and 157 were male. A summary of the cause of death is provided in [Table 8-1](#).

Table 8-1 Summary of the Cause of Death	
Cause of Death	Number of Cases
Sudden unexplained death including cardiac arrest	48
Suicide/suspected suicide/overdose	67
Organ failure; including multi-organ failure, DIC, hepatic and renal failure	47
Serious skin rash including SJS, TEN and serious rash	41
Seizure including status epilepticus	38
Death following in-utero exposure including intrauterine death, abortion spontaneous and induced	58
Unknown	51
Sub-total	350
All other terms have <10 reports e.g., pneumonia, cardiac failure	68
Total	418

Adverse event of Special Interest

The events of special interest associated with LTG treatment are: sudden death, serious skin rash, hypersensitivity reactions, blood dyscrasias, liver dysfunction, suicide events, and pregnancy outcomes.

Sudden Death

The sponsor indicates that cases relating to sudden death comprise 12% of fatal events. In addition the sponsor has discussion of a report from the literature by Aurlien D⁹ which concluded that an increase risk of sudden death from lamotrigine has not been excluded. The author argument is based on the property of lamotrigine which inhibits the cardiac rapid delayed rectifier potassium ion current (I_{kr}). The author presents an in vitro analysis which assesses the possible arrhythmogenic properties of AEDs using a whole cell patch-clamp recording technique to study the effects on I_{kr} channels. In this analysis the IC₅₀ ratio in vitro (the concentration when 50% inhibition is obtained compared with control values)/ therapeutic free plasma concentration is considered potentially relevant for values of approximately 30 and below. For lamotrigine it was found to be less than 10, indicating a significant and clinically relevant I_{kr} inhibition. This compares to a ratio of 30 for phenobarbital and 25 for phenytoin. Following this physiologic argument the author presents four outpatient case histories of patients on lamotrigine with sudden death. Review of the cases reveals potential alternate causes of sudden death however the article concludes that lamotrigine as a cause of increased risk for SUDEP has not been excluded.

In response to the argument of the I_{kr} the sponsor performs an AERS database analysis up to the first quarter of 2005. in this analysis the Multi-item Gamma Poisson Shrinker (MGPS) disproportionality methodology ([further characterized in the next section](#), "AERS Database Search"). This analysis compares the strength of association between lamotrigine and the preferred term (PT) sudden death. The same analysis is then performed for comparator AEDs (Carbamazepine, Clonazepam, Clorazepate, Ethosuximide, Ethotoin, Felbamate, Fosphenytoin, Gabapentin, Lamotrigine, Levetiracetam, Mephenytoin, Mesuximide, Oxcarbazepine, Phenobarbital, Phensuximide, Phenytoin, Primidone, Tiagabine, Topiramate, Trimethadione, Valproic Acid, Zonisamide). The sponsor analysis revealed the EB05 (further defined next section) value for lamotrigine to be less than 2 and also less than 5 of the 13 comparator AEDs, including three new generation and widely used anticonvulsants, [figure 8-1](#). In the subsequent section ("AERS Database Search") the reviewer updated this analysis to November 2009, also finding no signal for sudden death greater than several comparator AEDs.

9 Aurlien D, Taubøll E, Gjerstad L. Lamotrigine in idiopathic epilepsy – increased risk of cardiac death?. Acta Neurol Scand. 2007;115:119-203.

Figure 8-1; Sponsor Analysis EB05 lamotrigine and Comparator AEDs to Quarter 1, 2005

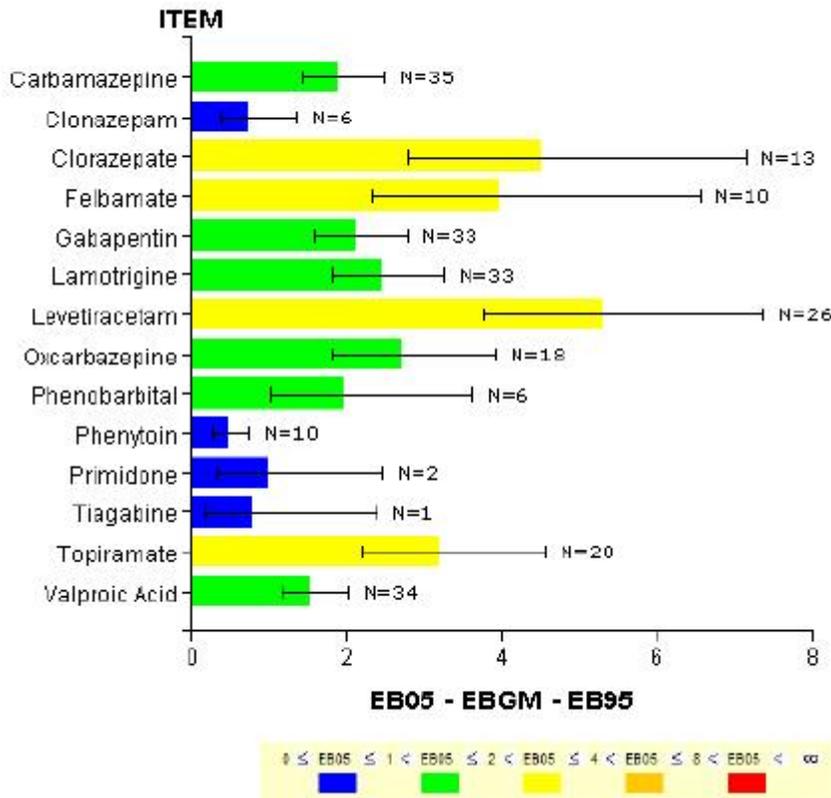


Figure 5

In addition to sudden death the sponsor has also presented analysis for additional adverse event of interest including serious rash, hypersensitivity reaction, blood dyscrasias, hepatic dysfunction, and suicide. The sponsor presentation of these adverse events is presented in the subsequent paragraphs.

Serious Skin Rash

Of the 7527 serious reports identified for this post-marketing review, 976 reports documented 1 or more of the following serious skin rash events (MedDRA preferred terms): SJS, TEN, and erythema multiforme. Four hundred and eight-nine serious skin rash reports were received from the US and 487 from the rest of the world (ROW). The incidence rate of serious skin rash received from the US and the ROW are graphically displayed and summarized in [table 8-2](#) and [figure 8-2](#), respectively.

Table 8-2	Patient Exposure(Patient-years)		Number of Serious Skin Rash Reports		Incidence of Reports (per 10,000 Patient-years) of Serious Skin Rash	
	USA	ROW	USA	ROW	USA	ROW
1997	68,287	124,646	3 ^a	3 ^a	-	-
1998	93,824	160,267	7	24	0.75	1.56
1999	124,332	199,591	10	20	0.80	1.00
2000	155,012	251,508	22	37	1.42	1.47
2001	194,822	297,824	19	34	0.98	1.14
2002	247,322	347,463	25	35	1.01	1.00
2003	322,439	392,277	37	44	1.15	1.12
2004	443,082	458,412	53	60	1.2	1.31
2005	567,218	474,404	95	78	1.67	1.64
2006	706,849	439,726	92	47	1.30	1.07
2007	842,466	460,274	83	55	0.98	1.19
2008	Not available	Not available	43	50	-	-
Total	-	-	489	487	-	-

^a reports received from 01 November 1997 to 31 December 1997; hence not appropriate to calculate reporting rate for 1997.

Figure 8-2; Incidence of Reports (per 10,000 Patient years) of Serious Skin Rash for the US and the Rest of the World (ROW)

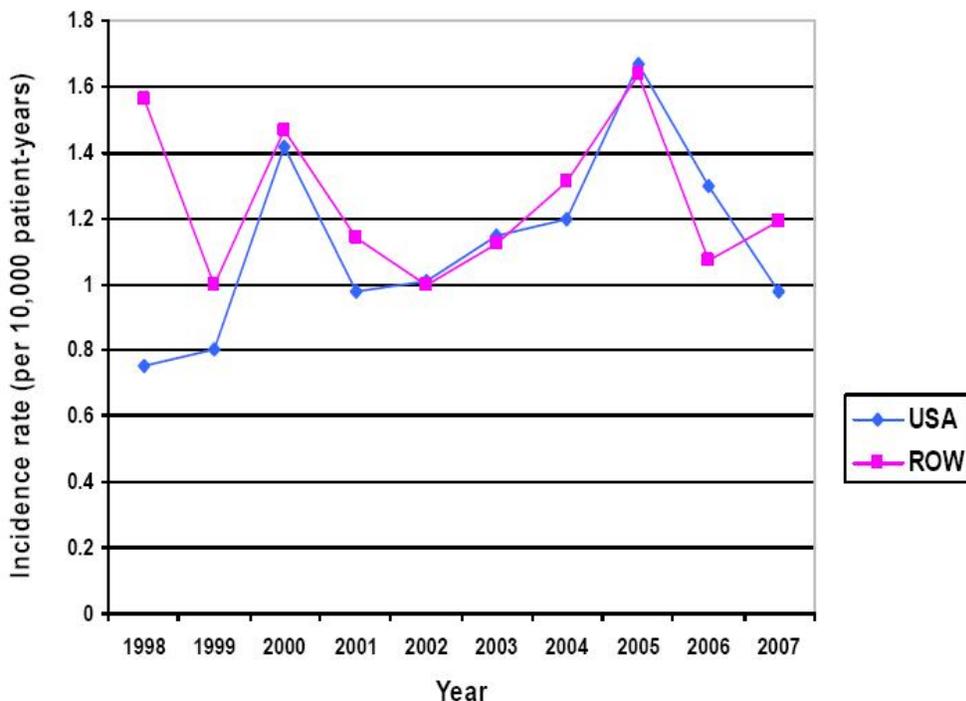


Figure 6

Hypersensitivity Reaction

For the period under review, there were a total of 286 reports concerning at least 1 of the following MedDRA preferred terms: hypersensitivity, drug hypersensitivity, DIC, and multi-organ failure. Of these 286 reports, 109 were from the US and 177 from the ROW. The incidence rate of hypersensitivity reactions received from the US and the ROW are summarized and graphically displayed in [Table 8-3](#) and [Figure 8-3](#), respectively.

Table 8-3	Patient Exposure(Patient-years)		Number of Hypersensitivity Reaction Reports		Incidence Rate (per 10,000Patient-years) of Hypersensitivity Reaction	
	USA	ROW	USA	ROW	USA	ROW
1997	68,287	124,646	1 ^a	3 ^a	-	-
1998	93,824	160,267	5	7	0.53	0.44
1999	124,332	199,591	2	8	0.16	0.40
2000	155,012	251,508	7	10	0.45	0.40
2001	194,822	297,824	6	9	0.31	0.30
2002	247,322	347,463	6	14	0.24	0.40
2003	322,439	392,277	13	19	0.40	0.48
2004	443,082	458,412	19	20	0.43	0.44
2005	567,218	474,404	12	27	0.21	0.57
2006	706,849	439,726	12	22	0.17	0.50
2007	842,466	460,274	14	23	0.17	0.50
2008	Not available	Not available	12	15	-	-
Total	-	-	109	177	-	-

^a reports received from 01 November 1997 to 31 December 1997; hence not appropriate to calculate reporting rate for 1997.

Figure 8-3; Incidence of Reports (per 10,000 Patient Years) of Hypersensitivity Reactions for the US and the Rest of the World (ROW)

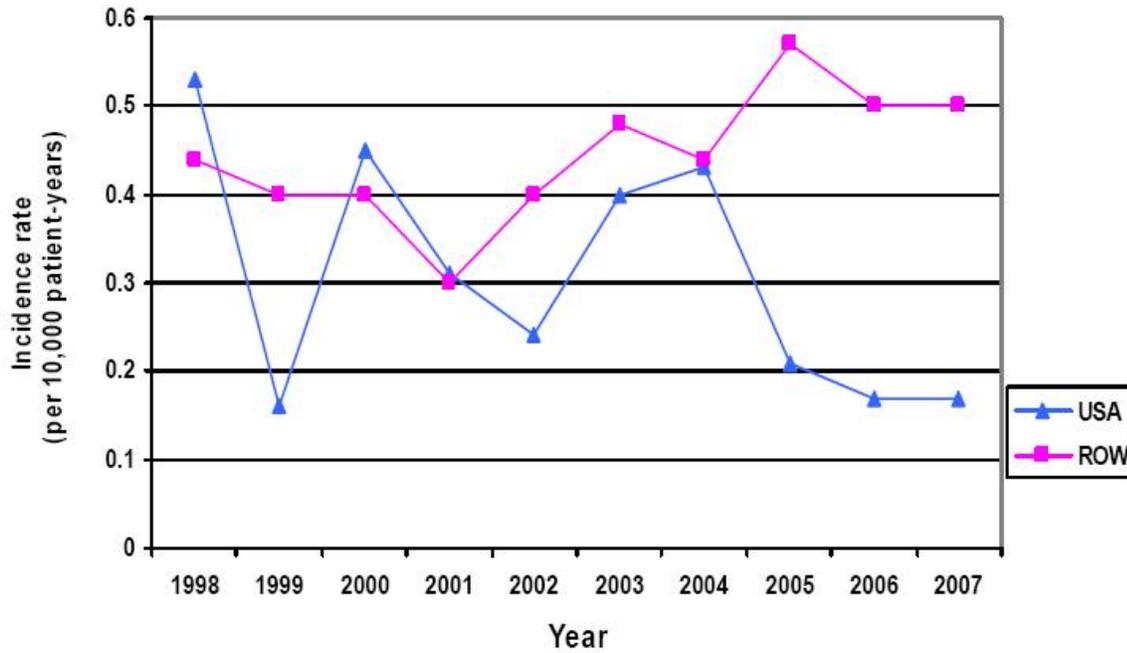


Figure 7

Blood Dyscrasia

Of the 7527 SAE reports identified during this reporting period, 453 reports concerned a blood dyscrasia, (i.e., agranulocytosis, anemia, aplastic anemia, aplasia pure red cell, granulocytopenia, leukopenia, neutropenia, pancytopenia, and thrombocytopenia).

One hundred and forty-three reports were received from the US, and 310 reports were received from the ROW. The incidence rate of blood dyscrasias received from the US and the ROW are summarized and graphically displayed in [table 8-4](#) and [figure 8-4](#) respectively.

Table 8-4	Patient Exposure (Patient-years)		Number of Blood Dyscrasia Reports		Incidence Rate (per 10,000 Patient-years) of Blood Dyscrasia	
	USA	ROW	USA	ROW	USA	ROW
Years						
1997	68,287	124,646	0 ^a	1 ^a	-	-
1998	93,824	160,267	1	18	0.11	1.12
1999	124,332	199,591	6	18	0.48	0.90
2000	155,012	251,508	3	29	0.19	1.15
2001	194,822	297,824	4	18	0.20	0.60
2002	247,322	347,463	9	18	0.36	0.52
2003	322,439	392,277	10	21	0.31	0.54
2004	443,082	458,412	24	40	0.54	0.87
2005	567,218	474,404	15	51	0.26	1.08
2006	706,849	439,726	28	41	0.40	0.93
2007	842,466	460,274	27	33	0.32	0.72
2008	Not available	Not available	16	22	-	-
Total	-	-	143	310	-	-

^a reports received from 01 November 1997 to 31 December 1997; hence not appropriate to calculate reporting rate for 1997.

Figure 8-4; Incidence Rate (per 10,000 Patient-years) of Blood Dyscrasias for the US and Rest of World (ROW)

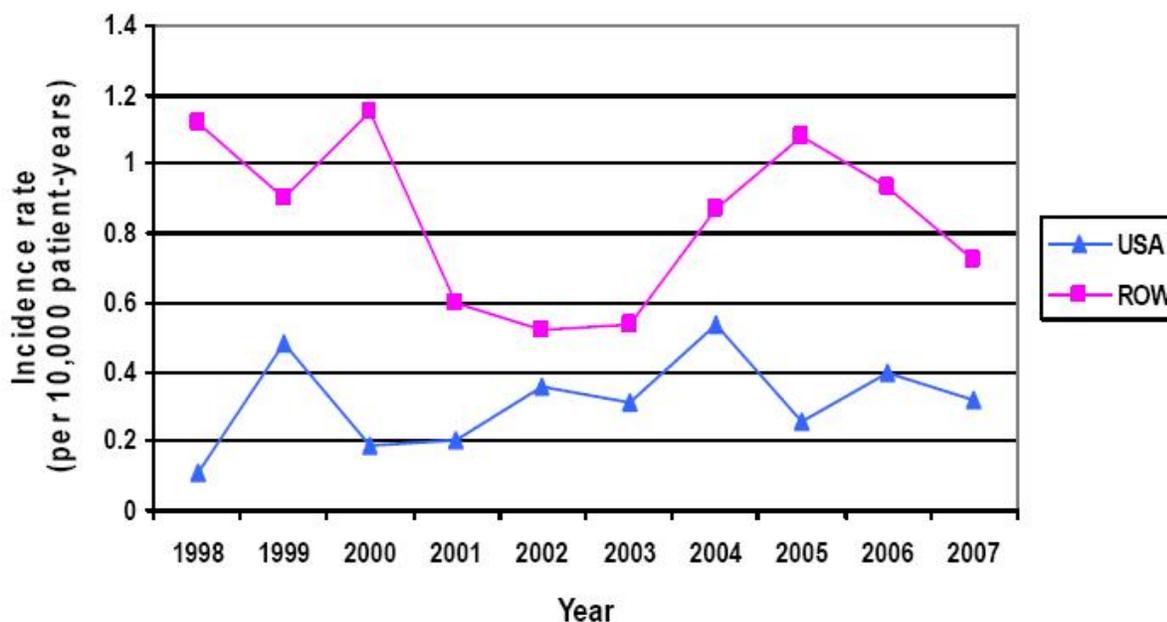


Figure 8

Hepatic dysfunction

The sponsor provides references to previously submitted updates concerning hepatic dysfunction. The reviewer performs an independent update based on relevant terms from the AERS database in the section below entitled “AERS Database Search” using search terms identified in [table 8-7](#).

Suicide and Suicide-related Events

The sponsor searched their safety database of 7527 SAE reports using the following preferred terms: Completed suicide, suicide attempt, suicidal ideation, depressional suicide, suicidal behavior, intentional overdose, and multiple drug overdose intentional. In addition, for the purpose of this document, reports of intentional drug misuse and overdose where the outcome was fatal were also retrieved and categorized as completed suicide. This search retrieved a total of 416 reports; see Table 105 for the categorization of the reports. In addition, reports concerning completed suicide or suicide attempt and an intentional overdose, these reports were categorized as completed suicide or suicide attempt.

Table 8-5 Summary of the Number of Suicide and Suicide-related Reports	
Suicide Event	No. of Reports

Completed suicide	66
Suicide attempt	202
Suicidal ideation	96
Depressional Suicide	3
Suicidal behaviour	2
Intentional overdose	47
Total reports	416

The sponsor also examined the AERS database up to the first quarter of 2007 using the MGPS algorithm to investigate whether there is a signal for suicide in relation to lamotrigine, [table 8-6](#). This analysis reveals no EB05 >1 for any of 5 chosen PTs. This analysis is updated by the reviewer in the next section (AERS Database Search) and results may be seen in [figure 8-11](#).

Table 8-6 Signal Scores for Suicide Related Events for lamotrigine from AERS				
Suicide Event	N	EB05a	EBGM	EB95
Completed suicide	63	0.49	0.605	0.74
Depression suicidal	3	0.442	1.13	2.486
Intentional overdose	63	0.5	0.617	0.755
Suicidal ideation	85	0.621	0.744	0.886
Suicide attempt	87	0.649	0.776	0.922

^a GSK uses EB05 ≥ 2 as a threshold for signal detection. This threshold ensures with a high degree of confidence that regardless of the number of reports, a particular drug-event combination is being reported at least twice as often as it would be if there were no association between the drug and the event.

AERS Database Search

In addition to the presentation from the sponsor database (up to first quarter 2005) an updated search of the AERS database using Empirica Signal is performed to evaluate the occurrence of sudden death and the adverse events of specific interest reviewed above. The database is searched from 1994 to November 19, 2009 and analysis applied using Multi-item Gamma Poisson Shrinker (MGPS) disproportionality algorithm. This algorithm quantifies reported drug-event associations by producing a set of values or scores which indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting rate of an event for a particular drug relative to all other drugs and events in the database. MGPS also calculates lower and upper 90% confidence limits for the EBGM values, denoted EB05 and EB95 respectively.

Using the MGPS methodology to evaluate the preferred term “sudden death’ lamotrigine is compared to other AEDs, including Carbamazepine, Clonazepam, Clorazepate, Felbamate, Gabapentin, Levetiracetam, Oxcarbazepine, Phenobarbital, Phenytoin, Primidone, Tiagabine, Topiramate, Valproic Acid. This analysis reveals an EB05 of 1.65 for lamotrigine, where a result >2 is considered a significant signal for occurrence

above background rate. The lamotrigine EB05 is similar to other widely used anticonvulsant agents, [figure 8-5](#). The frequency of sudden death has varied around an average of 2.5 cases per year with a low of 0 in the interval from 2001 to 2002, and a high of 6 between 2004 and 2005, [figure 8-6](#). The EB05 when examined by year, has also been < 2 from 2003 to current.

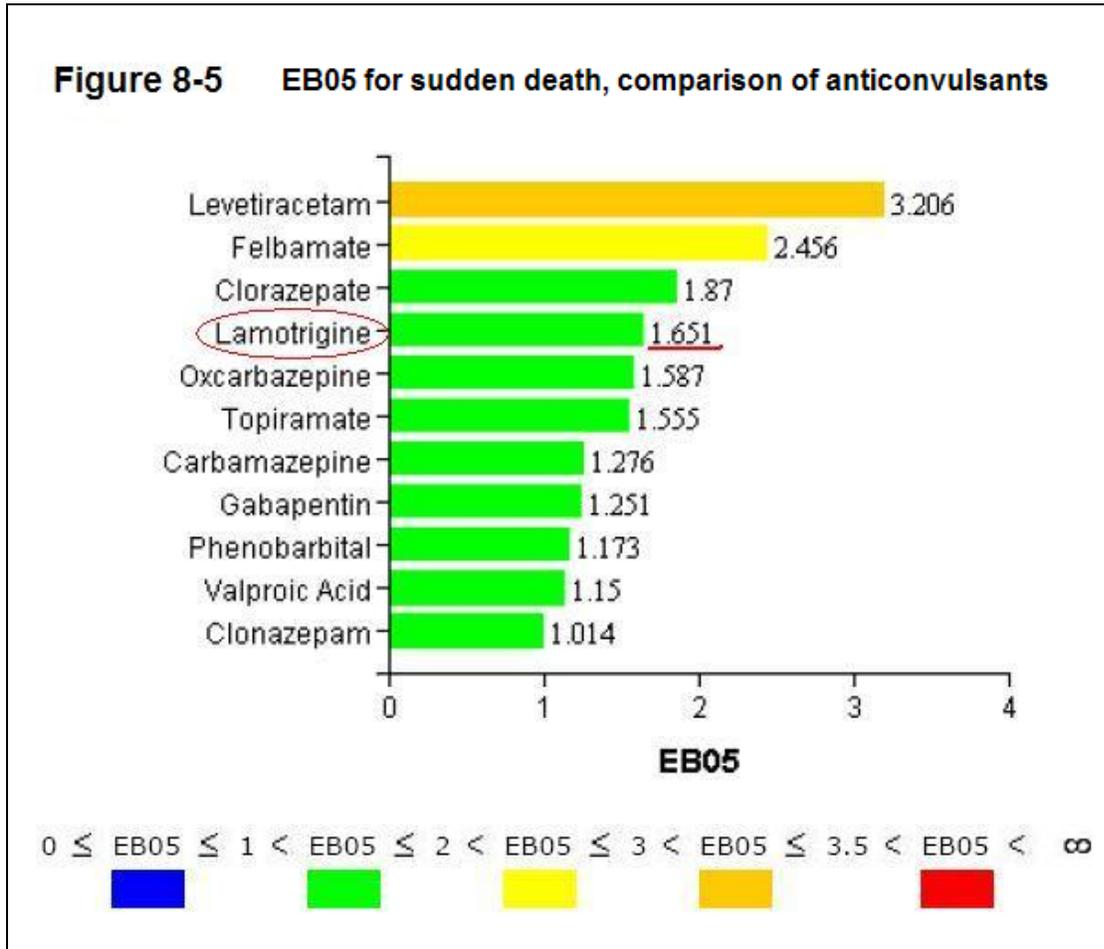


Figure 9

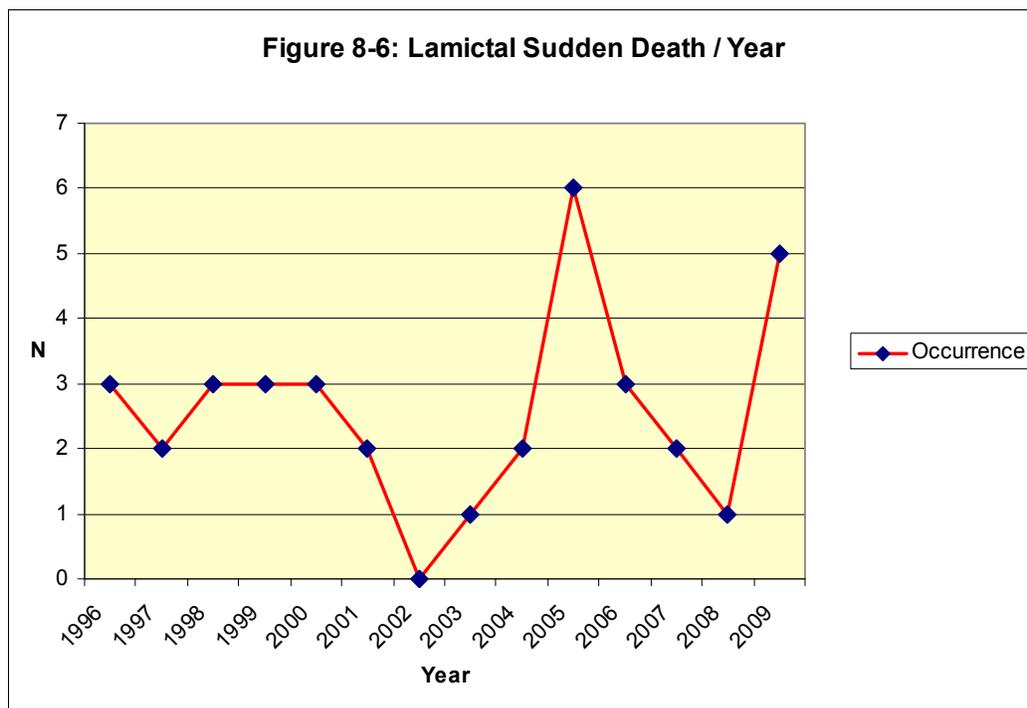


Figure 10

The additional drug related adverse events of special interest (serious skin rash, hypersensitivity reactions, blood dyscrasias, liver dysfunction, and suicide events) are also explored using MGPS methodology. The purpose of the exploration is to determine if there is a changing trend in the strength of association between lamotrigine and the event terms (cluster of related PTs, [table 8-7](#)) of interest, which represent the more serious drug related adverse effect associated with lamotrigine.

Search Strategy

Preferred terms are chosen to best capture the events of interest. Each area of interest and the selected PTs are shown in [table 8-7](#). Each combination of search terms and datamining run entitled Lamictal (S), (S) indicating suspect drug, was used to generate a year by year graphic illustration of the EB05 for the drug related adverse events of interest; these can be seen in the remainder of this section.

Topic of interest	Search Terms (PTs)
Suicide	Completed suicide, Depression suicidal, Suicidal behaviour, Suicidal ideation, Suicide attempt, intention overdose
Serious Rash	Stevens-Johnson syndrome, Toxic epidermal necrolysis, Erythema multiforme
All Rash	Rash
hypersensitivity	hypersensitivity, drug hypersensitivity, DIC, and multi-organ failure

Table 8-7 Datamining run Trade Name (S), Lamictal, Lamictal CD	
Topic of interest	Search Terms (PTs)
Blood dyscrasia	agranulocytosis, anaemia, aplastic anaemia, aplasia pure red cell, granulocytopenia, leukopenia, neutropenia, pancytopenia, and thrombocytopenia
Hepatic dysfunction	Acute hepatic failure, Alanine aminotransferase abnormal, Alanine aminotransferase increased, Aspartate aminotransferase abnormal, Aspartate aminotransferase increased, Bilirubin conjugated abnormal, Bilirubin conjugated increased, Biopsy liver abnormal, Blood bilirubin abnormal, Blood bilirubin increased, Blood bilirubin unconjugated increased, Chronic hepatic failure, Hepatic enzyme increased, Hepatic function abnormal, Hyperbilirubinaemia, Liver function test abnormal

Graphic Representation of EB05 for Lamictal (trade name (S) by Year for adverse events of interest; figures 8-3 to 8-8.

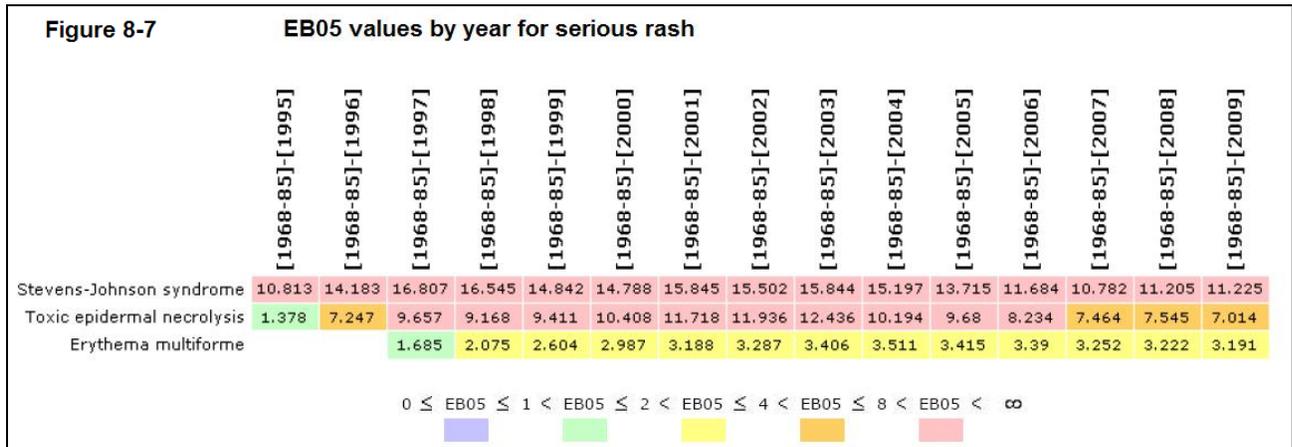


Figure 11

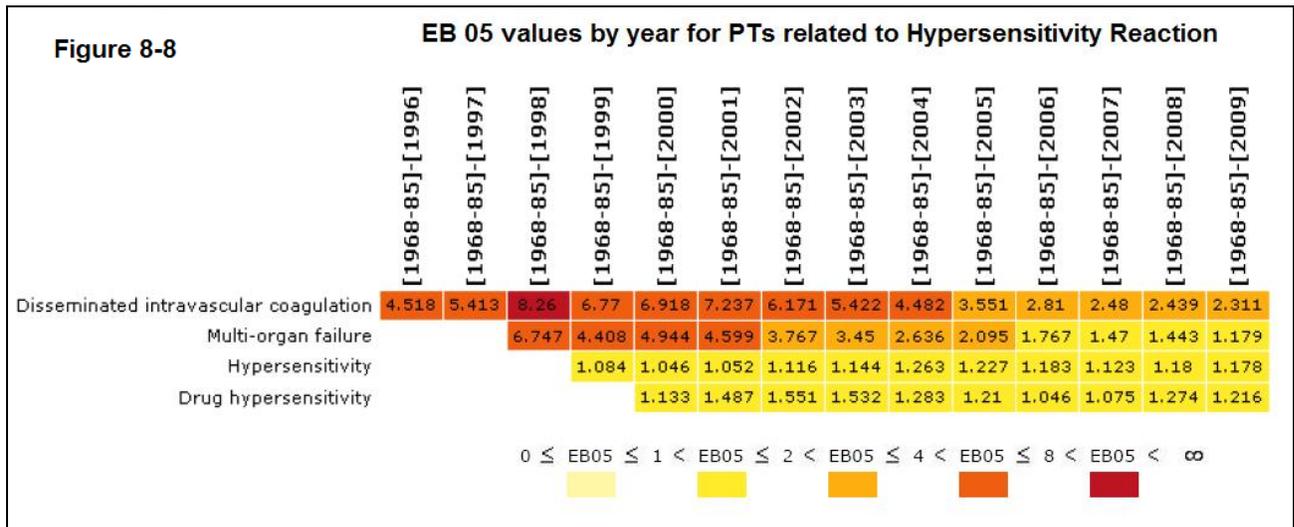


Figure 12

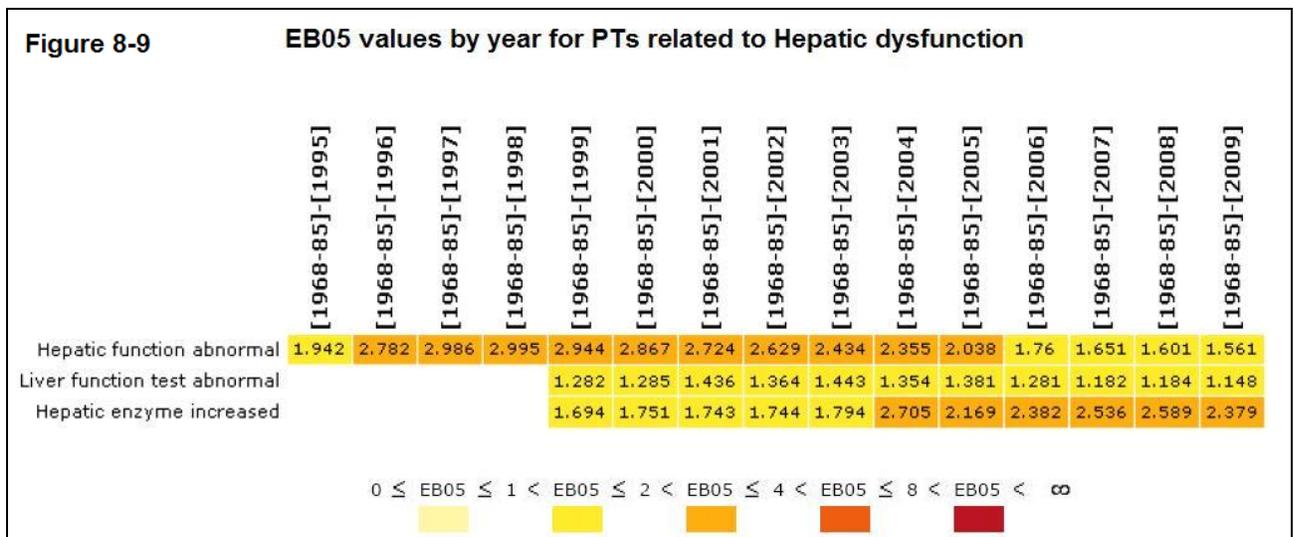


Figure 13

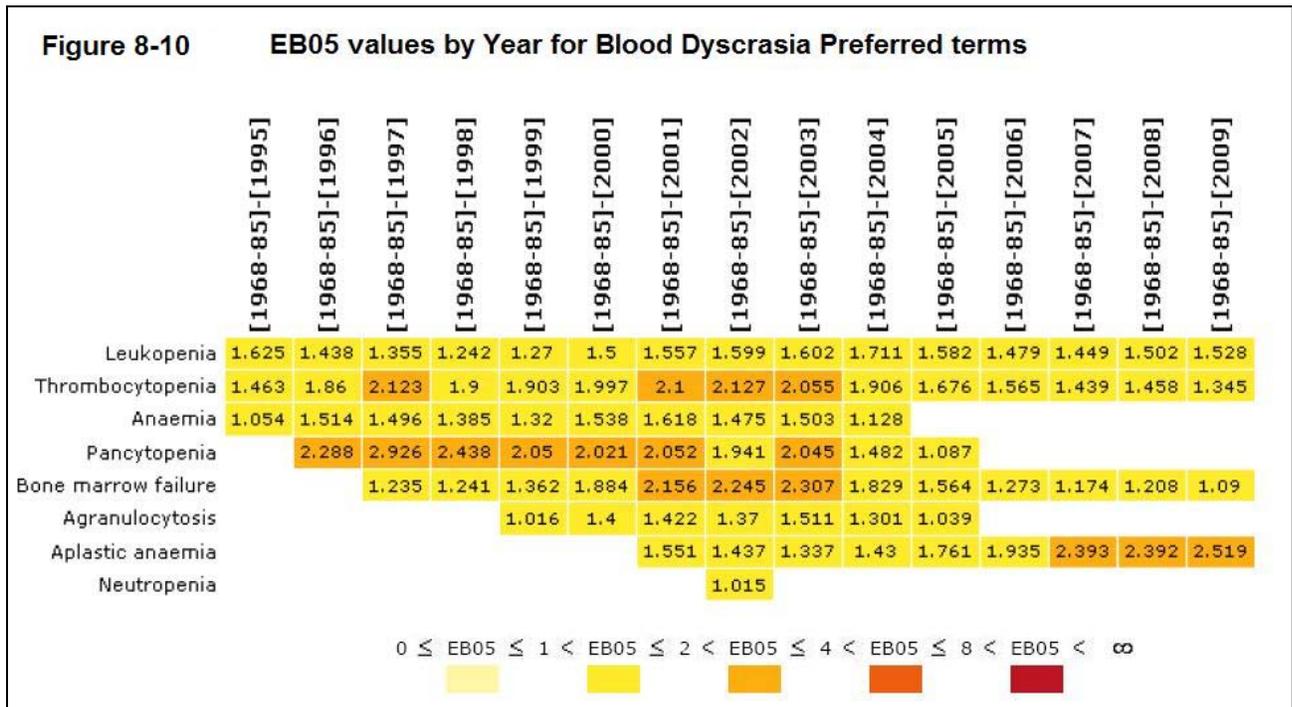


Figure 14

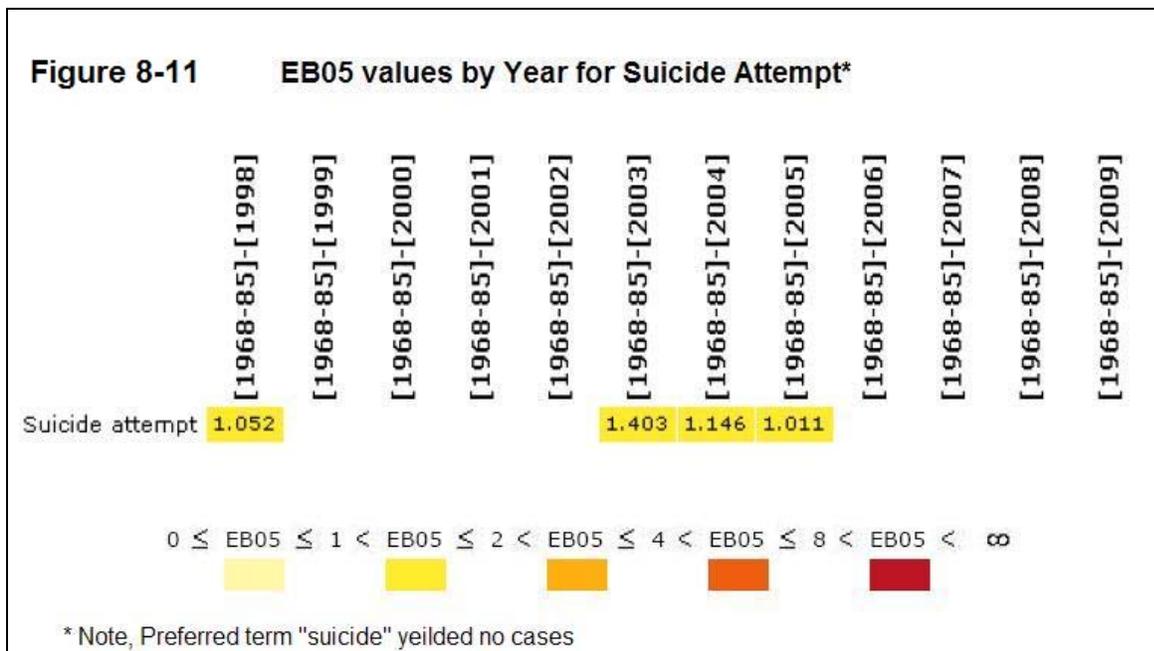


Figure 15

An additional search is performed to screen the AERS database for new or unexpected association between Lamictal and an adverse event. The strategy in this case is to

choose the suspect (in reports) drug (Lamictal) by trade name and analyze within all SOC for EB05 >2. This search revealed adverse effect which are anticipated with lamotrigine based on past experience and are present in labeling or related to labeled adverse effects.

Reviewer Comment: there is very extensive post marketing exposure to lamotrigine, first approval was in 1990 in Ireland and US first approval in 1994. Currently there is availability in over 100 countries and from launch until May 31, 2008 there has been 9.3 million patient years of exposure for all indications. Because of this extensive record the prior exposure and safety experience is an important consideration in approval of Lamictal XR for PGTC seizures.

The record indicates 418 reports of death since beginning marketing. 38 were due to status epilepticus and 58 intrauterine. The cases of status epilepticus cannot be linked with certainty to lamotrigine because status is a threat in the natural history of epilepsy. Those intrauterine cases may be related to the drug ingredient but occur in a state where there is understood risk of unknown consequences. The remaining 322 cases may be considered more directly linked to a catastrophic effect on an individual in the targeted approval population. A mechanism to analyze the magnitude of the threat of Lamictal related serious adverse effects is to examine the incidence in proportion to exposure and also to examine the occurrence of the most threatening adverse effects relative to the occurrence of those adverse effect in all other drugs (MGPS algorithm).

The sponsor has presented data on the adverse effect of special interest in Lamictal, those which are most threatening in the use of this agent which are sudden death (a concern in anticonvulsants due to the phenomena of SUDEP), serious rash, hepatic toxicity, blood dyscrasia and suicide. Suicide is again a concern of class effect. The EB05 for sudden death does not stand out among the anticonvulsants; the EB05 is less than 2, below the level generally considered as a safety signal. In addition there are three AEDs with EB05 greater than Lamictal, one in common use. The EB05 is very close to that of topiramate, the next lower EB05 among those examined. The reviewer also examined the incidence of sudden death per year, reported to the AERS database under the search term sudden death. The yearly incidence has been fairly stable with an average frequency of 2.56 case / year, a minimum of zero and maximum of six in 2005. This frequency is small considering the large exposure but neither the numerator nor denominators are certain. The frequency comes from a passive surveillance. The best remaining index of safety signal assessment is the MGPS algorithm which provides a rough indicator that there is not a drug specific safety signal.

The incidence of serious rash per 10,000 patient year of use per year shows stability, occurring in the range of 1 to 1.6 per 10,000 patient years per year. This data does not reveal evidence of a long term exposure related increase in frequency. This same conclusion can be drawn from the presentations of incidence per 10,000 patient years of exposure per year, of hypersensitivity reactions and blood dyscrasias. The sponsor does not report suicide and suicide related event in the same format, incidence per

10,000 patient years per year, but does report 416 events captured from appropriate PTs over the marketing interval. The meaning of this number is uncertain when attempting determine if this represents a safety signal. In this case again the reviewer looks to the MGPS algorithm to identify a safety signal. The AERS database search yielded an EB05 only for suicide attempt, although completed suicide was included as a term in the database query. An EB05 resulted only for 1998, 2003, 2004 and 2005 for suicide attempt. The maximum EB05 identified was in 2003 at a magnitude of 1.4, with the most recent appearing in 2005 of nearly unity (same as background). This does not point to a greater than expected safety signal for Lamictal.

The reviewer also explores serious rash, blood dyscrasia, and hepatic toxicity using the MGPS method. The EB05 for serious rash reveals a very strong signal for all relevant search terms, especially prominent for Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) with EB05 of 11.2 and 7.01 respectively. The EB05 values for SJS have declined from a maximum of 16.8 in 1997 but remains high, the values do not indicate a trend of increasing risk with sustained exposure of the population. The values for TEN have also decreased from a maximum of 12.4 in 2003 but remains high. The values do not indicate a trend of increasing risk with sustained exposure of the population. The values for erythema multiforme increased and have remained stable since 2003 but do not indicated a trend of increasing likelihood of risk with sustained exposure of the population. The values for SJS and TEN continue to indicate a frequency of occurrence 11 and 7 times greater compared to the background occurrence in all other drugs. This risk is commensurate with the current labeling which has a boxed warning.

The EB05 for the search terms multi-organ failure, hypersensitivity and drug hypersensitivity are low, maximum 1.2, indicating and do not indicate a safety signal, DIC (disseminated intravascular coagulation) an event which may be associated with a catastrophic systemic immunologic reaction is elevated at 2.3. This does indicate a modest safety signal for this event although only indirectly related to hypersensitivity reaction. The EB05 values have been decreasing for all terms since 2004 suggesting no elevated risk with sustained use in the population. The current strength of warning for hypersensitivity reaction in labeling, located in warnings and precautions, is directed by individual cases and the severe nature of the reaction rather than the EB05.

Only three of the 16 selected PTs for hepatic toxicity yield an EB05 value, these are hepatic function abnormal, liver function test abnormal and hepatic enzyme increased. There is no value for acute or chronic hepatic failure. Two of the three search terms have an EB05 <2 and only "hepatic enzyme increased" is above 2, and found to be 2.38. There is also no trend of increasing EB05 values over the years since 1995. These values indicated an overall low likelihood of a safety signal for hepatic toxicity. This is commensurate with the current strength of warning in labeling where the only hepatic toxicity related events are noted in clinical trial experience as "liver function tests abnormal". Hepatic toxicity may occur as part of the broad spectrum of organ system involvement that may occur in a severe hypersensitivity reaction; however the

aforementioned analysis is directed at the more specific occurrence of direct and stand alone hepatic toxicity from lamotrigine.

Nine PTs were selected for MGPS analysis of blood dyscrasias. The term pure red cell aplasia did not reveal and EB05 in any year. Of the remaining PTs only leukopenia and thrombocytopenia yielded and EB05 in all years since 1995, and only leukopenia, thrombocytopenia, bone marrow failure, and aplastic anemia have yielded an EB05 in the most current search year, 2009. The EB05 for leukopenia, thrombocytopenia, and bone marrow failure are <2. Neutropenia has an EB05 of 2.5 indicating a potential safety signal. In earlier years pancytopenia and bone marrow failure had an EB05 modestly >2. There is no trend in the values for increasing risk with sustained exposure of the population. Overall the risk of a safety signal for blood dyscrasias is not high and commensurate with the current strength of warning in labeling, present in section 5.4 (warnings and precautions).

Six PTs were chosen as search terms to perform an MGPS analysis of suicide. Only suicide attempt yielded an EB05 in years 1998, 2003-2005. The maximum EB05 was 1.4 in 2003 and the most recent in 2005 was 1.011. These values indicate a low likelihood of a safety signal for suicide associated with use of Lamictal that is greater than the occurrence in other drugs having adverse events in the AERS database. The risk of suicide is present in labeling due to analysis which found suicide to be a class effect of the anticonvulsant medications.

9 Appendices

Appendix 1: Subject 254, Study LAM30055

Subject 254 was a 57 year old male with a history of hepatitis B at time of event. The patient received oral extended-release lamotrigine tablet (dose-blinded) at an increasing dosage of 25 mg to 250 mg from 13 April 2007 to 30 July 2007. On [REDACTED] (b) (6) days after the start of investigational product, the subject developed moderate viral cirrhosis, moderate alcoholic cirrhosis and moderate hepatocellular cancer. The events were clinically significant (or requiring intervention). Treatment with investigational product was discontinued on 30 July 2007.

Follow up was received on September 10, 2007: [REDACTED] (b) (6) Abdomen CT scan: Multiple nodular lesions suggesting hepatocellular cancers and multiple "tiny hepatic cysts". The subject was withdrawn from the study. The SAE was confirmed as "hepatocellular cancer".

Follow up received on 21 September 2007:
On [REDACTED] (b) (6) magnetic resonance imaging and computer tomography confirmed the diagnosis of hepatocellular carcinoma.

Follow-up information received 09 November 2007:
The subject was hospitalized on [REDACTED] (b) (6) to undergo treatment of the hepatocellular cancer. Transcatheter arterial embolisation was conducted on [REDACTED] (b) (6). The subject was re-admitted on [REDACTED] (b) (6) and underwent a second transcatheter embolisation. A computed tomography scan of the abdomen was performed on [REDACTED] (b) (6). It was reported that 'the tumor has not been growing any more'. The subject's appetite and general condition was good.

At follow information of January 7, 2008 the subject condition was reported unchanged. At follow up information of January 30, 2008 the subject was reported to have a concurrent medical history of liver cirrhosis.

Follow up information received on April 11, 2008:
After treatment for hepatocellular cancer, the subject was followed up. There was no interval changed compared to previous visit. The investigator considered that further follow up was not needed, because the condition of the subject became stabilized. The event had improved on an unspecified date.

Follow up information received on December 30, 2008 reveals the subject died on [REDACTED] (b) (6) due to hepatocellular cancer. It was unknown whether an autopsy was performed.

Appendix 2: Subject 14, LEP105972

This 85-year-old female subject was enrolled in an open-label study of lamotrigine extended release in elderly subjects with epilepsy. The subject received oral lamotrigine at an increased dose of 50 mg to 400 mg from 16 December 2008. On 13 January 2008 the subject's total daily dose of lamotrigine was 200 mg.

Medical conditions at the time of the event included coronary artery disease and hypertension. Concomitant medications included magnesium hydroxide, omeprazole, ferrous sulfate, docusate calcium and lisinopril.

On [REDACTED] (b) (6) approximately [REDACTED] (b) (6) days after the start of lamotrigine, the subject developed severe hip fracture following a fall. The subject was hospitalised. An anteroposterior and a frogleg view x-ray of pelvis showed a displaced intertrochanteric left hip fracture. The subject underwent open reduction internal fixation of left hip on [REDACTED] (b) (6). The subject was treated with morphine, Norco, D5 1/2 NS + 20mEq KCl, Darvocet N 100, D5 + NS + KCl, cephazolin sodium, furosemide, paracetamol, D5NS, enoxaparin, and Senokot S. No action was taken with the investigational product as a result of this event.

On [REDACTED] (b) (6) approximately [REDACTED] (b) (6) days after the start of lamotrigine, the subject developed severe small intestine obstruction. A single view x-ray of abdomen showed marked dilation of loops of small bowel, and no colon was seen, suggesting a mechanical small bowel obstruction. The subject was treated with bisacodyl, Fleet enema, labetalol hydrochloride, ondansetron hydrochloride, sodium chloride, Metoclopramide hydrochloride, and hyoscine. Treatment with the investigational product was interrupted due to the small intestine obstruction, with the last dose taken on [REDACTED] (b) (6).

On [REDACTED] (b) (6) approximately [REDACTED] (b) (6) after the start of lamotrigine, the subject also experienced severe acute myocardial infarction. Relevant test results on [REDACTED] (b) (6) included creatine phosphokinase 179 u/l (normal range 35.0 - 350.0), creatine phosphokinase muscle band 3.3 ng/ml (normal range 0.0 - 6.1), and troponin I 0.04 ng/ml (normal range 0.00 - 0.05). An echocardiogram on [REDACTED] (b) (6) showed normal left ventricular systolic function, left ventricular hypertrophy, left atrial enlargement, mild mitral valve regurgitation, and impaired ventricular relaxation / diastolic dysfunction. Relevant test results on [REDACTED] (b) (6) included creatine phosphokinase 206 u/l, creatine phosphokinase muscle band 10.0 ng/ml, and troponin I 0.29 ng/ml. The subject was treated with lisinopril, metoprolol, enalapril, lorazepam, lignocaine hydrochloride, and morphine. Following discussion with the subject's family the investigator determined that the subject was not suitable for further intervention, and elected for comfort care. The subject died on [REDACTED] (b) (6) due to the acute myocardial infarction. The hip fracture and small intestine obstruction were unresolved at the time of death. An autopsy was not performed. The investigator considered that there was no reasonable possibility that the hip

fracture, small intestine obstruction and acute myocardial infarction may have been caused by lamotrigine.

9.1 Literature Review/References

See Footnotes

9.2 Labeling Recommendations

Completed

9.3 Advisory Committee Meeting

None recommended

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22509

ORIG-1

SMITHKLINE
BEECHAM CORP
DBA
GLAXOSMITHKLIN
E

LAMICTAL
XR(LAMOTRIGINE)ORAL
TABLETS

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

/s/

STEVEN T DINSMORE
01/28/2010

NORMAN HERSHKOWITZ
01/28/2010

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
14.	<p>Do there appear to be the requisite number of adequate and well-controlled studies in the application?</p> <p>Pivotal Study #1 LAM100036 Indication: PGTCs, patients 13 yrs and older.</p> <p>Pivotal Study #2 LAM30055 Indication: conversion to Lamictal XR monotherapy in patients 13 years of age and older with partial seizures. LAM30055 will be submitted for safety information only.</p> <p>Development Program- partial seizures: NDA 22115 LAM100034:</p>				<p>The cover letter states: <i>This application consists of two completed, clinical studies evaluating this formulation in patients with epilepsy</i> LAM100036 <i>(adjunctive treatment of PGTC seizures in patients age 13 years or older) and</i> LAM30055 <i>(conversion to lamotrigine XR monotherapy in patients 13 years of age and older with partial seizures).</i> LAM30055 will be submitted for safety information only.</p> <p>The ISS indicates that analysis will include integrated data from 2 adjunctive clinical studies (LAM100036 and LAM100034), 1 monotherapy study (LAM30055) and 5 healthy volunteer studies ((LAM102611, LAM10014, LAM10005 [Part A], LEP111102, and LAM105379)</p>
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			Age: only 10 randomized <16, draft labeling indication ≥ 13 yo.
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Primary efficacy endpoint for Lam100036 was % Δ from baseline in weekly PGTC seizure frequency during DB treatment phase.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?				24 of 153 patients randomized were from US. Subgroup of US efficacy- placebo/treatment were NS
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			Sponsor followed extensive formatting requested by Dr. Kapcala
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?			X	TQT study performed in past on IR, doses 100mg, 300mg and 400mg- not submitted with this submission
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate	X			In All Clinical Studies (LAM100036,

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?				LAM100034, and LAM30055), a total of 372 (57%) and 268 (41%) subjects in the All LTG XR group were exposed to LTG XR for at least 24 and 52 weeks, respectively
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			Adverse events in this ISS were coded using the Medical Dictionary for Regulatory Activities (MedDRA v11.0) coding system-p62 ISS
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			Safety behavior is well characterized from IR form.
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Sponsor has submitted request for Partial Waiver for conducting pediatric studies for patients below 13 years of age. Argument: IR form more appropriate for this age range.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		24 of 153 patients randomized were from US. Subgroup of US efficacy- placebo/treatment were NS
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			Define file links to datasets appropriately. SZ by weeks dataset contains primary efficacy endpoint data
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _____X_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Site Inspections

Site inspections have been requested for the following non-US sites: 12924 and 12927 due to high enrollment. Combined these sites account for 27% of total study enrollment

Site inspection has been requested for the following US site: 7535, this site has the largest single US enrollment, accounting for 37.5% of US enrollment.

Steven Dinsmore 5/21/09

 Reviewing Medical Officer Date

Norman Hershkowitz 5/21/09

 Clinical Team Leader Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

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

/s/

Steven T Dinsmore
6/5/2009 08:51:43 AM
MEDICAL OFFICER

Norman Hershkowitz
6/7/2009 05:00:56 PM
MEDICAL OFFICER