CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 22-115/S-006

Trade Name: Lamictal XR

Generic Name: lamotrigine

Sponsor: GlaxoSmithKline

Approval Date: April 25, 2011

Indications: Monotherapy in patients 13 years of age and older with partial seizures who are receiving therapy with a single antiepileptic drug (AED).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-115/S-006

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-115/S-006

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022115/S-006

NDA APPROVAL

GlaxoSmithKline
Attention: Elizabeth McConnell, PharmD
Associate Director, Neurology, US Regulatory Affairs
PO Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Dr. McConnell:

Please refer to your Supplemental New Drug Application (sNDA) dated March 31, 2010, received March 31, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Lamictal XR (lamotrigine) Extended-Release tablets.

We also refer to our approval letter dated April 25, 2011 which contained the following error: The last bullet of the section of the MedGuide entitled "What Should I Tell My Healthcare Provider Before Taking Lamictal XR" contained the following sentence: *Breastfeeding while taking LAMICTAL XR is not recommended.* This sentence is being removed from the updated approved label.

This replacement approval letter incorporates the correction of the error. The effective approval date will remain April 25, 2011, the date of the original approval letter.

We also acknowledge receipt of your amendments dated May 27, 2010; July 30, 2010; October 28, 2010; November 18, 2010; November 19, 2010; February 8, 2011; February 14, 2011; February 25, 2011; March 18, 2011; your risk evaluation and mitigation strategy (REMS) assessment dated April 19, 2010(2); April 21, 2011 and April 25, 2011.

This "Prior Approval" supplemental new drug application proposes monotherapy in patients 13 years of age and older with partial seizures who are receiving therapy with a single antiepileptic drug (AED). This supplemental new drug application also provides for elimination of the approved REMS.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

We note that your April 25, 2011, submission includes final printed labeling (FPL) for your package insert and Medication Guide. We have not reviewed this FPL. You are responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

Pediatrics
We are granting a waiver of the requirements under PREA for Lamictal conversion to monotherapy in pediatric patients ages 1 month to less then 13 years for the same reason as the waiver granted for the immediate release formulation of Lamictal, which is described in our April 14, 2010 letter. The reason for granting the waiver is because necessary studies are impossible or highly impracticable because:

- conducting a placebo-controlled trial would not be feasible due to ethical considerations, and
- historical control studies are not possible due to the lack of suitable historical data.

We are waiving the pediatric study requirement for ages birth up to 1 month because the necessary studies are impossible or highly impracticable, as there are too few children in this age group with the disease to study.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Lamictal XR (lamotrigine) Extended-Release tablets was originally approved on May 29, 2009, and the most recent REMS modification was approved on April 14, 2010. The REMS consists of a Medication Guide and a timetable for submission of assessments of the REMS.

On April 19, 2011, you propose that FDA no longer require a REMS for Lamictal XR (lamotrigine) Extended-Release tablets.

We have determined that it is no longer necessary to include the Medication Guide as an element of the approved REMS, and that a REMS is no longer necessary to ensure that the benefits of Lamictal XR (lamotrigine) Extended-Release tablets outweigh its risks. Therefore, we agree with your proposal and a REMS for Lamictal XR (lamotrigine) Extended-Release tablets is no longer required.

We remind you that the Medication Guide will continue to be part of the approved labeling in accordance with 21 CFR 208.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Stephanie N. Keefe, Regulatory Project Manager, at (301) 796-4098.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE: Content of Labeling

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

/s/

ERIC P BASTINGS on behalf of RUSSELL G KATZ
04/25/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-115/S-006

OTHER ACTION LETTER(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022115/S-006

SUPPLEMENT APPROVAL
RELEASE REMS REQUIREMENT

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/s/

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RUSSELL G KATZ
04/25/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LAMICTAL XR safely and effectively. See full prescribing information for LAMICTAL XR.

LAMICTAL XR (lamotrigine) Extended-Release Tablets
Initial U.S. Approval: 1994

WARNING: SERIOUS SKIN RASHES

See full prescribing information for complete boxed warning.

Cases of life-threatening serious rashes, including Stevens-Johnson syndrome and toxic epidermal necrolysis, and/or rash-related death have been caused by lamotrigine. The rate of serious rash is greater in pediatric patients than in adults. Additional factors that may increase the risk of rash include (5.1):

- **coadministration with valproate**
- **exceeding recommended initial dose of LAMICTAL XR**
- **exceeding recommended dose escalation for LAMICTAL XR.**

Benign rashes are also caused by lamotrigine; however, it is not possible to predict which rashes will prove to be serious or life threatening. LAMICTAL XR should be discontinued at the first sign of rash, unless the rash is clearly not drug related. (5.1)

---------- RECENT MAJOR CHANGES ----------

Indications and Usage, Monotherapy (1.2)	April 2011
Dosage and Administration, Conversion from Adjunctive Therapy to Monotherapy (2.3)	April 2011
Warnings and Precautions, Aseptic Meningitis (5.6)	October 2010

---------- INDICATIONS AND USAGE ----------

LAMICTAL XR is an antiepileptic drug (AED) indicated for:

- adjunctive therapy for primary generalized tonic-clonic (PGTC) seizures and partial onset seizures with or without secondary generalization in patients ≥13 years of age. (1.1)
- conversion to monotherapy in patients ≥13 years of age with partial seizures who are receiving treatment with a single AED. (1.2)
- Limitation of use: Safety and effectiveness in patients less than 13 years of age have not been established. (1.3)

---------- DOSAGE AND ADMINISTRATION ----------

- Do not exceed the recommended initial dosage and subsequent dose escalation. (2.1)
- Initiation of adjunctive therapy and conversion to monotherapy requires slow titration dependent on concomitant AEDs; the prescriber must refer to the appropriate algorithm in Dosage and Administration (2.2, 2.3)
  - Adjunct therapy target therapeutic dose range is 200 to 600 mg daily and is dependent on concomitant AEDs. (2.2)
  - Conversion to monotherapy: Target therapeutic dosage range is 250 to 300 mg daily. (2.3)
- Conversion from immediate-release lamotrigine to LAMICTAL XR: The initial dose of LAMICTAL XR should match the total daily dose of the immediate-release lamotrigine. Patients should be closely monitored for seizure control after conversion. (2.4)
- Do not restart LAMICTAL XR in patients who discontinued due to rash unless the potential benefits clearly outweigh the risks. (2.1, 5.1)
- Adjustments to maintenance doses are likely in patients starting or stopping estrogen-containing oral contraceptives. (2.1, 5.8)
- Discontinuation: Taper over a period of at least 2 weeks (approximately 50% dose reduction per week). (2.1, 5.9)

---------- DOSAGE FORMS AND STRENGTHS ----------

Extended-release tablets: 25 mg, 50 mg, 100 mg, 200 mg, and 300 mg. (3.1, 16)

---------- CONTRAINDICATIONS ----------

Hypersensitivity to the drug or its ingredients. (Boxed Warning, 4)

---------- WARNINGS AND PRECAUTIONS ----------

- Life-threatening serious rash and/or rash-related death: Discontinue at the first sign of rash, unless the rash is clearly not drug related. (Boxed Warning, 5.1)
- Fatal or life-threatening hypersensitivity reaction: Monitor for early signs of hypersensitivity (e.g., fever, lymphadenopathy), which may present without rash; if signs present, patient should be evaluated immediately. Discontinue LAMICTAL XR if alternate etiology is not found. (5.2)
- Acute multiorgan failure has resulted (some cases fatal). Monitor for hypersensitivity signs with multiple organ dysfunction. (5.3)
- Blood dyscrasias (e.g., neutropenia, thrombocytopenia, pancytopenia): May occur, either with or without an associated hypersensitivity syndrome. Monitor for signs of anemia, unexpected infection, or bleeding. (5.4)
- Suicidal behavior and ideation: Monitor for suicidal thoughts or behaviors. (5.5)
- Aseptic meningitis: Monitor for signs of meningitis. (5.6)
- Medication errors due to product name confusion: Strongly advise patients to visually inspect tablets to verify the received drug is correct. (3.2, 5.7, 16, 17.10)

---------- ADVERSE REACTIONS ----------

- Most common adverse reactions with use as adjunctive therapy (treatment difference between LAMICTAL XR and placebo ≥4%) are dizziness, tremor/intention tremor, vomiting, and diplopia. (6.1)
- Most common adverse reactions with use as monotherapy were similar to those seen with previous studies conducted with immediate-release lamotrigine and LAMICTAL XR. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

- Valproate increases lamotrigine concentrations more than 2-fold. (7, 12.3)
- Carbamazepine, phenytoin, phenobarbital, and primidone decrease lamotrigine concentrations by approximately 40%. (7, 12.3)
- Estrogen-containing oral contraceptives and rifampin also decrease lamotrigine concentrations by approximately 50%. (7, 12.3)

---------- USE IN SPECIFIC POPULATIONS ----------

- Pregnancy: Based on animal data may cause fetal harm. Pregnancy registry available. (8.1)
- Hepatic impairment: Dosage adjustments required in patients with moderate and severe liver impairment. (2.1, 8.6)
- Renal impairment: Reduced maintenance doses may be effective for patients with significant renal impairment. (2.1, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

*****Sections or subsections omitted from the full prescr bing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS SKIN RASHES

LAMICTAL® XR™ can cause serious rashes requiring hospitalization and discontinuation of treatment. The incidence of these rashes, which have included Stevens-Johnson syndrome, is approximately 0.8% (8 per 1,000) in pediatric patients (aged 2 to 16 years) receiving immediate-release lamotrigine as adjunctive therapy for epilepsy and 0.3% (3 per 1,000) in adults on adjunctive therapy for epilepsy. In a prospectively followed cohort of 1,983 pediatric patients (aged 2 to 16 years) with epilepsy taking adjunctive immediate-release lamotrigine, there was 1 rash-related death. LAMICTAL XR is not approved for patients less than 13 years of age. In worldwide postmarketing experience, rare cases of toxic epidermal necrolysis and/or rash-related death have been reported in adult and pediatric patients, but their numbers are too few to permit a precise estimate of the rate.

The risk of serious rash caused by treatment with LAMICTAL XR is not expected to differ from that with immediate-release lamotrigine. However, the relatively limited treatment experience with LAMICTAL XR makes it difficult to characterize the frequency and risk of serious rashes caused by treatment with LAMICTAL XR.

Other than age, there are as yet no factors identified that are known to predict the risk of occurrence or the severity of rash caused by LAMICTAL XR. There are suggestions, yet to be proven, that the risk of rash may also be increased by (1) coadministration of LAMICTAL XR with valproate (includes valproic acid and divalproex sodium), (2) exceeding the recommended initial dose of LAMICTAL XR, or (3) exceeding the recommended dose escalation for LAMICTAL XR. However, cases have occurred in the absence of these factors.

Nearly all cases of life-threatening rashes caused by immediate-release lamotrigine have occurred within 2 to 8 weeks of treatment initiation. However, isolated cases have occurred after prolonged treatment (e.g., 6 months). Accordingly, duration of therapy cannot be relied upon as means to predict the potential risk heralded by the first appearance of a rash.

Although benign rashes are also caused by LAMICTAL XR, it is not possible to predict reliably which rashes will prove to be serious or life threatening. Accordingly, LAMICTAL XR should ordinarily be discontinued at the first sign of rash, unless the rash is clearly not drug related. Discontinuation of treatment may not prevent a rash from becoming life threatening or permanently disabling or disfiguring *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

1.1 Adjunctive Therapy

LAMICTAL XR is indicated as adjunctive therapy for primary generalized tonic-clonic (PGTC) seizures and partial onset seizures with or without secondary generalization in patients ≥13 years of age.

1.2 Monotherapy

LAMICTAL XR is indicated for conversion to monotherapy in patients ≥13 years of age with partial seizures who are receiving treatment with a single antiepileptic drug (AED).

Safety and effectiveness of LAMICTAL XR have not been established (1) as initial monotherapy or (2) for simultaneous conversion to monotherapy from two or more concomitant AEDs.

1.3 Limitation of Use

Safety and effectiveness of LAMICTAL XR for use in patients less than 13 years of age have not been established.

2 DOSAGE AND ADMINISTRATION

LAMICTAL XR Extended-Release Tablets are taken once daily, with or without food. Tablets must be swallowed whole and must not be chewed, crushed, or divided.

2.1 General Dosing Considerations

Rash: There are suggestions, yet to be proven, that the risk of severe, potentially life-threatening rash may be increased by (1) coadministration of LAMICTAL XR with valproate, (2) exceeding the recommended initial dose of LAMICTAL XR, or (3) exceeding the recommended dose escalation for LAMICTAL XR. However, cases have occurred in the absence of these factors *[see Boxed Warning]*. Therefore, it is important that the dosing recommendations be followed closely.

The risk of nonserious rash may be increased when the recommended initial dose and/or the rate of dose escalation for LAMICTAL XR is exceeded and in patients with a history of allergy or rash to other AEDs.

LAMICTAL XR Patient Titration Kits provide LAMICTAL XR at doses consistent with the recommended titration schedule for the first 5 weeks of treatment, based upon concomitant medications for patients with partial onset seizures, and are intended to help reduce the potential for rash. The use of LAMICTAL XR Patient Titration Kits is recommended for appropriate patients who are starting or restarting LAMICTAL XR *[see How Supplied/Storage and Handling (16)]*.

It is recommended that LAMICTAL XR not be restarted in patients who discontinued due to rash associated with prior treatment with lamotrigine, unless the potential benefits clearly outweigh the risks. If the decision is made to restart a patient who has discontinued LAMICTAL XR, the need to restart with the initial dosing recommendations should be assessed. The greater the interval of time since the previous dose, the greater consideration should be given to restarting with the initial dosing recommendations. If a patient has discontinued lamotrigine for a

period of more than 5 half-lives, it is recommended that initial dosing recommendations and guidelines be followed. The half-life of lamotrigine is affected by other concomitant medications *[see Clinical Pharmacology (12.3)]*.

LAMICTAL XR Added to Drugs Known to Induce or Inhibit Glucuronidation: Drugs other than those listed in the Clinical Pharmacology section *[see Clinical Pharmacology (12.3)]* have not been systematically evaluated in combination with lamotrigine. Because lamotrigine is metabolized predominantly by glucuronic acid conjugation, drugs that are known to induce or inhibit glucuronidation may affect the apparent clearance of lamotrigine and doses of LAMICTAL XR may require adjustment based on clinical response.

Target Plasma Levels: A therapeutic plasma concentration range has not been established for lamotrigine. Dosing of LAMICTAL XR should be based on therapeutic response *[see Clinical Pharmacology (12.3)]*.

Women Taking Estrogen-Containing Oral Contraceptives: *Starting LAMICTAL XR in Women Taking Estrogen-Containing Oral Contraceptives:* Although estrogen-containing oral contraceptives have been shown to increase the clearance of lamotrigine *[see Clinical Pharmacology (12.3)]*, no adjustments to the recommended dose-escalation guidelines for LAMICTAL XR should be necessary solely based on the use of estrogen-containing oral contraceptives. Therefore, dose escalation should follow the recommended guidelines for initiating adjunctive therapy with LAMICTAL XR based on the concomitant AED or other concomitant medications (see Table 1). See below for adjustments to maintenance doses of LAMICTAL XR in women taking estrogen-containing oral contraceptives.

Adjustments to the Maintenance Dose of LAMICTAL XR in Women Taking Estrogen-Containing Oral Contraceptives:

(1) Taking Estrogen-Containing Oral Contraceptives: For women not taking carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine glucuronidation *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*, the maintenance dose of LAMICTAL XR will in most cases need to be increased by as much as 2-fold over the recommended target maintenance dose in order to maintain a consistent lamotrigine plasma level *[see Clinical Pharmacology (12.3)]*.

(2) Starting Estrogen-Containing Oral Contraceptives: In women taking a stable dose of LAMICTAL XR and not taking carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine glucuronidation *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*, the maintenance dose will in most cases need to be increased by as much as 2-fold in order to maintain a consistent lamotrigine plasma level. The dose increases should begin at the same time that the oral contraceptive is introduced and continue, based on clinical response, no more rapidly than 50 to 100 mg/day every week. Dose increases should not exceed the recommended rate (see Table 1) unless lamotrigine plasma levels or clinical response support larger increases. Gradual transient increases in lamotrigine plasma levels may occur during the week of inactive hormonal preparation (pill-free week), and these increases will be greater if dose increases are made in the days before or during the week of

inactive hormonal preparation. Increased lamotrigine plasma levels could result in additional adverse reactions, such as dizziness, ataxia, and diplopia. If adverse reactions attributable to LAMICTAL XR consistently occur during the pill-free week, dose adjustments to the overall maintenance dose may be necessary. Dose adjustments limited to the pill-free week are not recommended. For women taking LAMICTAL XR in addition to carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine glucuronidation *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*, no adjustment to the dose of LAMICTAL XR should be necessary.

(3) Stopping Estrogen-Containing Oral Contraceptives: For women not taking carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine glucuronidation *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*, the maintenance dose of LAMICTAL XR will in most cases need to be decreased by as much as 50% in order to maintain a consistent lamotrigine plasma level. The decrease in dose of LAMICTAL XR should not exceed 25% of the total daily dose per week over a 2-week period, unless clinical response or lamotrigine plasma levels indicate otherwise *[see Clinical Pharmacology (12.3)]*. For women taking LAMICTAL XR in addition to carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine glucuronidation *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*, no adjustment to the dose of LAMICTAL XR should be necessary.

Women and Other Hormonal Contraceptive Preparations or Hormone Replacement Therapy: The effect of other hormonal contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not been systematically evaluated. It has been reported that ethinylestradiol, not progestogens, increased the clearance of lamotrigine up to 2-fold, and the progestin-only pills had no effect on lamotrigine plasma levels. Therefore, adjustments to the dosage of LAMICTAL XR in the presence of progestogens alone will likely not be needed.

Patients With Hepatic Impairment: Experience in patients with hepatic impairment is limited. Based on a clinical pharmacology study in 24 patients with mild, moderate, and severe liver impairment *[see Use in Specific Populations (8.6), Clinical Pharmacology (12.3)]*, the following general recommendations can be made. No dosage adjustment is needed in patients with mild liver impairment. Initial, escalation, and maintenance doses should generally be reduced by approximately 25% in patients with moderate and severe liver impairment without ascites and 50% in patients with severe liver impairment with ascites. Escalation and maintenance doses may be adjusted according to clinical response.

Patients With Renal Impairment: Initial doses of LAMICTAL XR should be based on patients' concomitant medications (see Table 1); reduced maintenance doses may be effective for patients with significant renal impairment *[see Use in Specific Populations (8.7), Clinical Pharmacology (12.3)]*. Few patients with severe renal impairment have been evaluated during chronic treatment with immediate-release lamotrigine. Because there is inadequate experience in this population, LAMICTAL XR should be used with caution in these patients.

Discontinuation Strategy: For patients receiving LAMICTAL XR in combination with other AEDs, a re-evaluation of all AEDs in the regimen should be considered if a change in seizure control or an appearance or worsening of adverse reactions is observed.

If a decision is made to discontinue therapy with LAMICTAL XR, a step-wise reduction of dose over at least 2 weeks (approximately 50% per week) is recommended unless safety concerns require a more rapid withdrawal *[see Warnings and Precautions (5.9)]*.

Discontinuing carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine glucuronidation should prolong the half-life of lamotrigine; discontinuing valproate should shorten the half-life of lamotrigine.

2.2 Adjunctive Therapy for Primary Generalized Tonic-Clonic and Partial Onset Seizures

This section provides specific dosing recommendations for patients ≥13 years of age. Specific dosing recommendations are provided depending upon concomitant AED or other concomitant medications.

Table 1. Escalation Regimen for LAMICTAL XR in Patients ≥13 Years of Age

	For Patients TAKING Valproate[a]	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]
Weeks 1 and 2	25 mg every *other* day	25 mg every day	50 mg every day
Weeks 3 and 4	25 mg every day	50 mg every day	100 mg every day
Week 5	50 mg every day	100 mg every day	200 mg every day
Week 6	100 mg every day	150 mg every day	300 mg every day
Week 7	150 mg every day	200 mg every day	400 mg every day
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]

[a] Valproate has been shown to inhibit glucuronidation and decrease the apparent clearance of lamotrigine *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*.

[b] These drugs induce lamotrigine glucuronidation and increase clearance *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*. Other drugs which have similar effects include estrogen-containing oral contraceptives *[see Drug Interactions (7), Clinical Pharmacology (12.3)]*. Dosing recommendations for oral contraceptives can be found in General Dosing Considerations *[see Dosage and Administration (2.1)]*. Patients on rifampin, or other drugs that induce lamotrigine glucuronidation and increase clearance, should follow the same dosing titration/maintenance regimen as that used with anticonvulsants that have this effect.

[c] Dose increases at week 8 or later should not exceed 100 mg daily at weekly intervals.

2.3 Conversion From Adjunctive Therapy to Monotherapy

The goal of the transition regimen is to attempt to maintain seizure control while mitigating the risk of serious rash associated with the rapid titration of LAMICTAL XR.

The recommended maintenance dosage range of LAMICTAL XR as monotherapy is 250 to 300 mg given once daily.

The recommended initial dose and subsequent dose escalations for LAMICTAL XR should not be exceeded *[see Boxed Warning]*.

Conversion From Adjunctive Therapy With Carbamazepine, Phenytoin, Phenobarbital, or Primidone to Monotherapy With LAMICTAL XR: After achieving a dosage of 500 mg/day of LAMICTAL XR using the guidelines in Table 1, the concomitant enzyme-inducing AED should be withdrawn by 20% decrements each week over a 4-week period. Two weeks after completion of withdrawal of the enzyme-inducing AED, the dosage of LAMICTAL XR may be decreased no faster than 100 mg/day each week to achieve the monotherapy maintenance dosage range of 250 to 300 mg/day.

The regimen for the withdrawal of the concomitant AED is based on experience gained in the controlled monotherapy clinical trial using immediate-release lamotrigine.

Conversion From Adjunctive Therapy With Valproate to Monotherapy With LAMICTAL XR: The conversion regimen involves the 4 steps outlined in Table 2.

Table 2. Conversion From Adjunctive Therapy With Valproate to Monotherapy With LAMICTAL XR in Patients ≥13 Years of Age With Epilepsy

	LAMICTAL XR	Valproate
Step 1	Achieve a dosage of 150 mg/day according to guidelines in Table 1.	Maintain established stable dose.
Step 2	Maintain at 150 mg/day.	Decrease dosage by decrements no greater than 500 mg/day/week to 500 mg/day and then maintain for 1 week.
Step 3	Increase to 200 mg/day.	Simultaneously decrease to 250 mg/day and maintain for 1 week.
Step 4	Increase to 250 or 300 mg/day.	Discontinue.

Conversion From Adjunctive Therapy With Antiepileptic Drugs Other Than Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate to Monotherapy With LAMICTAL XR: After achieving a dosage of 250 to 300 mg/day of LAMICTAL XR using the guidelines in Table 1, the concomitant AED should be withdrawn by 20% decrements each week over a 4-week period. No adjustment to the monotherapy dose of LAMICTAL XR is needed.

2.4 Conversion From Immediate-Release Lamotrigine Tablets to LAMICTAL XR

Patients may be converted directly from immediate-release lamotrigine to LAMICTAL XR Extended-Release Tablets. The initial dose of LAMICTAL XR should match the total daily dose of immediate-release lamotrigine. However, some subjects on concomitant enzyme-inducing agents may have lower plasma levels of lamotrigine on conversion and should be monitored *[see Clinical Pharmacology (12.3)]*.

Following conversion to LAMICTAL XR, all patients (but especially those on drugs that induce lamotrigine glucuronidation) should be closely monitored for seizure control *[see Drug Interactions (7)]*. Depending on the therapeutic response after conversion, the total daily dose may need to be adjusted within the recommended dosing instructions (Table 1).

3 DOSAGE FORMS AND STRENGTHS

3.1 Extended-Release Tablets

25 mg, yellow with white center, round, biconvex, film-coated tablets printed with "LAMICTAL" and "XR 25."

50 mg, green with white center, round, biconvex, film-coated tablets printed with "LAMICTAL" and "XR 50."

100 mg, orange with white center, round, biconvex, film-coated tablets printed with "LAMICTAL" and "XR 100."

200 mg, blue with white center, round, biconvex, film-coated tablets printed with "LAMICTAL" and "XR 200."

300 mg, gray with white center, caplet-shaped, film-coated tablets printed with "LAMICTAL" and "XR 300."

3.2 Potential Medication Errors

Patients should be strongly advised to visually inspect their tablets to verify that they are receiving LAMICTAL XR, as opposed to other medications, and that they are receiving the correct formulation of lamotrigine each time they fill their prescription. Depictions of the LAMICTAL XR tablets can be found in the Medication Guide.

4 CONTRAINDICATIONS

LAMICTAL XR is contraindicated in patients who have demonstrated hypersensitivity (e.g., rash, angioedema, acute urticaria, extensive pruritus, mucosal ulceration) to the drug or its ingredients *[see Boxed Warning, Warnings and Precautions (5.1, 5.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Skin Rashes

The risk of serious rash caused by treatment with LAMICTAL XR is not expected to differ from that with immediate-release lamotrigine *[see Boxed Warning]*. However, the relatively limited treatment experience with LAMICTAL XR makes it difficult to characterize the frequency and risk of serious rashes caused by treatment with LAMICTAL XR.

Pediatric Population: The incidence of serious rash associated with hospitalization and discontinuation of immediate-release lamotrigine in a prospectively followed cohort of pediatric

patients (aged 2 to 16 years) with epilepsy receiving adjunctive therapy with immediate-release lamotrigine was approximately 0.8% (16 of 1,983). When 14 of these cases were reviewed by 3 expert dermatologists, there was considerable disagreement as to their proper classification. To illustrate, one dermatologist considered none of the cases to be Stevens-Johnson syndrome; another assigned 7 of the 14 to this diagnosis. There was 1 rash-related death in this 1,983-patient cohort. Additionally, there have been rare cases of toxic epidermal necrolysis with and without permanent sequelae and/or death in US and foreign postmarketing experience.

There is evidence that the inclusion of valproate in a multidrug regimen increases the risk of serious, potentially life-threatening rash in pediatric patients. In pediatric patients who used valproate concomitantly, 1.2% (6 of 482) experienced a serious rash compared with 0.6% (6 of 952) patients not taking valproate.

LAMICTAL XR is not approved in patients less than 13 years of age.

Adult Population: Serious rash associated with hospitalization and discontinuation of immediate-release lamotrigine occurred in 0.3% (11 of 3,348) of adult patients who received immediate-release lamotrigine in premarketing clinical trials of epilepsy. In worldwide postmarketing experience, rare cases of rash-related death have been reported, but their numbers are too few to permit a precise estimate of the rate.

Among the rashes leading to hospitalization were Stevens-Johnson syndrome, toxic epidermal necrolysis, angioedema, and a rash associated with a variable number of the following systemic manifestations: fever, lymphadenopathy, facial swelling, and hematologic and hepatologic abnormalities.

There is evidence that the inclusion of valproate in a multidrug regimen increases the risk of serious, potentially life-threatening rash in adults. Specifically, of 584 patients administered immediate-release lamotrigine with valproate in epilepsy clinical trials, 6 (1%) were hospitalized in association with rash; in contrast, 4 (0.16%) of 2,398 clinical trial patients and volunteers administered immediate-release lamotrigine in the absence of valproate were hospitalized.

Patients With History of Allergy or Rash to Other Antiepileptic Drugs: The risk of nonserious rash may be increased when the recommended initial dose and/or the rate of dose escalation for LAMICTAL XR is exceeded and in patients with a history of allergy or rash to other AEDs.

5.2 Hypersensitivity Reactions

Hypersensitivity reactions, some fatal or life threatening, have also occurred. Some of these reactions have included clinical features of multiorgan failure/dysfunction, including hepatic abnormalities and evidence of disseminated intravascular coagulation. It is important to note that early manifestations of hypersensitivity (e.g., fever, lymphadenopathy) may be present even though a rash is not evident. If such signs or symptoms are present, the patient should be evaluated immediately. LAMICTAL XR should be discontinued if an alternative etiology for the signs or symptoms cannot be established.

Prior to initiation of treatment with LAMICTAL XR, the patient should be instructed that a rash or other signs or symptoms of hypersensitivity (e.g., fever,

lymphadenopathy) may herald a serious medical event and that the patient should report any such occurrence to a physician immediately.

5.3 Acute Multiorgan Failure

Multiorgan failure, which in some cases has been fatal or irreversible, has been observed in patients receiving immediate-release lamotrigine. Fatalities associated with multiorgan failure and various degrees of hepatic failure have been reported in 2 of 3,796 adult patients and 4 of 2,435 pediatric patients who received immediate-release lamotrigine in epilepsy clinical trials. Rare fatalities from multiorgan failure have been reported in compassionate plea and postmarketing use. The majority of these deaths occurred in association with other serious medical events, including status epilepticus and overwhelming sepsis, and hantavirus, making it difficult to identify the initial cause.

Additionally, 3 patients (a 45-year-old woman, a 3.5-year-old boy, and an 11-year-old girl) developed multiorgan dysfunction and disseminated intravascular coagulation 9 to 14 days after immediate-release lamotrigine was added to their AED regimens. Rash and elevated transaminases were also present in all patients and rhabdomyolysis was noted in 2 patients. Both pediatric patients were receiving concomitant therapy with valproate, while the adult patient was being treated with carbamazepine and clonazepam. All patients subsequently recovered with supportive care after treatment with immediate-release lamotrigine was discontinued.

5.4 Blood Dyscrasias

There have been reports of blood dyscrasias with immediate-release lamotrigine that may or may not be associated with the hypersensitivity syndrome. These have included neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia, and, rarely, aplastic anemia and pure red cell aplasia.

5.5 Suicidal Behavior and Ideation

AEDs, including LAMICTAL XR, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (monotherapy and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately 1 case of suicidal thinking or behavior for every 530 patients treated. There were 4 suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number of events is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as 1 week after starting treatment with AEDs and persisted for the duration of treatment assessed.

Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanism of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5 to 100 years) in the clinical trials analyzed.

Table 3 shows absolute and relative risk by indication for all evaluated AEDs.

Table 3. Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients With Events per 1,000 Patients	Drug Patients With Events per 1,000 Patients	Relative Risk: Incidence of Events in Drug Patients/ Incidence in Placebo Patients	Risk Difference: Additional Drug Patients With Events per 1,000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing LAMICTAL XR or any other AED must balance the risk of suicidal thoughts or behavior with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Patients, their caregivers, and families should be informed that AEDs increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of the signs and symptoms of depression; any unusual changes in mood or behavior; or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

5.6 Aseptic Meningitis

Therapy with lamotrigine increases the risk of developing aseptic meningitis. Because of the potential for serious outcomes of untreated meningitis due to other causes, patients should also be evaluated for other causes of meningitis and treated as appropriate.

Postmarketing cases of aseptic meningitis have been reported in pediatric and adult patients taking lamotrigine for various indications. Symptoms upon presentation have included headache, fever, nausea, vomiting, and nuchal rigidity. Rash, photophobia, myalgia, chills,

altered consciousness, and somnolence were also noted in some cases. Symptoms have been reported to occur within 1 day to one and a half months following the initiation of treatment. In most cases, symptoms were reported to resolve after discontinuation of lamotrigine. Re-exposure resulted in a rapid return of symptoms (from within 30 minutes to 1 day following re-initiation of treatment) that were frequently more severe. Some of the patients treated with LAMICTAL who developed aseptic meningitis had underlying diagnoses of systemic lupus erythematosus or other autoimmune diseases.

Cerebrospinal fluid (CSF) analyzed at the time of clinical presentation in reported cases was characterized by a mild to moderate pleocytosis, normal glucose levels, and mild to moderate increase in protein. CSF white blood cell count differentials showed a predominance of neutrophils in a majority of the cases, although a predominance of lymphocytes was reported in approximately one third of the cases. Some patients also had new onset of signs and symptoms of involvement of other organs (predominantly hepatic and renal involvement), which may suggest that in these cases the aseptic meningitis observed was part of a hypersensitivity reaction *[see Warnings and Precautions (5.2)]*.

5.7 Potential Medication Errors

Medication errors involving LAMICTAL have occurred. In particular, the names LAMICTAL or lamotrigine can be confused with the names of other commonly used medications. Medication errors may also occur between the different formulations of LAMICTAL. To reduce the potential of medication errors, write and say LAMICTAL XR clearly. Depictions of the LAMICTAL XR Extended-Release Tablets can be found in the Medication Guide. Each LAMICTAL XR tablet has a distinct color and white center, and is printed with "LAMICTAL XR" and the tablet strength. These distinctive features serve to identify the different presentations of the drug and thus may help reduce the risk of medication errors. LAMICTAL XR is supplied in round, unit-of-use bottles with orange caps containing 30 tablets. The label on the bottle includes a depiction of the tablets that further communicates to patients and pharmacists that the medication is LAMICTAL XR and the specific tablet strength included in the bottle. The unit-of-use bottle with a distinctive orange cap and distinctive bottle label features serves to identify the different presentations of the drug and thus may help to reduce the risk of medication errors. To avoid the medication error of using the wrong drug or formulation, patients should be strongly advised to visually inspect their tablets to verify that they are LAMICTAL XR each time they fill their prescription.

5.8 Concomitant Use With Oral Contraceptives

Some estrogen-containing oral contraceptives have been shown to decrease serum concentrations of lamotrigine *[see Clinical Pharmacology (12.3)]*. **Dosage adjustments will be necessary in most patients who start or stop estrogen-containing oral contraceptives while taking LAMICTAL XR** *[see Dosage and Administration (2.1)]*. During the week of inactive hormone preparation (pill-free week) of oral contraceptive therapy, plasma lamotrigine levels are expected to rise, as much as doubling at the end of the week. Adverse reactions consistent with elevated levels of lamotrigine, such as dizziness, ataxia, and diplopia, could occur.

5.9 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)]*.

5.10 Status Epilepticus

Valid estimates of the incidence of treatment-emergent status epilepticus among patients treated with immediate-release lamotrigine are difficult to obtain because reporters participating in clinical trials did not all employ identical rules for identifying cases. At a minimum, 7 of 2,343 adult patients had episodes that could unequivocally be described as status epilepticus. In addition, a number of reports of variably defined episodes of seizure exacerbation (e.g., seizure clusters, seizure flurries) were made.

5.11 Sudden Unexplained Death in Epilepsy

During the premarketing development of immediate-release lamotrigine, 20 sudden and unexplained deaths were recorded among a cohort of 4,700 patients with epilepsy (5,747 patient-years of exposure).

Some of these could represent seizure-related deaths in which the seizure was not observed, e.g., at night. This represents an incidence of 0.0035 deaths per patient-year. Although this rate exceeds that expected in a healthy population matched for age and sex, it is within the range of estimates for the incidence of sudden unexplained death in patients with epilepsy not receiving lamotrigine (ranging from 0.0005 for the general population of patients with epilepsy, to 0.004 for a recently studied clinical trial population similar to that in the clinical development program for immediate-release lamotrigine, to 0.005 for patients with refractory epilepsy). Consequently, whether these figures are reassuring or suggest concern depends on the comparability of the populations reported upon to the cohort receiving immediate-release lamotrigine and the accuracy of the estimates provided. Probably most reassuring is the similarity of estimated sudden unexplained death in epilepsy (SUDEP) rates in patients receiving immediate-release lamotrigine and those receiving other AEDs, chemically unrelated to each other, that underwent clinical testing in similar populations. Importantly, that drug is chemically unrelated to lamotrigine. This evidence suggests, although it certainly does not prove, that the high SUDEP rates reflect population rates, not a drug effect.

5.12 Addition of LAMICTAL XR to a Multidrug Regimen That Includes Valproate

Because valproate reduces the clearance of lamotrigine, the dosage of lamotrigine in the presence of valproate is less than half of that required in its absence *[see Dosage and Administration (2.1, 2.2), Drug Interactions (7)]*.

5.13 Binding in the Eye and Other Melanin-Containing Tissues

Because lamotrigine binds to melanin, it could accumulate in melanin-rich tissues over time. This raises the possibility that lamotrigine may cause toxicity in these tissues after extended use. Although ophthalmological testing was performed in one controlled clinical trial,

the testing was inadequate to exclude subtle effects or injury occurring after long-term exposure. Moreover, the capacity of available tests to detect potentially adverse consequences, if any, of lamotrigine binding to melanin is unknown *[see Clinical Pharmacology (12.2)]*.

Accordingly, although there are no specific recommendations for periodic ophthalmological monitoring, prescribers should be aware of the possibility of long-term ophthalmologic effects.

5.14 Laboratory Tests

Plasma Concentrations of Lamotrigine: The value of monitoring plasma concentrations of lamotrigine in patients treated with LAMICTAL XR has not been established. Because of the possible pharmacokinetic interactions between lamotrigine and other drugs, including AEDs (see Table 6), monitoring of the plasma levels of lamotrigine and concomitant drugs may be indicated, particularly during dosage adjustments. In general, clinical judgment should be exercised regarding monitoring of plasma levels of lamotrigine and other drugs and whether or not dosage adjustments are necessary.

Effect on Leukocytes: Treatment with LAMICTAL XR caused an increased incidence of subnormal (below the reference range) values in some hematology analytes (e.g., total white blood cells, monocytes). The treatment effect (LAMICTAL XR % - Placebo %) incidence of subnormal counts was 3% for total white blood cells and 4% for monocytes.

6 ADVERSE REACTIONS

The following adverse reactions are described in more detail in the *Warnings and Precautions* section of the label:

- Serious skin rashes *[see Warnings and Precautions (5.1)]*
- Hypersensitivity reactions *[see Warnings and Precautions (5.2)]*
- Acute multiorgan failure *[see Warnings and Precautions (5.3)]*
- Blood dyscrasias *[see Warnings and Precautions (5.4)]*
- Suicidal behavior and ideation *[see Warnings and Precautions (5.5)]*
- Aseptic meningitis *[see Warnings and Precautions (5.6)]*
- Withdrawal seizures *[see Warnings and Precautions (5.9)]*
- Status epilepticus *[see Warnings and Precautions (5.10)]*
- Sudden unexplained death in epilepsy *[see Warnings and Precautions (5.11)]*

6.1 Clinical Trial Experience With LAMICTAL XR for Treatment of Primary Generalized Tonic-Clonic and Partial Onset Seizures

Most Common Adverse Reactions in Clinical Studies: *Adjunctive Therapy in Patients With Epilepsy:* Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

LAMICTAL XR has been evaluated for safety in patients ≥13 years of age with PGTC and partial onset seizures. The most commonly observed adverse reactions in these 2 double-blind, placebo-controlled trials of adjunctive therapy with LAMICTAL XR were, in order of

decreasing incidence (treatment difference between LAMICTAL XR and placebo ≥4%): dizziness, tremor/intention tremor, vomiting, and diplopia.

In these 2 trials, adverse reactions led to withdrawal of 4 (2%) patients in the group receiving placebo and 10 (5%) patients in the group receiving LAMICTAL XR. Dizziness was the most common reason for withdrawal in the group receiving LAMICTAL XR (5 patients [3%]). The next most common adverse reactions leading to withdrawal in 2 patients each (1%) were rash, headache, nausea, and nystagmus.

Table 4 displays the incidence of adverse reactions in these two 19-week, double-blind, placebo-controlled studies of patients with PGTC and partial onset seizures.

Table 4. Adverse Reaction Incidence in Double-Blind, Placebo-Controlled Adjunctive Trials of Patients With Epilepsy (Adverse Reactions ≥2% of Patients Treated With LAMICTAL XR and Numerically More Frequent Than in the Placebo Group)

Body System/Adverse Reaction	LAMICTAL XR (n = 190) %	Placebo (n = 195) %
Ear and labyrinth disorders		
Vertigo	3	<1
Eye disorders		
Diplopia	5	<1
Vision blurred	3	2
Gastrointestinal disorders		
Nausea	7	4
Vomiting	6	3
Diarrhea	5	3
Constipation	2	<1
Dry mouth	2	1
General disorders and administration site conditions		
Asthenia and fatigue	6	4
Infections and infestations		
Sinusitis	2	1
Metabolic and nutritional disorders		
Anorexia	3	2
Musculoskeletal and connective tissue disorder		
Myalgia	2	0

Nervous system		
Dizziness	14	6
Tremor and intention tremor	6	1
Somnolence	5	3
Cerebellar coordination and balance disorder	3	0
Nystagmus	2	<1
Psychiatric disorders		
Depression	3	<1
Anxiety	3	0
Respiratory, thoracic, and mediastinal disorders		
Pharyngolaryngeal pain	3	2
Vascular disorder		
Hot flush	2	0

Note: In these trials the incidence of nonserious rash was 2% for LAMICTAL XR and 3% for placebo. In clinical trials evaluating immediate-release lamotrigine, the rate of serious rash was 0.3% in adults on adjunctive therapy for epilepsy *[see Boxed Warning]*.

Adverse reactions were also analyzed to assess the incidence of the onset of an event in the titration period, and in the maintenance period, and if adverse reactions occurring in the titration phase persisted in the maintenance phase.

The incidence for many adverse reactions caused by treatment with LAMICTAL XR was increased relative to placebo (i.e., treatment difference between LAMICTAL XR and placebo ≥2%) in either the titration or maintenance phases of the study. During the titration phase, an increased incidence (shown in descending order of % treatment difference) was observed for diarrhea, nausea, vomiting, somnolence, vertigo, myalgia, hot flush, and anxiety. During the maintenance phase, an increased incidence was observed for dizziness, tremor, and diplopia. Some adverse reactions developing in the titration phase were notable for persisting (>7 days) into the maintenance phase. These "persistent" adverse reactions included somnolence and dizziness.

There were inadequate data to evaluate the effect of dose and/or concentration on the incidence of adverse reactions because, although patients were randomized to different target doses based upon concomitant AED, the plasma exposure was expected to be generally similar among all patients receiving different doses. However, in a randomized, parallel study comparing placebo and 300 and 500 mg/day of immediate-release lamotrigine, the incidence of the most common adverse reactions (≥5%) such as ataxia, blurred vision, diplopia, and dizziness were dose related. Less common adverse reactions (<5%) were not assessed for dose-response relationships.

Monotherapy in Patients With Epilepsy: Adverse reactions observed in this study were generally similar to those observed and attributed to drug in adjunctive and monotherapy immediate-release lamotrigine and adjunctive LAMICTAL XR placebo-controlled studies. Only

2 adverse events, nasopharyngitis and upper respiratory tract infection, were observed at a rate of ≥3% and not reported at a similar rate in previous studies. Because this study did not include a placebo control group, causality could not be established *[see Clinical Studies (14.3)]*.

6.2 Other Adverse Reactions Observed During the Clinical Development of Immediate-Release Lamotrigine

All reported reactions are included except those already listed in the previous tables or elsewhere in the labeling, those too general to be informative, and those not reasonably associated with the use of the drug.

Adjunctive Therapy in Adults With Epilepsy: In addition to the adverse reactions reported above from the development of LAMICTAL XR, the following adverse reactions with an uncertain relationship to lamotrigine were reported during the clinical development of immediate-release lamotrigine for treatment of epilepsy in adults. These reactions occurred in ≥2% of patients receiving immediate-release lamotrigine and more frequently than in the placebo group.

Body as a Whole: Headache, flu syndrome, fever, neck pain.

Musculoskeletal: Arthralgia.

Nervous: Insomnia, convulsion, irritability, speech disorder, concentration disturbance.

Respiratory: Pharyngitis, cough increased.

Skin and Appendages: Rash, pruritus.

Urogenital (female patients only): Vaginitis, amenorrhea, dysmenorrhea.

Monotherapy in Adults With Epilepsy: In addition to the adverse reactions reported above from the development of LAMICTAL XR, the following adverse reactions with an uncertain relationship to lamotrigine were reported during the clinical development of immediate-release lamotrigine for treatment of epilepsy in adults. These reactions occurred in >2% of patients receiving immediate-release lamotrigine and more frequently than in the placebo group.

Body as a Whole: Chest pain.

Digestive: Rectal hemorrhage, peptic ulcer.

Metabolic and Nutritional: Weight decrease, peripheral edema.

Nervous: Hypesthesia, libido increase, decreased reflexes.

Respiratory: Epistaxis, dyspnea.

Skin and Appendages: Contact dermatitis, dry skin, sweating.

Special Senses: Vision abnormality.

Urogenital (female patients only): Dysmenorrhea.

Other Clinical Trial Experience: Immediate-release lamotrigine has been administered to 6,694 individuals for whom complete adverse reaction data was captured during all clinical trials, only some of which were placebo controlled.

Adverse reactions are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *frequent* adverse reactions are

defined as those occurring in at least 1/100 patients; *infrequent* adverse reactions are those occurring in 1/100 to 1/1,000 patients; *rare* adverse reactions are those occurring in fewer than 1/1,000 patients.

Cardiovascular System: Infrequent: Hypertension, palpitations, postural hypotension, syncope, tachycardia, vasodilation.

Dermatological: Infrequent: Acne, alopecia, hirsutism, maculopapular rash, urticaria. *Rare:* Leukoderma, multiforme erythema, petechial rash, pustular rash.

Digestive System: Infrequent: Dysphagia, liver function tests abnormal, mouth ulceration. *Rare:* Gastrointestinal hemorrhage, hemorrhagic colitis, hepatitis, melena and stomach ulcer.

Endocrine System: Rare: Goiter, hypothyroidism.

Hematologic and Lymphatic System: Infrequent: Ecchymosis, leukopenia. *Rare:* Anemia, eosinophilia, fibrin decrease, fibrinogen decrease, iron deficiency anemia, leukocytosis, lymphocytosis, macrocytic anemia, petechia, thrombocytopenia.

Metabolic and Nutritional Disorders: Infrequent: Aspartate transaminase increased. *Rare:* Alcohol intolerance, alkaline phosphatase increase, alanine transaminase increase, bilirubinemia, gamma glutamyl transpeptidase increase, hyperglycemia.

Musculoskeletal System: Rare: Muscle atrophy, pathological fracture, tendinous contracture.

Nervous System: Frequent: Confusion. *Infrequent:* Akathisia, apathy, aphasia, depersonalization, dysarthria, dyskinesia, euphoria, hallucinations, hostility, hyperkinesia, hypertonia, libido decreased, memory decrease, mind racing, movement disorder, myoclonus, panic attack, paranoid reaction, personality disorder, psychosis, stupor. *Rare:* Choreoathetosis, delirium, delusions, dysphoria, dystonia, extrapyramidal syndrome, hemiplegia, hyperalgesia, hyperesthesia, hypokinesia, hypotonia, manic depression reaction, neuralgia, paralysis, peripheral neuritis.

Respiratory System: Rare: Hiccup, hyperventilation.

Special Senses: Frequent: Amblyopia. *Infrequent:* Abnormality of accommodation, conjunctivitis, dry eyes, ear pain, photophobia, taste perversion, tinnitus. *Rare:* Deafness, lacrimation disorder, oscillopsia, parosmia, ptosis, strabismus, taste loss, uveitis, visual field defect.

Urogenital System: Infrequent: Abnormal ejaculation, hematuria, impotence, menorrhagia, polyuria, urinary incontinence. *Rare:* Acute kidney failure, breast neoplasm, creatinine increase, female lactation, kidney failure, kidney pain, nocturia, urinary retention, urinary urgency.

6.3 Postmarketing Experience With Immediate-Release Lamotrigine

The following adverse events (not listed above in clinical trials or other sections of the prescribing information) have been identified during postapproval use of immediate-release lamotrigine. Because these events are reported voluntarily from a population of uncertain size, it

is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic: Agranulocytosis, hemolytic anemia, lymphadenopathy not associated with hypersensitivity disorder.

Gastrointestinal: Esophagitis.

Hepatobiliary Tract and Pancreas: Pancreatitis.

Immunologic: Lupus-like reaction, vasculitis.

Lower Respiratory: Apnea.

Musculoskeletal: Rhabdomyolysis has been observed in patients experiencing hypersensitivity reactions.

Neurology: Exacerbation of Parkinsonian symptoms in patients with pre-existing Parkinson's disease, tics.

Non-site Specific: Progressive immunosuppression.

7 DRUG INTERACTIONS

Significant drug interactions with lamotrigine are summarized in Table 5. Additional details of these drug interaction studies, which were conducted using immediate-release lamotrigine, are provided in the Clinical Pharmacology section *[see Clinical Pharmacology (12.3)]*.

Table 5. Established and Other Potentially Significant Drug Interactions

Concomitant Drug	Effect on Concentration of Lamotrigine or Concomitant Drug	Clinical Comment
Estrogen-containing oral contraceptive preparations containing 30 mcg ethinylestradiol and 150 mcg levonorgestrel	↓ lamotrigine ↓ levonorgestrel	Decreased lamotrigine levels approximately 50%. Decrease in levonorgestrel component by 19%.
Carbamazepine and carbamazepine epoxide	↓ lamotrigine ? CBZ epoxide	Addition of carbamazepine decreases lamotrigine concentration approximately 40%. May increase carbamazepine epoxide levels.
Phenobarbital/Primidone	↓ lamotrigine	Decreased lamotrigine concentration approximately 40%.
Phenytoin	↓ lamotrigine	Decreased lamotrigine concentration approximately 40%.

Rifampin	↓ lamotrigine	Decreased lamotrigine AUC approximately 40%.
Valproate	↑ lamotrigine ? valproate	Increased lamotrigine concentrations slightly more than 2-fold. Decreased valproate concentrations an average of 25% over a 3-week period then stabilized in healthy volunteers; no change in controlled clinical trials in epilepsy patients.

↓ = Decreased (induces lamotrigine glucuronidation).
↑ = Increased (inhibits lamotrigine glucuronidation).
? = Conflicting data.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

As with other AEDs, physiological changes during pregnancy may affect lamotrigine concentrations and/or therapeutic effect. There have been reports of decreased lamotrigine concentrations during pregnancy and restoration of pre-partum concentrations after delivery. Dosage adjustments may be necessary to maintain clinical response.

Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. In animal studies, lamotrigine was developmentally toxic at doses lower than those administered clinically. LAMICTAL XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When lamotrigine was administered to pregnant mice, rats, or rabbits during the period of organogenesis (oral doses of up to 125, 25, and 30 mg/kg, respectively), reduced fetal body weight and increased incidences of fetal skeletal variations were seen in mice and rats at doses that were also maternally toxic. The no-effect doses for embryo-fetal developmental toxicity in mice, rats, and rabbits (75, 6.25, and 30 mg/kg, respectively) are similar to (mice and rabbits) or less than the human dose of 400 mg/day on a body surface area (mg/m^2) basis.

In a study in which pregnant rats were administered lamotrigine (oral doses of 5 or 25 mg/kg) during the period of organogenesis and offspring were evaluated postnatally, behavioral abnormalities were observed in exposed offspring at both doses. The lowest effect dose for developmental neurotoxicity in rats is less than the human dose of 400 mg/day on a mg/m^2 basis. Maternal toxicity was observed at the higher dose tested.

When pregnant rats were administered lamotrigine (oral doses of 5, 10, or 20 mg/kg) during the latter part of gestation, increased offspring mortality (including stillbirths) was seen at all doses. The lowest effect dose for peri/postnatal developmental toxicity in rats is less than the human dose of 400 mg/day on a mg/m^2 basis. Maternal toxicity was observed at the two highest doses tested.

Lamotrigine decreases fetal folate concentrations in rat, an effect known to be associated with adverse pregnancy outcomes in animals and humans.

Pregnancy Registry: To provide information regarding the effects of in utero exposure to LAMICTAL XR, physicians are advised to recommend that pregnant patients taking LAMICTAL XR enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll-free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org.

8.2 Labor and Delivery

The effect of LAMICTAL XR on labor and delivery in humans is unknown.

8.3 Nursing Mothers

Preliminary data indicate that lamotrigine is excreted in human milk. Caution should be exercised when LAMICTAL XR is administered to a nursing woman.

8.4 Pediatric Use

LAMICTAL XR is indicated as adjunctive therapy for PGTC and partial onset seizures with or without secondary generalization in patients ≥13 years of age. Safety and effectiveness of LAMICTAL XR for any use in patients less than 13 years of age have not been established.

Immediate-release lamotrigine is indicated for adjunctive therapy in patients ≥2 years of age for partial seizures, the generalized seizures of Lennox-Gastaut syndrome, and PGTC seizures.

Safety and efficacy of immediate-release lamotrigine, used as adjunctive treatment for partial seizures, were not demonstrated in a small, randomized, double-blind, placebo-controlled withdrawal study in very young pediatric patients (aged 1 to 24 months). Immediate-release lamotrigine was associated with an increased risk for infectious adverse reactions (lamotrigine 37%, placebo 5%), and respiratory adverse reactions (lamotrigine 26%, placebo 5%). Infectious adverse reactions included bronchiolitis, bronchitis, ear infection, eye infection, otitis externa, pharyngitis, urinary tract infection, and viral infection. Respiratory adverse reactions included nasal congestion, cough, and apnea.

In a juvenile animal study in which lamotrigine (oral doses of 5, 15, or 30 mg/kg) was administered to young rats (postnatal days 7-62), decreased viability and growth were seen at the highest dose tested and long-term behavioral abnormalities (decreased locomotor activity, increased reactivity, and learning deficits in animals tested as adults) were observed at the two highest doses. The no-effect dose for adverse effects on neurobehavioral development is less than the human dose of 400 mg/day on a mg/m^2 basis.

8.5 Geriatric Use

Clinical studies of LAMICTAL XR for epilepsy did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects or exhibit a different safety profile than that of younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing

range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

8.6 Patients With Hepatic Impairment

Experience in patients with hepatic impairment is limited. Based on a clinical pharmacology study with immediate-release lamotrigine in 24 patients with mild, moderate, and severe liver impairment *[see Clinical Pharmacology (12.3)]*, the following general recommendations can be made. No dosage adjustment is needed in patients with mild liver impairment. Initial, escalation, and maintenance doses should generally be reduced by approximately 25% in patients with moderate and severe liver impairment without ascites and 50% in patients with severe liver impairment with ascites. Escalation and maintenance doses may be adjusted according to clinical response *[see Dosage and Administration (2.1)]*.

8.7 Patients With Renal Impairment

Lamotrigine is metabolized mainly by glucuronic acid conjugation, with the majority of the metabolites being recovered in the urine. In a small study comparing a single dose of immediate-release lamotrigine in patients with varying degrees of renal impairment with healthy volunteers, the plasma half-life of lamotrigine was approximately twice as long in the patients with significant renal impairment *[see Clinical Pharmacology (12.3)]*.

Initial doses of LAMICTAL XR should be based on patients' AED regimens; reduced maintenance doses may be effective for patients with significant renal impairment. Few patients with severe renal impairment have been evaluated during chronic treatment with lamotrigine. Because there is inadequate experience in this population, LAMICTAL XR should be used with caution in these patients *[see Dosage and Administration (2.1)]*.

10 OVERDOSAGE

10.1 Human Overdose Experience

Overdoses involving quantities up to 15 g have been reported for immediate-release lamotrigine, some of which have been fatal. Overdose has resulted in ataxia, nystagmus, increased seizures, decreased level of consciousness, coma, and intraventricular conduction delay.

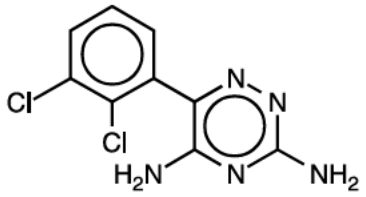
10.2 Management of Overdose

There are no specific antidotes for lamotrigine. Following a suspected overdose, hospitalization of the patient is advised. General supportive care is indicated, including frequent monitoring of vital signs and close observation of the patient. If indicated, emesis should be induced; usual precautions should be taken to protect the airway. It is uncertain whether hemodialysis is an effective means of removing lamotrigine from the blood. In 6 renal failure patients, about 20% of the amount of lamotrigine in the body was removed by hemodialysis during a 4-hour session. A Poison Control Center should be contacted for information on the management of overdosage of LAMICTAL XR.

11 DESCRIPTION

LAMICTAL XR (lamotrigine), an AED of the phenyltriazine class, is chemically unrelated to existing AEDs. Its chemical name is 3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine,

its molecular formula is $C_9H_7N_5Cl_2$, and its molecular weight is 256.09. Lamotrigine is a white to pale cream-colored powder and has a pK_a of 5.7. Lamotrigine is very slightly soluble in water (0.17 mg/mL at 25°C) and slightly soluble in 0.1 M HCl (4.1 mg/mL at 25°C). The structural formula is:



LAMICTAL XR Extended-Release Tablets are supplied for oral administration as 25-mg (yellow with white center), 50-mg (green with white center), 100-mg (orange with white center), 200-mg (blue with white center), and 300-mg (gray with white center) tablets. Each tablet contains the labeled amount of lamotrigine and the following inactive ingredients: glycerol monostearate, hypromellose, lactose monohydrate, magnesium stearate, methacrylic acid copolymer dispersion, polyethylene glycol 400, polysorbate 80, silicon dioxide (25-mg and 50-mg tablets only), titanium dioxide, triethyl citrate, iron oxide black (50-mg and 300-mg tablets only), iron oxide yellow (25-mg, 50-mg, 100-mg tablets only), iron oxide red (100-mg tablet only), FD&C Blue No. 2 Aluminum Lake (200-mg tablet only). Tablets are printed with edible black ink.

LAMICTAL XR Extended-Release Tablets contain a modified-release eroding formulation as the core. The tablets are coated with a clear enteric coat and have an aperture drilled through the coats on both faces of the tablet (DiffCORE™) to enable a controlled release of drug in the acidic environment of the stomach. The combination of this and the modified-release core are designed to control the dissolution rate of lamotrigine over a period of approximately 12 to 15 hours, leading to a gradual increase in serum lamotrigine levels.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanism(s) by which lamotrigine exerts its anticonvulsant action is unknown. In animal models designed to detect anticonvulsant activity, lamotrigine was effective in preventing seizure spread in the maximum electroshock and pentylenetetrazol tests, and prevented seizures in the visually and electrically evoked after-discharge tests for antiepileptic activity. Lamotrigine also displayed inhibitory properties in a kindling model in rats both during kindling development and in the fully kindled state. The relevance of these models to human epilepsy, however, is not known.

One proposed mechanism of action of lamotrigine, the relevance of which remains to be established in humans, involves an effect on sodium channels. In vitro pharmacological studies suggest that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing neuronal

membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (e.g., glutamate and aspartate).

Effect of Lamotrigine on N-Methyl d-Aspartate-Receptor Mediated Activity: Lamotrigine did not inhibit N-methyl d-aspartate (NMDA)-induced depolarizations in rat cortical slices or NMDA-induced cyclic GMP formation in immature rat cerebellum, nor did lamotrigine displace compounds that are either competitive or noncompetitive ligands at this glutamate receptor complex (CNQX, CGS, TCHP). The IC_{50} for lamotrigine effects on NMDA-induced currents (in the presence of 3 μM of glycine) in cultured hippocampal neurons exceeded 100 μM.

12.2 Pharmacodynamics

Folate Metabolism: In vitro, lamotrigine inhibited dihydrofolate reductase, the enzyme that catalyzes the reduction of dihydrofolate to tetrahydrofolate. Inhibition of this enzyme may interfere with the biosynthesis of nucleic acids and proteins. When oral daily doses of lamotrigine were given to pregnant rats during organogenesis, fetal, placental, and maternal folate concentrations were reduced. Significantly reduced concentrations of folate are associated with teratogenesis *[see Use in Specific Populations (8.1)]*. Folate concentrations were also reduced in male rats given repeated oral doses of lamotrigine. Reduced concentrations were partially returned to normal when supplemented with folinic acid.

Cardiovascular: In dogs, lamotrigine is extensively metabolized to a 2-N-methyl metabolite. This metabolite causes dose-dependent prolongation of the PR interval, widening of the QRS complex, and, at higher doses, complete AV conduction block. Similar cardiovascular effects are not anticipated in humans because only trace amounts of the 2-N-methyl metabolite (<0.6% of lamotrigine dose) have been found in human urine *[see Clinical Pharmacology (12.3)]*. However, it is conceivable that plasma concentrations of this metabolite could be increased in patients with a reduced capacity to glucuronidate lamotrigine (e.g., in patients with liver disease, patients taking concomitant medications that inhibit glucuronidation).

12.3 Pharmacokinetics

In comparison to immediate-release lamotrigine, the plasma lamotrigine levels following administration of LAMICTAL XR are not associated with any significant changes in trough plasma concentrations, and are characterized by lower peaks, longer time to peaks, and lower peak-to-trough fluctuation, as described in detail below.

Absorption: Lamotrigine is absorbed after oral administration with negligible first-pass metabolism. The bioavailability of lamotrigine is not affected by food.

In an open-label, crossover study of 44 subjects with epilepsy receiving concomitant AEDs, the steady-state pharmacokinetics of lamotrigine were compared following administration of equivalent total doses of LAMICTAL XR given once daily with those of lamotrigine immediate-release given twice daily. In this study, the median time to peak concentration (T_{max}) following administration of LAMICTAL XR was 4 to 6 hours in patients taking carbamazepine, phenytoin, phenobarbital, or primidone; 9 to 11 hours in patients taking valproate; and 6 to 10 hours in patients taking AEDs other than carbamazepine, phenytoin, phenobarbital, primidone,

or valproate. In comparison, the median T_{max} following administration of immediate-release lamotrigine was between 1 and 1.5 hours.

The steady-state trough concentrations for extended-release lamotrigine were similar to or higher than those of immediate-release lamotrigine depending on concomitant AED (Table 6). A mean reduction in the lamotrigine C_{max} by 11% to 29% was observed for LAMICTAL XR compared to immediate-release lamotrigine, resulting in a decrease in the peak-to-trough fluctuation in serum lamotrigine concentrations. However, in some subjects receiving enzyme-inducing AEDs, a reduction in C_{max} of 44% to 77% was observed. The degree of fluctuation was reduced by 17% in patients taking enzyme-inducing AEDs; 34% in patients taking valproate; and 37% in patients taking AEDs other than carbamazepine, phenytoin, phenobarbital, primidone, or valproate. LAMICTAL XR and immediate-release lamotrigine regimens were similar with respect to area under the curve (AUC, a measure of the extent of bioavailability) for patients receiving AEDs other than those known to induce the metabolism of lamotrigine. The relative bioavailability of extended-release lamotrigine was approximately 21% lower than immediate-release lamotrigine in subjects receiving enzyme-inducing AEDs. However, a reduction in exposure of up to 70% was observed in some subjects in this group when they switched to LAMICTAL XR. Therefore, doses may need to be adjusted in some subjects based on therapeutic response.

Table 6. Steady-State Bioavailability of LAMICTAL XR Relative to Immediate-Release Lamotrigine at Equivalent Daily Doses (Ratio of Extended-Release to Immediate-Release 90% CI)

Concomitant Antiepileptic Drug	AUC $_{(0\text{-}24ss)}$	C_{max}	C_{min}
Enzyme-inducing antiepileptic drugs[a]	0.79 (0.69, 0.90)	0.71 (0.61, 0.82)	0.99 (0.89, 1.09)
Valproate	0.94 (0.81, 1.08)	0.88 (0.75, 1.03)	0.99 (0.88, 1.10)
Antiepileptic drugs other than enzyme-inducing antiepileptic drugs[a] or valproate	1.00 (0.88, 1.14)	0.89 (0.78, 1.03)	1.14 (1.03, 1.25)

[a] Enzyme-inducing antiepileptic drugs include carbamazepine, phenytoin, phenobarbital, and primidone.

Dose Proportionality: In healthy volunteers not receiving any other medications and given LAMICTAL XR once daily, the systemic exposure to lamotrigine increased in direct proportion to the dose administered over the range of 50 to 200 mg. At doses between 25 and 50 mg, the increase was less than dose proportional, with a 2-fold increase in dose resulting in an approximately 1.6-fold increase in systemic exposure.

Distribution: Estimates of the mean apparent volume of distribution (Vd/F) of lamotrigine following oral administration ranged from 0.9 to 1.3 L/kg. Vd/F is independent of

dose and is similar following single and multiple doses in both patients with epilepsy and in healthy volunteers.

Protein Binding: Data from in vitro studies indicate that lamotrigine is approximately 55% bound to human plasma proteins at plasma lamotrigine concentrations from 1 to 10 mcg/mL (10 mcg/mL is 4 to 6 times the trough plasma concentration observed in the controlled efficacy trials). Because lamotrigine is not highly bound to plasma proteins, clinically significant interactions with other drugs through competition for protein binding sites are unlikely. The binding of lamotrigine to plasma proteins did not change in the presence of therapeutic concentrations of phenytoin, phenobarbital, or valproate. Lamotrigine did not displace other AEDs (carbamazepine, phenytoin, phenobarbital) from protein-binding sites.

Metabolism: Lamotrigine is metabolized predominantly by glucuronic acid conjugation; the major metabolite is an inactive 2-N-glucuronide conjugate. After oral administration of 240 mg of ^{14}C-lamotrigine (15 μCi) to 6 healthy volunteers, 94% was recovered in the urine and 2% was recovered in the feces. The radioactivity in the urine consisted of unchanged lamotrigine (10%), the 2-N-glucuronide (76%), a 5-N-glucuronide (10%), a 2-N-methyl metabolite (0.14%), and other unidentified minor metabolites (4%).

Enzyme Induction: The effects of lamotrigine on the induction of specific families of mixed-function oxidase isozymes have not been systematically evaluated.

Following multiple administrations (150 mg twice daily) to normal volunteers taking no other medications, lamotrigine induced its own metabolism, resulting in a 25% decrease in $t_{½}$ and a 37% increase in CL/F at steady state compared with values obtained in the same volunteers following a single dose. Evidence gathered from other sources suggests that self-induction by lamotrigine may not occur when lamotrigine is given as adjunctive therapy in patients receiving enzyme-inducing drugs such as carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine glucuronidation *[see Drug Interactions (7)]*.

Elimination: The elimination half-life and apparent clearance of lamotrigine following oral administration of immediate-release lamotrigine to adult patients with epilepsy and healthy volunteers is summarized in Table 7. Half-life and apparent clearance vary depending on concomitant AEDs.

Since the half-life of lamotrigine following administration of single doses of immediate-release lamotrigine is comparable to that observed following administration of LAMICTAL XR, similar changes in the half-life of lamotrigine would be expected for LAMICTAL XR.

Table 7. Mean[a] Pharmacokinetic Parameters of Immediate-Release Lamotrigine in Healthy Volunteers and Adult Patients With Epilepsy

Adult Study Population	Number of Subjects	$t_{½}$: Elimination Half-life (hr)	CL/F: Apparent Plasma Clearance (mL/min/kg)
Healthy volunteers taking no other medications:			
Single-dose lamotrigine	179	32.8 (14.0-103.0)	0.44 (0.12-1.10)
Multiple-dose lamotrigine	36	25.4 (11.6-61.6)	0.58 (0.24-1.15)
Healthy volunteers taking valproate:			
Single-dose lamotrigine	6	48.3 (31.5-88.6)	0.30 (0.14-0.42)
Multiple-dose lamotrigine	18	70.3 (41.9-113.5)	0.18 (0.12-0.33)
Patients with epilepsy taking valproate only:			
Single-dose lamotrigine	4	58.8 (30.5-88.8)	0.28 (0.16-0.40)
Patients with epilepsy taking carbamazepine, phenytoin, phenobarbital, or primidone[b] plus valproate:			
Single-dose lamotrigine	25	27.2 (11.2-51.6)	0.53 (0.27-1.04)
Patients with epilepsy taking carbamazepine, phenytoin, phenobarbital, or primidone: [b]			
Single-dose lamotrigine	24	14.4 (6.4-30.4)	1.10 (0.51-2.22)
Multiple-dose lamotrigine	17	12.6 (7.5-23.1)	1.21 (0.66-1.82)

[a] The majority of parameter means determined in each study had coefficients of variation between 20% and 40% for half-life and CL/F and between 30% and 70% for T_{max}. The overall mean values were calculated from individual study means that were weighted based on the number of volunteers/patients in each study. The numbers in parentheses below each parameter mean represent the range of individual volunteer/patient values across studies.

[b] Carbamazepine, phenobarbital, phenytoin, and primidone have been shown to increase the apparent clearance of lamotrigine. Estrogen-containing oral contraceptives and other drugs such as rifampin that induce lamotrigine glucuronidation have also been shown to increase the apparent clearance of lamotrigine *[see Drug Interactions (7)]*.

Drug Interactions: The apparent clearance of lamotrigine is affected by the coadministration of certain medications *[see Warnings and Precautions (5.8, 5.12), Drug Interactions (7)]*.

The net effects of drug interactions with lamotrigine are summarized in Table 8. Details of the drug interaction studies, which were done using immediate-release lamotrigine, are provided in Table 8.

Table 8. Summary of Drug Interactions With Lamotrigine

Drug	Drug Plasma Concentration With Adjunctive Lamotrigine[a]	Lamotrigine Plasma Concentration With Adjunctive Drugs[b]
Oral contraceptives (e.g., ethinylestradiol/levonorgestrel[c])	↔[d]	↓
Bupropion	Not assessed	↔
Carbamazepine	↔	↓
Carbamazepine epoxide[e]	?	
Felbamate	Not assessed	↔
Gabapentin	Not assessed	↔
Levetiracetam	↔	↔
Lithium	↔	Not assessed
Olanzapine	↔	↔[f]
Oxcarbazepine	↔	↔
10-monohydroxy oxcarbazepine metabolite[g]	↔	
Phenobarbital/primidone	↔	↓
Phenytoin	↔	↓
Pregabalin	↔	↔
Rifampin	Not assessed	↓
Topiramate	↔[h]	↔
Valproate	↓	↑
Valproate + phenytoin and/or carbamazepine	Not assessed	↔
Zonisamide	Not assessed	↔

[a] From adjunctive clinical trials and volunteer studies.

[b] Net effects were estimated by comparing the mean clearance values obtained in adjunctive clinical trials and volunteer studies.

[c] The effect of other hormonal contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not been systematically evaluated in clinical trials, although the effect may be similar to that seen with the ethinylestradiol/levonorgestrel combinations.

[d] Modest decrease in levonorgestrel.

[e] Not administered, but an active metabolite of carbamazepine.

[f] Slight decrease, not expected to be clinically relevant.

[g] Not administered, but an active metabolite of oxcarbazepine.

[h] Slight increase, not expected to be clinically relevant.

↔ = No significant effect.

? = Conflicting data.

Estrogen-Containing Oral Contraceptives: In 16 female volunteers, an oral contraceptive preparation containing 30 mcg ethinylestradiol and 150 mcg levonorgestrel increased the apparent clearance of lamotrigine (300 mg/day) by approximately 2-fold with mean decreases in AUC of 52% and in C_{max} of 39%. In this study, trough serum lamotrigine concentrations gradually increased and were approximately 2-fold higher on average at the end of the week of the inactive hormone preparation compared with trough lamotrigine concentrations at the end of the active hormone cycle.

Gradual transient increases in lamotrigine plasma levels (approximate 2-fold increase) occurred during the week of inactive hormone preparation (pill-free week) for women not also taking a drug that increased the clearance of lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or other drugs such as rifampin that induce lamotrigine glucuronidation) *[see Drug Interactions (7)]*. The increase in lamotrigine plasma levels will be greater if the dose of LAMICTAL XR is increased in the few days before or during the pill-free week. Increases in lamotrigine plasma levels could result in dose-dependent adverse reactions.

In the same study, coadministration of lamotrigine (300 mg/day) in 16 female volunteers did not affect the pharmacokinetics of the ethinylestradiol component of the oral contraceptive preparation. There were mean decreases in the AUC and C_{max} of the levonorgestrel component of 19% and 12%, respectively. Measurement of serum progesterone indicated that there was no hormonal evidence of ovulation in any of the 16 volunteers, although measurement of serum FSH, LH, and estradiol indicated that there was some loss of suppression of the hypothalamic-pituitary-ovarian axis.

The effects of doses of lamotrigine other than 300 mg/day have not been systematically evaluated in controlled clinical trials.

The clinical significance of the observed hormonal changes on ovulatory activity is unknown. However, the possibility of decreased contraceptive efficacy in some patients cannot

be excluded. Therefore, patients should be instructed to promptly report changes in their menstrual pattern (e.g., break-through bleeding).

Dosage adjustments may be necessary for women receiving estrogen-containing oral contraceptive preparations *[see Dosage and Administration (2.1)]*.

Other Hormonal Contraceptives or Hormone Replacement Therapy: The effect of other hormonal contraceptive preparations or hormone replacement therapy on the pharmacokinetics of lamotrigine has not been systematically evaluated. It has been reported that ethinylestradiol, not progestogens, increased the clearance of lamotrigine up to 2-fold, and the progestin-only pills had no effect on lamotrigine plasma levels. Therefore, adjustments to the dosage of LAMICTAL XR in the presence of progestogens alone will likely not be needed.

Bupropion: The pharmacokinetics of a 100-mg single dose of lamotrigine in healthy volunteers (n = 12) were not changed by coadministration of bupropion sustained-release formulation (150 mg twice daily) starting 11 days before lamotrigine.

Carbamazepine: Lamotrigine has no appreciable effect on steady-state carbamazepine plasma concentration. Limited clinical data suggest there is a higher incidence of dizziness, diplopia, ataxia, and blurred vision in patients receiving carbamazepine with lamotrigine than in patients receiving other AEDs with lamotrigine *[see Adverse Reactions (6.1)]*. The mechanism of this interaction is unclear. The effect of lamotrigine on plasma concentrations of carbamazepine-epoxide is unclear. In a small subset of patients (n = 7) studied in a placebo-controlled trial, lamotrigine had no effect on carbamazepine-epoxide plasma concentrations, but in a small, uncontrolled study (n = 9), carbamazepine-epoxide levels increased.

The addition of carbamazepine decreases lamotrigine steady-state concentrations by approximately 40%.

Esomeprazole: In a study of 30 subjects, coadministration of LAMICTAL XR with esomeprazole resulted in no significant change in lamotrigine levels and a small decrease in T_{max}. The levels of gastric pH were not altered compared with pre-lamotrigine dosing.

Felbamate: In a study of 21 healthy volunteers, coadministration of felbamate (1,200 mg twice daily) with lamotrigine (100 mg twice daily for 10 days) appeared to have no clinically relevant effects on the pharmacokinetics of lamotrigine.

Folate Inhibitors: Lamotrigine is a weak inhibitor of dihydrofolate reductase. Prescribers should be aware of this action when prescribing other medications that inhibit folate metabolism.

Gabapentin: Based on a retrospective analysis of plasma levels in 34 patients who received lamotrigine both with and without gabapentin, gabapentin does not appear to change the apparent clearance of lamotrigine.

Levetiracetam: Potential drug interactions between levetiracetam and lamotrigine were assessed by evaluating serum concentrations of both agents during placebo-controlled clinical trials. These data indicate that lamotrigine does not influence the pharmacokinetics of levetiracetam and that levetiracetam does not influence the pharmacokinetics of lamotrigine.

Lithium: The pharmacokinetics of lithium were not altered in healthy subjects (n = 20) by coadministration of lamotrigine (100 mg/day) for 6 days.

Olanzapine: The AUC and C_{max} of olanzapine were similar following the addition of olanzapine (15 mg once daily) to lamotrigine (200 mg once daily) in healthy male volunteers (n = 16) compared with the AUC and C_{max} in healthy male volunteers receiving olanzapine alone (n = 16).

In the same study, the AUC and C_{max} of lamotrigine were reduced on average by 24% and 20%, respectively, following the addition of olanzapine to lamotrigine in healthy male volunteers compared with those receiving lamotrigine alone. This reduction in lamotrigine plasma concentrations is not expected to be clinically relevant.

Oxcarbazepine: The AUC and C_{max} of oxcarbazepine and its active 10-monohydroxy oxcarbazepine metabolite were not significantly different following the addition of oxcarbazepine (600 mg twice daily) to lamotrigine (200 mg once daily) in healthy male volunteers (n = 13) compared with healthy male volunteers receiving oxcarbazepine alone (n = 13).

In the same study, the AUC and C_{max} of lamotrigine were similar following the addition of oxcarbazepine (600 mg twice daily) to lamotrigine in healthy male volunteers compared with those receiving lamotrigine alone. Limited clinical data suggest a higher incidence of headache, dizziness, nausea, and somnolence with coadministration of lamotrigine and oxcarbazepine compared with lamotrigine alone or oxcarbazepine alone.

Phenobarbital, Primidone: The addition of phenobarbital or primidone decreases lamotrigine steady-state concentrations by approximately 40%.

Phenytoin: Lamotrigine has no appreciable effect on steady-state phenytoin plasma concentrations in patients with epilepsy. The addition of phenytoin decreases lamotrigine steady-state concentrations by approximately 40%.

Pregabalin: Steady-state trough plasma concentrations of lamotrigine were not affected by concomitant pregabalin (200 mg 3 times daily) administration. There are no pharmacokinetic interactions between lamotrigine and pregabalin.

Rifampin: In 10 male volunteers, rifampin (600 mg/day for 5 days) significantly increased the apparent clearance of a single 25-mg dose of lamotrigine by approximately 2-fold (AUC decreased by approximately 40%).

Topiramate: Topiramate resulted in no change in plasma concentrations of lamotrigine. Administration of lamotrigine resulted in a 15% increase in topiramate concentrations.

Valproate: When lamotrigine was administered to healthy volunteers (n = 18) receiving valproate, the trough steady-state valproate plasma concentrations decreased by an average of 25% over a 3-week period, and then stabilized. However, adding lamotrigine to the existing therapy did not cause a change in valproate plasma concentrations in either adult or pediatric patients in controlled clinical trials.

The addition of valproate increased lamotrigine steady-state concentrations in normal volunteers by slightly more than 2-fold. In one study, maximal inhibition of lamotrigine clearance was reached at valproate doses between 250 and 500 mg/day and did not increase as the valproate dose was further increased.

Zonisamide: In a study of 18 patients with epilepsy, coadministration of zonisamide (200 to 400 mg/day) with lamotrigine (150 to 500 mg/day for 35 days) had no significant effect on the pharmacokinetics of lamotrigine.

Known Inducers or Inhibitors of Glucuronidation: Drugs other than those listed above have not been systematically evaluated in combination with lamotrigine. Since lamotrigine is metabolized predominately by glucuronic acid conjugation, drugs that are known to induce or inhibit glucuronidation may affect the apparent clearance of lamotrigine, and doses of LAMICTAL XR may require adjustment based on clinical response.

Other: Results of in vitro experiments suggest that clearance of lamotrigine is unlikely to be reduced by concomitant administration of amitriptyline, clonazepam, clozapine, fluoxetine, haloperidol, lorazepam, phenelzine, risperidone, sertraline, or trazodone.

Results of in vitro experiments suggest that lamotrigine does not reduce the clearance of drugs eliminated predominantly by CYP2D6.

Special Populations: *Patients With Renal Impairment:* Twelve volunteers with chronic renal failure (mean creatinine clearance: 13 mL/min, range: 6 to 23) and another 6 individuals undergoing hemodialysis were each given a single 100-mg dose of immediate-release lamotrigine. The mean plasma half-lives determined in the study were 42.9 hours (chronic renal failure), 13.0 hours (during hemodialysis), and 57.4 hours (between hemodialysis) compared with 26.2 hours in healthy volunteers. On average, approximately 20% (range: 5.6 to 35.1) of the amount of lamotrigine present in the body was eliminated by hemodialysis during a 4-hour session *[see Dosage and Administration (2.1)]*.

Hepatic Disease: The pharmacokinetics of lamotrigine following a single 100-mg dose of immediate-release lamotrigine were evaluated in 24 subjects with mild, moderate, and severe hepatic impairment (Child-Pugh Classification system) and compared with 12 subjects without hepatic impairment. The patients with severe hepatic impairment were without ascites (n = 2) or with ascites (n = 5). The mean apparent clearances of lamotrigine in patients with mild (n = 12), moderate (n = 5), severe without ascites (n = 2), and severe with ascites (n = 5) liver impairment were 0.30 ± 0.09, 0.24 ± 0.1, 0.21 ± 0.04, and 0.15 ± 0.09 mL/min/kg, respectively, as compared with 0.37 ± 0.1 mL/min/kg in the healthy controls. Mean half-lives of lamotrigine in patients with mild, moderate, severe without ascites, and severe with ascites hepatic impairment were 46 ± 20, 72 ± 44, 67 ± 11, and 100 ± 48 hours, respectively, as compared with 33 ± 7 hours in healthy controls *[see Dosage and Administration (2.1)]*.

Elderly: The pharmacokinetics of lamotrigine following a single 150-mg dose of immediate-release lamotrigine were evaluated in 12 elderly volunteers between the ages of 65 and 76 years (mean creatinine clearance: 61 mL/min, range: 33 to 108 mL/min). The mean half-life of lamotrigine in these subjects was 31.2 hours (range: 24.5 to 43.4 hours), and the mean clearance was 0.40 mL/min/kg (range: 0.26 to 0.48 mL/min/kg).

Gender: The clearance of lamotrigine is not affected by gender. However, during dose escalation of immediate-release lamotrigine in one clinical trial in patients with epilepsy on

a stable dose of valproate (n = 77), mean trough lamotrigine concentrations, unadjusted for weight, were 24% to 45% higher (0.3 to 1.7 mcg/mL) in females than in males.

Race: The apparent oral clearance of lamotrigine was 25% lower in non-Caucasians than Caucasians.

Pediatric Patients: Safety and effectiveness of LAMICTAL XR for use in patients less than 13 years of age have not been established.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of carcinogenicity was seen in mouse or rat following oral administration of lamotrigine for up to 2 years at doses up to 30 mg/kg/day and 10 to 15 mg/kg/day in mouse and rat, respectively. The highest doses tested are less than the human dose of 400 mg/day on a body surface area (mg/m^2) basis.

Lamotrigine was negative in *in vitro* gene mutation (Ames and mouse lymphoma *tk*) assays and in clastogenicity (*in vitro* human lymphocyte and *in vivo* rat bone marrow) assays.

No evidence of impaired fertility was detected in rats given oral doses of lamotrigine up to 20 mg/kg/day. The highest dose tested is less than the human dose of 400 mg/day on a mg/m^2 basis.

14 CLINICAL STUDIES

14.1 Adjunctive Therapy for Primary Generalized Tonic-Clonic Seizures

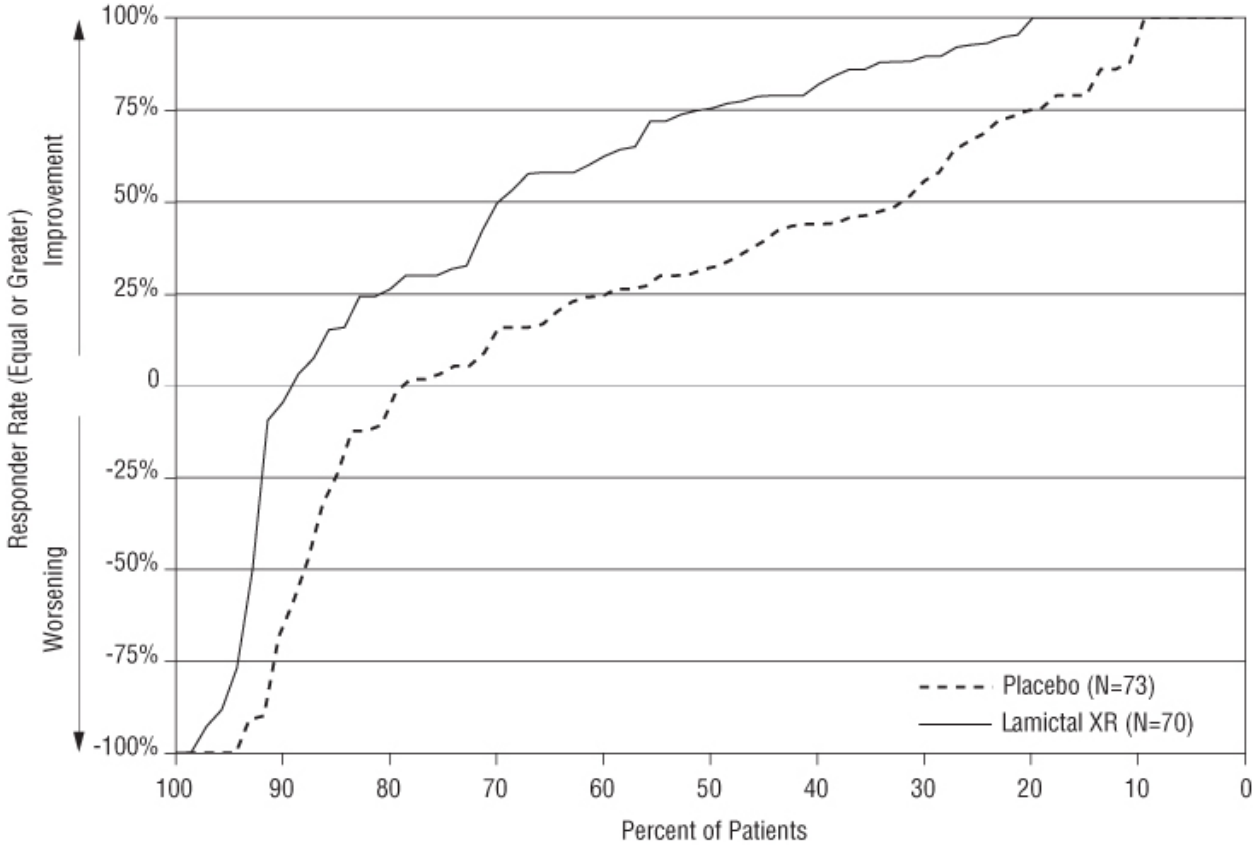
The effectiveness of LAMICTAL XR as adjunctive therapy was established in PGTC seizures in a 19-week, international, multicenter, double-blind, randomized, placebo-controlled study in 143 patients 13 years of age and older (n = 70 on LAMICTAL XR and n = 73 on placebo). Patients with at least 3 PGTC seizures during an 8-week baseline phase were randomized to 19 weeks of treatment with LAMICTAL XR or placebo added to their current AED regimen of up to 2 drugs. Patients were dosed on a fixed-dose regimen, with target doses ranging from 200 to 500 mg/day of LAMICTAL XR based on concomitant AED(s) (target dose = 200 mg for valproate, 300 mg for AEDs not altering plasma lamotrigine levels, and 500 mg for enzyme-inducing AEDs).

The primary efficacy endpoint was percent change from baseline in PGTC seizure frequency during the double-blind treatment phase. For the intent-to-treat population, the median percent reduction in PGTC seizure frequency was 75% in patients treated with LAMICTAL XR and 32% in patients treated with placebo, a difference that was statistically significant, defined as a 2-sided *P* value ≤ 0.05.

Figure 1 presents the percentage of patients (X-axis) with a percent reduction in PGTC seizure frequency (responder rate) from baseline through the entire treatment period at least as great as that represented on the Y-axis. A positive value on the Y-axis indicates an improvement from baseline (i.e., a decrease in seizure frequency), while a negative value indicates a worsening from baseline (i.e., an increase in seizure frequency). Thus, in a display of this type, a curve for an effective treatment is shifted to the left of the curve for placebo. The proportion of patients

achieving any particular level of reduction in PGTC seizure frequency was consistently higher for the group treated with LAMICTAL XR compared with the placebo group. For example, 70% of patients randomized to LAMICTAL XR experienced a 50% or greater reduction in PGTC seizure frequency, compared with 32% of patients randomized to placebo. Patients with an increase in seizure frequency >100% are represented on the Y-axis as equal to or greater than -100%.

Figure 1. Proportion of Patients by Responder Rate for LAMICTAL XR and Placebo Group (Primary Generalized Tonic-Clonic Seizures Study)



14.2 Adjunctive Therapy for Partial Onset Seizures

The effectiveness of immediate-release lamotrigine as adjunctive therapy was initially established in 3 pivotal, multicenter, placebo-controlled, double-blind clinical trials in 355 adults with refractory partial onset seizures.

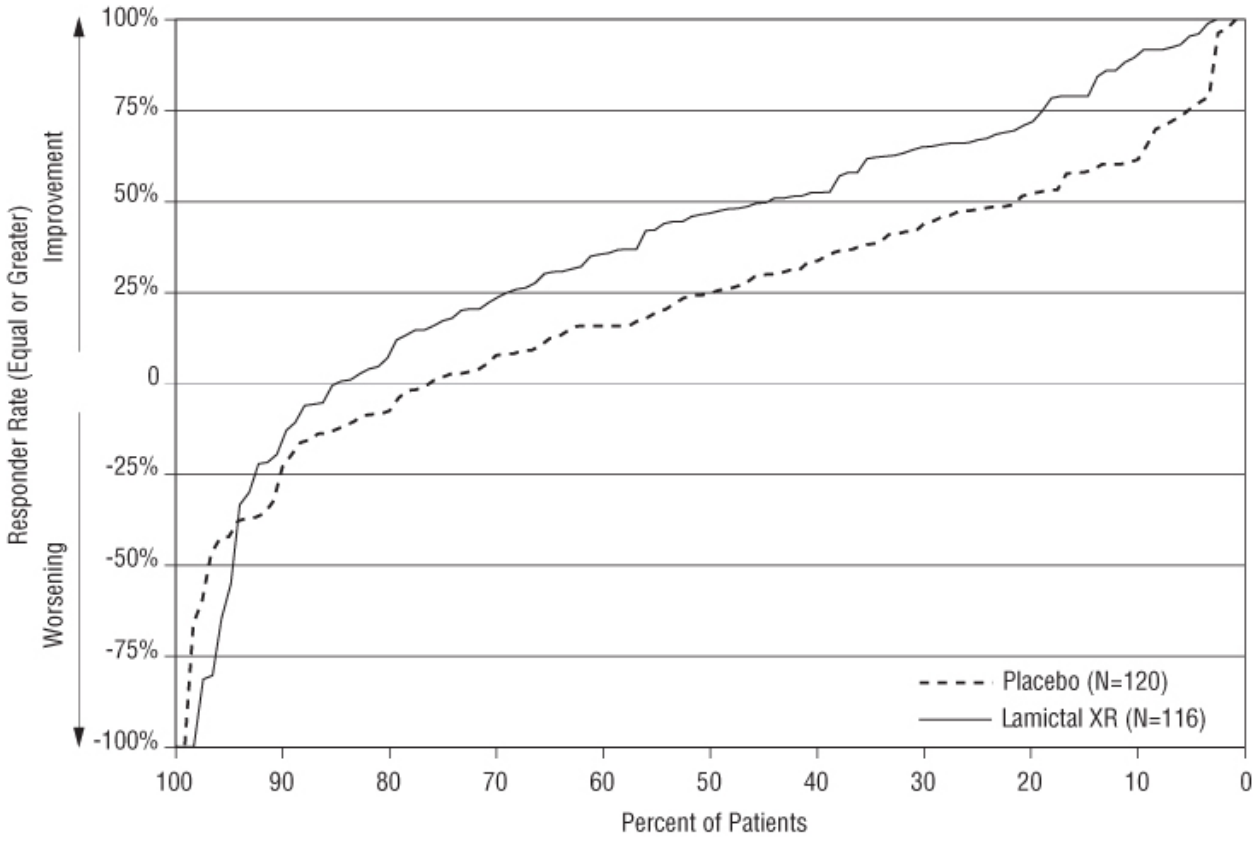
The effectiveness of LAMICTAL XR as adjunctive therapy in partial onset seizures, with or without secondary generalization, was established in a 19-week, multicenter, double-blind, placebo-controlled trial in 236 patients 13 years of age and older (approximately 93% of patients were aged 16 to 65 years). Approximately 36% were from the U.S. and approximately 64% were from other countries including Argentina, Brazil, Chile, Germany, India, Korea, Russian Federation, and Ukraine. Patients with at least 8 partial onset seizures during an 8-week prospective baseline phase (or 4-week prospective baseline coupled with a 4-week historical

baseline documented with seizure diary data) were randomized to treatment with LAMICTAL XR (n = 116) or placebo (n = 120) added to their current regimen of 1 or 2 AEDs. Approximately half of the patients were taking 2 concomitant AEDs at baseline. Target doses ranged from 200 to 500 mg/day of LAMICTAL XR based on concomitant AED (target dose = 200 mg for valproate, 300 mg for AEDs not altering plasma lamotrigine, and 500 mg for enzyme-inducing AEDs). The median partial seizure frequency per week at baseline was 2.3 for LAMICTAL XR and 2.1 for placebo.

The primary endpoint was the median percent change from baseline in partial onset seizure frequency during the entire double-blind treatment phase. The median percent reductions in weekly partial onset seizures were 47% in patients treated with LAMICTAL XR and 25% on placebo, a difference that was statistically significant, defined as a 2-sided *P* value ≤0.05.

Figure 2 presents the percentage of patients (X-axis) with a percent reduction in partial seizure frequency (responder rate) from baseline through the entire treatment period at least as great as that represented on the Y-axis. The proportion of patients achieving any particular level of reduction in partial seizure frequency was consistently higher for the group treated with LAMICTAL XR compared with the placebo group. For example, 44% of patients randomized to LAMICTAL XR experienced a 50% or greater reduction in partial seizure frequency compared with 21% of patients randomized to placebo.

Figure 2. Proportion of Patients by Responder Rate for LAMICTAL XR and Placebo Group (Partial Onset Seizure Study)



14.3 Conversion to Monotherapy for Partial Onset Seizures

The effectiveness of LAMICTAL XR as monotherapy for partial onset seizures was established in a historical-control trial in 223 adults with partial seizures. The historical control methodology is described in a publication by French, et al. *[see References (15)]*. Briefly, in this study, patients were randomized to ultimately receive either Lamictal XR 300 mg or 250 mg once a day, and their responses were compared to those of a historical control group. The historical control consisted of a pooled analysis of the control groups from 8 studies of similar design, which utilized a subtherapeutic dose of an AED as a comparator. Statistical superiority to the historical control was considered to be demonstrated if the upper 95% confidence interval for the proportion of patients meeting escape criteria in patients receiving LAMICTAL XR remained below the lower 95% prediction interval of 65.3% derived from the historical control data.

In this study, patients ≥13 years of age experienced at least 4 partial seizures during an 8-week baseline period with at least 2 seizures occurring during each of 2 consecutive 4-week periods while receiving valproate or a non–enzyme-inducing AED. LAMICTAL XR was added to either valproate or a non–enzyme-inducing AED over a 6- to 7-week period followed by the gradual withdrawal of the background AED. Patients were then continued on monotherapy with LAMICTAL XR for 12 weeks. The escape criteria were one or more of the following:

(1) doubling of average monthly seizure count during any 28 consecutive days, (2) doubling of highest consecutive 2-day seizure frequency during the entire treatment phase, (3) emergence of a new seizure type compared to baseline (4) clinically significant prolongation of generalized tonic-clonic seizures or worsening of seizure considered by the investigator to require intervention. These criteria were similar to those in the 8 controlled trials from which the historical control group was constituted.

The upper 95% confidence limits of the proportion of subjects meeting escape criteria (40.2% at 300 mg/day and 44.5% at 250 mg/day) were below the threshold of 65.3% derived from the historical control data.

Although the study population was not fully comparable to the historical controlled population and the study was not fully blinded, numerous sensitivity analyses supported the primary results. Efficacy was further supported by the established effectiveness of the immediate-release formulation as monotherapy.

15 REFERENCES

1. French JA, Wang S, Warnock B, Temkin N. Historical control monotherapy design in the treatment of epilepsy. *Epilepsia*. 2010; 54:1936-1943.

16 HOW SUPPLIED/STORAGE AND HANDLING

LAMICTAL XR (lamotrigine) Extended-Release Tablets

25 mg, yellow with a white center, round, biconvex, film-coated tablets printed on one face in black ink with “LAMICTAL” and “XR 25”, unit-of-use bottles of 30 with orange caps (NDC 0173-0754-00).

50 mg, green with a white center, round, biconvex, film-coated tablets printed on one face in black ink with “LAMICTAL” and “XR 50”, unit-of-use bottles of 30 with orange caps (NDC 0173-0755-00).

100 mg, orange with a white center, round, biconvex, film-coated tablets printed on one face in black ink with “LAMICTAL” and “XR 100”, unit-of-use bottles of 30 with orange caps (NDC 0173-0756-00).

200 mg, blue with a white center, round, biconvex, film-coated tablets printed on one face in black ink with “LAMICTAL” and “XR 200”, unit-of-use bottles of 30 with orange caps (NDC 0173-0757-00).

300 mg, gray with a white center, caplet-shaped, film-coated tablets printed on one face in black ink with “LAMICTAL” and “XR 300”, unit-of-use bottles of 30 with orange caps (NDC 0173-0761-00).

LAMICTAL XR (lamotrigine) Patient Titration Kit for Patients Taking Valproate (Blue XR Kit)

25 mg, yellow with a white center, round, biconvex, film-coated tablets printed on one face in black ink with “LAMICTAL” and “XR 25” and 50 mg, green with a white center, round, biconvex, film-coated tablets printed on one face in black ink with “LAMICTAL” and “XR 50”; blisterpack of 21/25-mg tablets and 7/50-mg tablets (NDC 0173-0758-00).

LAMICTAL XR (lamotrigine) Patient Titration Kit for Patients Taking Carbamazepine, Phenytoin, Phenobarbital, or Primidone, and Not Taking Valproate (Green XR Kit)

50 mg, green with a white center, round, biconvex, film-coated tablets printed on one face in black ink with "LAMICTAL" and "XR 50"; 100 mg, orange with a white center, round, biconvex, film-coated tablets printed on one face in black ink with "LAMICTAL" and "XR 100"; and 200 mg, blue with a white center, round, biconvex, film-coated tablets printed on one face in black ink with "LAMICTAL" and "XR 200"; blisterpack of 14/50-mg tablets, 14/100-mg tablets, and 7/200-mg tablets (NDC 0173-0759-00).

LAMICTAL XR (lamotrigine) Patient Titration Kit for Patients Not Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate (Orange XR Kit)

25 mg, yellow with a white center, round, biconvex, film-coated tablets printed on one face in black ink with "LAMICTAL" and "XR 25"; 50 mg, green with a white center, round, biconvex, film-coated tablets printed on one face in black ink with "LAMICTAL" and "XR 50"; and 100 mg, orange with a white center, round, biconvex, film-coated tablets printed on one face in black ink with "LAMICTAL" and "XR 100"; blisterpack of 14/25-mg tablets, 14/50-mg tablets, and 7/100-mg tablets (NDC 0173-0760-00).

Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

17.1 Rash

Prior to initiation of treatment with LAMICTAL XR, the patient should be instructed that a rash or other signs or symptoms of hypersensitivity (e.g., fever, lymphadenopathy) may herald a serious medical event and that the patient should report any such occurrence to a physician immediately.

17.2 Suicidal Thinking and Behavior

Patients, their caregivers, and families should be counseled that AEDs, including LAMICTAL XR, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression; any unusual changes in mood or behavior; or the emergence of suicidal thoughts, behavior, or thoughts about self-harm. Behaviors of concern should be reported immediately to healthcare providers.

17.3 Worsening of Seizures

Patients should be advised to notify their physicians if worsening of seizure control occurs.

17.4 Central Nervous System Adverse Effects

Patients should be advised that LAMICTAL XR may cause dizziness, somnolence, and other symptoms and signs of central nervous system depression. Accordingly, they should be advised neither to drive a car nor to operate other complex machinery until they have gained

sufficient experience on LAMICTAL XR to gauge whether or not it adversely affects their mental and/or motor performance.

17.5 Blood Dyscrasias and/or Acute Multiorgan Failure

Patients should be advised of the possibility of blood dyscrasias and/or acute multiorgan failure and to contact their physician immediately if they experience any signs or symptoms of these conditions *[see Warnings and Precautions (5.3, 5.4)]*.

17.6 Pregnancy

Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy. Patients should be advised to notify their physicians if they intend to breastfeed or are breastfeeding an infant.

Patients should also be encouraged to enroll in the NAAED Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy. To enroll, patients can call the toll-free number 1-888-233-2334 *[see Use in Specific Populations (8.1)]*.

17.7 Oral Contraceptive Use

Women should be advised to notify their physicians if they plan to start or stop use of oral contraceptives or other female hormonal preparations. Starting estrogen-containing oral contraceptives may significantly decrease lamotrigine plasma levels and stopping estrogen-containing oral contraceptives (including the pill-free week) may significantly increase lamotrigine plasma levels *[see Warnings and Precautions (5.8), Clinical Pharmacology (12.3)]*. Women should also be advised to promptly notify their physicians if they experience adverse reactions or changes in menstrual pattern (e.g., break-through bleeding) while receiving LAMICTAL XR in combination with these medications.

17.8 Discontinuing LAMICTAL XR

Patients should be advised to notify their physicians if they stop taking LAMICTAL XR for any reason and not to resume LAMICTAL XR without consulting their physicians.

17.9 Aseptic Meningitis

Patients should be advised that LAMICTAL XR may cause aseptic meningitis. Patients should be advised to notify their physicians immediately if they develop signs and symptoms of meningitis such as headache, fever, nausea, vomiting, stiff neck, rash, abnormal sensitivity to light, myalgia, chills, confusion, or drowsiness while taking LAMICTAL XR.

17.10 Potential Medication Errors

Medication errors involving LAMICTAL have occurred. In particular the names LAMICTAL or lamotrigine can be confused with the names of other commonly used medications. Medication errors may also occur between the different formulations of LAMICTAL. To reduce the potential of medication errors, write and say LAMICTAL XR clearly. Depictions of the LAMICTAL XR Extended-Release Tablets can be found in the Medication Guide. Each LAMICTAL XR tablet has a distinct color and white center, and is printed with “LAMICTAL XR” and the tablet strength. These distinctive features serve to identify the different presentations of the drug and thus may help reduce the risk of medication

errors. LAMICTAL XR is supplied in round, unit-of-use bottles with orange caps containing 30 tablets. The label on the bottle includes a depiction of the tablets that further communicates to patients and pharmacists that the medication is LAMICTAL XR and the specific tablet strength included in the bottle. The unit-of-use bottle with a distinctive orange cap and distinctive bottle label features serves to identify the different presentations of the drug and thus may help to reduce the risk of medication errors. **To avoid a medication error of using the wrong drug or formulation, patients should be strongly advised to visually inspect their tablets to verify that they are LAMICTAL XR each time they fill their prescription and to immediately talk to their doctor/pharmacist if they receive a LAMICTAL XR tablet without a white center and without "LAMICTAL XR" and the strength printed on the tablet as they may have received the wrong medication** *[see Dosage Forms and Strengths (3), How Supplied/Storage and Handling (16)]*.

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GlaxoSmithKline
Research Triangle Park, NC 27709

April 2011
LXR:7PI

MEDICATION GUIDE

LAMICTAL® (la-MIK-tal) XR™ (lamotrigine) Extended-Release Tablets

Read this Medication Guide before you start taking LAMICTAL XR and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment. If you have questions about LAMICTAL XR, ask your healthcare provider or pharmacist.

What is the most important information I should know about LAMICTAL XR?

1. **LAMICTAL XR may cause a serious skin rash that may cause you to be hospitalized or to stop LAMICTAL XR; it may rarely cause death.**

There is no way to tell if a mild rash will develop into a more serious reaction. These serious skin reactions are more likely to happen when you begin taking LAMICTAL XR, within the first 2 to 8 weeks of treatment. But it can happen in people who have taken LAMICTAL XR for any period of time. Children between 2 to 16 years of age have a higher chance of getting this serious skin reaction while taking lamotrigine. LAMICTAL XR is not approved for use in children less than 13 years of age.

The risk of getting a rash is higher if you:

- take LAMICTAL XR while taking valproate [DEPAKENE (valproic acid) or DEPAKOTE (divalproex sodium)].
- take a higher starting dose of LAMICTAL XR than your healthcare provider prescribed.
- increase your dose of LAMICTAL XR faster than prescribed.

LAMICTAL XR can also cause other types of allergic reactions or serious problems that may affect organs and other parts of your body like the liver or blood cells. You may or may not have a rash with these types of reactions.

Call your healthcare provider right away if you have any of the following:

- **a skin rash**
- **hives**
- **fever**
- **swollen lymph glands**
- **painful sores in the mouth or around your eyes**
- **swelling of your lips or tongue**
- **yellowing of your skin or eyes**
- **unusual bruising or bleeding**
- **severe fatigue or weakness**
- **severe muscle pain**
- **frequent infections**

These symptoms may be the first signs of a serious reaction. A healthcare provider should examine you to decide if you should continue taking LAMICTAL XR.

2. Like other antiepileptic drugs, LAMICTAL XR may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.

Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempt to commit suicide
- new or worse depression
- new or worse anxiety
- feeling agitated or restless
- panic attacks

- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

Do not stop LAMICTAL XR without first talking to a healthcare provider.

- Stopping LAMICTAL XR suddenly can cause serious problems.
- Suicidal thoughts or actions can be caused by things other than medicines. If you have suicidal thoughts or actions, your healthcare provider may check for other causes.

How can I watch for early symptoms of suicidal thoughts and actions?

- Pay attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled.
- Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

3. LAMICTAL XR may rarely cause aseptic meningitis, a serious inflammation of the protective membrane that covers the brain and spinal cord.

Call your healthcare provider right away if you have any of the following symptoms:

- Headache
- Fever
- Nausea
- Vomiting
- Stiff neck
- Rash
- Unusual sensitivity to light
- Muscle pains
- Chills
- Confusion
- Drowsiness

Meningitis has many causes other than LAMICTAL XR, which your doctor would check for if you developed meningitis while taking LAMICTAL XR.

LAMICTAL XR can have other serious side effects. For more information ask your healthcare provider or pharmacist. Tell your healthcare provider if you have any side effect that bothers you. Be sure to read the section below entitled "What are the possible side effects of LAMICTAL XR?"

4. Patients prescribed LAMICTAL have sometimes been given the wrong medicine because many medicines have names similar to LAMICTAL, so always check that you receive LAMICTAL XR.

Taking the wrong medication can cause serious health problems. When your healthcare provider gives you a prescription for LAMICTAL XR:

- Make sure you can read it clearly.
- Talk to your pharmacist to check that you are given the correct medicine.
- Each time you fill your prescription, check the tablets you receive against the pictures of the tablets below.

These pictures show the distinct wording, colors, and shapes of the tablets that help to identify the right strength of LAMICTAL XR. Immediately call your pharmacist if you receive a LAMICTAL XR tablet that does not look like one of the tablets shown below, as you may have received the wrong medication.

LAMICTAL XR (lamotrigine) Extended-Release Tablets

 **25 mg, yellow with white center** **Imprinted with LAMICTAL XR 25**	 **50 mg, green with white center** **Imprinted with LAMICTAL XR 50**	 **100 mg, orange with white center** **Imprinted with LAMICTAL XR 100**
 **200 mg, blue with white center** **Imprinted with LAMICTAL XR 200**	 **300 mg, gray with white center** **Imprinted with LAMICTAL XR 300**	

What is LAMICTAL XR?

LAMICTAL XR is a prescription medicine used:

- together with other medicines to treat primary generalized tonic-clonic seizures and partial onset seizures in people 13 years of age and older.
- alone to treat partial seizures when changing from certain other medicines used in people 13 years and older. It is not known if LAMICTAL XR is safe or effective in children less than 13 years of age. Other forms of lamotrigine can be used in children aged 2 to 12 years.

Who should not take LAMICTAL XR?

You should not take LAMICTAL XR if you have had an allergic reaction to lamotrigine or to any of the inactive ingredients in LAMICTAL XR. See the end of this leaflet for a complete list of ingredients in LAMICTAL XR.

What should I tell my healthcare provider before taking LAMICTAL XR?

Before taking LAMICTAL XR, tell your healthcare provider about all of your medical conditions, including if you:

- have had a rash or allergic reaction to another antiseizure medicine.
- have or have had depression, mood problems, or suicidal thoughts or behavior.
- are taking oral contraceptives (birth control pills) or other female hormonal medicines. Do not start or stop taking birth control pills or other female hormonal medicine until you have talked with your healthcare provider. Tell your healthcare provider if you have any changes in your menstrual pattern such as breakthrough bleeding. Stopping these medicines may cause side effects (such as dizziness, lack of coordination, or double vision). Starting these medicines may lessen how well LAMICTAL XR works.
- are pregnant or plan to become pregnant. It is not known if LAMICTAL XR will harm your unborn baby. If you become pregnant while taking LAMICTAL XR, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic drugs during pregnancy.
- are breastfeeding. LAMICTAL XR can pass into your breast milk. You and your healthcare provider should decide if you should take LAMICTAL XR or breastfeed. Breastfeeding while taking LAMICTAL XR is not recommended.

Tell your healthcare provider about all the medicines you take or if you are planning to take a new medicine, including prescription and non-prescription medicines, vitamins, and herbal supplements. Using LAMICTAL XR with certain other medicines can affect each other, causing side effects.

How should I take LAMICTAL XR?

- Take LAMICTAL XR exactly as prescribed.
- Your healthcare provider may change your dose. Do not change your dose without talking to your healthcare provider.
- Do not stop taking LAMICTAL XR without talking to your healthcare provider. Stopping LAMICTAL XR suddenly may cause serious problems. For example, if you have epilepsy and you stop taking LAMICTAL XR suddenly, you may get seizures that do not stop. Talk with your healthcare provider about how to stop LAMICTAL XR slowly.
- If you miss a dose of LAMICTAL XR, take it as soon as you remember. If it is almost time for your next dose, just skip the missed dose. Take the next dose at your regular time. **Do not take 2 doses at the same time.**

- You may not feel the full effect of LAMICTAL XR for several weeks.
- If you have epilepsy, tell your healthcare provider if your seizures get worse or if you have any new types of seizures.
- LAMICTAL XR can be taken with or without food.
- Do not chew, crush, or divide LAMICTAL XR.
- Swallow LAMICTAL XR tablets whole.
- If you have trouble swallowing LAMICTAL XR Tablets, tell your healthcare provider because there may be another form of lamotrigine you can take.
- If you receive LAMICTAL XR in a blisterpack, examine the blisterpack before use. Do not use if blisters are torn, broken, or missing.

What should I avoid while taking LAMICTAL XR?

- Do not drive a car or operate complex, hazardous machinery until you know how LAMICTAL XR affects you.

What are possible side effects of LAMICTAL XR?

- See "What is the most important information I should know about LAMICTAL XR?"

Common side effects of LAMICTAL XR include:

- Dizziness
- Tremor
- Double vision
- Nausea
- Vomiting
- Trouble with balance and coordination
- Anxiety

Other common side effects that have been reported with another form of lamotrigine include headache, sleepiness, blurred vision, runny nose, and rash.

Tell your healthcare provider about any side effect that bothers you or that does not go away. These are not all the possible side effects of LAMICTAL XR. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store LAMICTAL XR?

- Store LAMICTAL XR at room temperature between 59^{o}F to 86^{o}F (15^{o}C to 30^{o}C).
- **Keep LAMICTAL XR and all medicines out of the reach of children.**

General information about LAMICTAL XR

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use LAMICTAL XR for a condition for which it was not prescribed. Do not give LAMICTAL XR to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about LAMICTAL XR. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about LAMICTAL XR that is written for healthcare professionals.

For more information, go to www.lamictalxr.com or call 1-888-825-5249.

What are the ingredients in LAMICTAL XR?

Active ingredient: Lamotrigine.
Inactive ingredients: glycerol monostearate, hypromellose, lactose monohydrate, magnesium stearate, methacrylic acid copolymer dispersion, polyethylene glycol 400, polysorbate 80, silicon dioxide (25-mg and 50-mg tablets only), titanium dioxide, triethyl citrate, iron oxide black (50-mg and 300-mg tablets only), iron oxide yellow (25-mg, 50-mg, 100-mg tablets only), iron oxide red (100-mg tablet only), FD&C Blue No. 2 Aluminum Lake (200-mg tablet only). Tablets are printed with edible black ink.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

LAMICTAL XR is a trademark of GlaxoSmithKline.
DEPAKENE and DEPAKOTE are registered trademarks of Abbott Laboratories.

GlaxoSmithKline
Research Triangle Park, NC 27709

April 2011
LXR:6MG

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-115/S-006

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: 022115/S006

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Bastings, Eric
Best, Jeanine
Burke, Laurie
Dinsmore, Steven
El Hage, Antoine
Feibus, Karen
Freed, Lois
Hershkowitz, Norman
Jin, Kun
Katz, Russell
Keefe, Stephanie
Ling, Xiang
Mathis, Lisa
Purohit-Sheth, Tejashri
Summers, Kelly
Toure, Hamet
Tran, Quynh-Van
Wu, Ta-Chen
Yan, Jun

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-115/S-006

OFFICE DIRECTOR MEMO

MEMORANDUM

DATE: April 23, 2011

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

TO: File, NDA 22-115/S-006

SUBJECT: Action Memo for NDA 22-115/Supplement 006, for the use of Lamictal XR (lamotrigine) Extended Release Tablets as Monotherapy in Patients with Partial Seizures

NDA 22-115, for the use of Lamictal XR (lamotrigine) Extended Release Tablets as monotherapy in patients with partial seizures, was submitted by GlaxoSmithKline Inc., on 3/31/10. Lamictal XR is currently approved for use as adjunctive therapy in the treatment of partial onset seizures and primary generalized seizures in patients 13 years old and older. An immediate release (IR) formulation is approved for both adjunctive therapy for partial seizures in adults and children and adjunctive therapy for Lennox-Gastaut in children and adults. The IR formulation is also approved as monotherapy for partial seizures.

This application contains the results of a single trial, in which patients who received one of two doses of Lamictal XR were compared to a historical control group. The use of a historical control comparator raises numerous methodological and interpretive questions unique in the study of treatments of epilepsy; for these reasons, this application was discusses at a meeting of Peripheral and Central Nervous Systems Advisory Committee (PCNS AC) on 3/10/11.

The application has been reviewed by Dr. Steven Dinsmore, medical reviewer, Drs. Xiang Ling and Tristan Massie, statisticians, and Dr. Norman Hershkowitz, neurology team leader, and Cross Discipline Team Leader (CDTL) for this application.

In this memo, I will provide some relevant background that provides a justification for the use of a historical control trial in this setting, a brief review of the data in the application, and the rationale for the division's decision on the application.

In recent years, the Agency has become convinced that the community of experts in epilepsy considers studies in which patients with epilepsy receive only placebo (monotherapy) unethical, given beliefs about leaving such patients untreated. As a result, one can imagine several potential routes to obtaining a monotherapy claim for an anticonvulsant treatment (almost all of which are

initially approved on the basis of studies done in the adjunctive setting), including the following:

1) **No additional studies required**-it is possible that effectiveness as monotherapy might be extrapolated from evidence of effectiveness as adjunctive treatment, the latter derived from adequate controlled trials, and which have served as the basis for approval of the treatment as adjunctive treatment. In this approach, it is assumed that a treatment that is effective in the presence of (widely varying) concomitant anticonvulsant drugs must be effective as sole treatment. The Agency has not accepted this approach, given the uncertainties about the validity of such extrapolation, and, especially, the absence of information about what dose might be effective as monotherapy. In the case before us, it is worth noting that the dose of Lamictal IR that is approved as monotherapy is 500 mg/day (see below; the dose of Lamictal XR being proposed as being effective as monotherapy is 250-300 mg/day).

   Here it might also be noted that the division has typically required at least one controlled trial demonstrating the effectiveness of a controlled release preparation when an immediate release preparation is already approved for the same indication. We do this (even when the total exposure [AUC] for the two products may be essentially identical) because we are not certain whether any particular pattern of absorption is critical to effectiveness. In this regard, it should be noted that the 24 hour AUCs of Lamictal XR and Lamictal IR are about the same, though it appears that the AUC of Lamictal XR is lower than that of the IR when it is given concomitantly with enzyme-inducing drugs.

2) **Active controlled studies**-in this setting, the goal is to demonstrate "equivalent" effects between the proposed treatment and an effective, active comparator. Although in this study design all patients receive "active" treatment (and, therefore, the ethical problem of patients receiving no treatment does not arise), the interpretation of such studies is problematic. Specifically, a finding of no difference between the two groups can be interpreted in two ways: either both drugs were effective, or both drugs were ineffective. Although it is usually taken as a given that a finding of equivalence implies that the new drug is effective (because the comparator is an "effective" drug), it is not always clear, in the given trial performed, that the active comparator was, in fact, effective. It is well known that drugs known to be effective in general, may not demonstrate effectiveness in a given study. The only way to be "certain" that an effective treatment was effective in a given study in which it served as an active comparator is to have a robust experience of controlled trials with that active comparator in which it has been shown to distinguish itself from placebo in virtually every study. If this is the case, it might be reasonable to conclude that this treatment will be effective in any subsequent studies

in which it is used as an active comparator, and, therefore, any study of that sort in which the proposed treatment is shown to be "equivalent" to the active comparator might reasonably be interpreted as demonstrating the effectiveness of the new treatment. However, the division has concluded that there is no such sufficiently robust clinical trial experience with any anticonvulsant that might be used as an active comparator in a study of a new treatment that would make a finding of no difference interpretable. For this reason, we have not accepted active controlled trials that demonstrate no difference as evidence of effectiveness for a new treatment as monotherapy.

Of course, if a new treatment was found to be superior to an active comparator in a monotherapy study, that would be acceptable evidence of effectiveness for the new treatment. However, few if any sponsors have considered such an outcome likely in such a design, and, therefore, these studies have not been proposed.

3) **Natural history control**-In this design, all patients in the study receive the new treatment, and their responses are compared to the "natural history" of the untreated condition, as documented in previous cohorts of one sort or another (prospectively followed, retrospectively created, etc.). The division has not accepted this approach, given the paucity of useful natural history data in patients with partial seizures.

4) **True historical control**-In this design, responses in patients treated with the new drug are compared to the responses in a group of previous patients similar to those in the new study, whose response data were obtained under similar circumstances as those that obtain in the new study (for example, data in the control patients could have been obtained in previous studies whose critical conditions are similar to those in the new trial). In such a study, the goal may be to show an "equivalence" between the new drug and the historical control (an outcome that the division has, as described above, considered uninterpretable) or superiority to the historical control, an outcome that, all other things being equal, could be potentially interpretable.

The division has never accepted the use of such a "true" historical control design because of numerous potential difficulties in their interpretation, even if the goal was to show superiority of the new drug to the historical control group.

Primary among these difficulties is the lack of assurance that the patients in the control group and the treated group are "identical". Specifically, in the typical trial, patients are randomized to one of several treatments that are then compared. Randomization assures that the factors that might be related to response (or lack of response) to treatment are equitably distributed to the treatment groups. In this way, there is no bias (at least due to this cause).

Critically, it should be pointed out that not only can randomization be relied upon to equitably distribute those factors that we expect to be related to responsiveness to treatment (for example, severity of disease, duration of disease, concomitant medications, country, background standard of care, etc.), but randomization will equitably distribute those factors that might be related to responsiveness to treatment, ***but that are unknown to us***, of which there may be many. Any attempt to create a historical control group that resembles, as much as possible, the treatment group in a new study cannot, by definition, be certain to have matched the groups on critical factors that are unknown, but important.

Other elements of historical controlled trials also contribute to their "weakness" as useful trials, including the fact that, typically (as is the case in this application), all patients in the trial are aware that they are on active medication. This fact raises the question about the comparability of the responses seen in the new study compared to those seen in the historical control group, given that the latter patients might have been enrolled in blinded, placebo controlled studies. Further, historical control data gathered in the past might yield response data quite different than that gathered in contemporary studies, for many reasons. This is another factor that weakens an historical controlled study, compared to a study with an adequate contemporaneous control group.

Despite these important weaknesses, and in an attempt to develop a practical trial design that might be able to provide interpretable data on the effectiveness of anticonvulsants as monotherapy, Dr. Jacqueline French (then of the University of Pennsylvania) and her colleagues developed an approach that relies on the comparison of a newly treated group with a historical control group created from the control groups of previously performed adequate and well controlled monotherapy studies of anticonvulsants.

In brief, the new control group is based on the data from the control groups in 8 previously performed monotherapy studies. These 8 studies were of extremely similar design (though they were not identical). In form, each of these studies enrolled patients not well controlled on at least one AED. Study drug was then added on to the background AED(s). Study drug was either a dose of an anticonvulsant thought to be effective or a dose of an AED (either the study drug or another standard drug) thought to be not fully effective (so called pseudo-placebo control). Over a (varying) period of several weeks, the background AED(s) were withdrawn, leaving patients either on the "full" dose of the new drug, or the pseudo-placebo. Patients were then followed until they met one of four Escape Criteria, or completed the study. The proportions of patients who met Escape Criteria were then compared between the two groups.

The response in the historical control group created by French et al is based on the responses seen in the pseudo-placebo groups in these 8 studies. A total of 10 studies were actually performed using a similar design, but 2 were excluded

from consideration because of differences in either Escape Criteria (one study used only 3, not 4 Escape Criteria, and only one of these was identical to those used in the other studies) or Inclusion Criteria (in one study, patients could have failed no more that 1 AED [compared to the other studies that required previous failure on at least 1 AED], and could have as few as 1 seizure/month, compared to the other studies, in which patients had 2-4 seizures/month). French and colleagues identified appropriate studies by searching the literature and inquiring their colleagues about similarly designed trials that may have been performed and not published. We have searched our records as well, and have identified no similar studies beyond those included in these analyses.

As discussed above, the historical control group proposed by French et al is derived from the control groups (pseudo-placebo) from the 8 previously conducted monotherapy studies.

In these studies, the period during which the background AED(s) were withdrawn varied from 4-10 weeks, and the treatment period on monotherapy varied from 11-16 weeks. Patients in these studies had 2-4 partial seizures/month and were receiving 1 or 2 background AEDs (5 studies allowed up to 2 AEDs). In 7 of the studies, patients had simple partial, complex partial, and secondarily generalized seizures; in one study, patients had only partial and/or secondarily generalized seizures. The exit criteria in these trials were very similar and have been presented by French et al as listed below:

1) A two fold increase in partial seizure frequency in any 28 day period compared to baseline. Apparently, the specific 28 day period used varied among the studies. As will be discussed later, Dr. Ling performed analyses of the current Lamictal XR study using what can be called a "rolling" tally, in which serial 28 day intervals were calculated starting at Day 1 of the double blind phase; this analysis is considered conservative, and all of these "rolling" 28 day periods in the Lamictal XR study were examined to see if a patient met this criterion in any of these periods. The available data did not permit a re-analysis of the historical control cohort in this way.
2) A two fold increase in the greatest consecutive 2 day seizure frequency occurring in the baseline phase.
3) The occurrence of a single generalized tonic clonic seizure if none had occurred during the previous 6 months (one study), within the 2 years prior to enrollment (one study), during baseline (4 studies), or "emergence of a more severe seizure type" (one study).
4) Prolongation or worsening of seizure duration or frequency considered to require intervention (three studies required that this criterion be met by a generalized seizure, and four studies described a similar criterion, requiring the occurrence of status epilepticus and/or serial seizures)

In these 8 trials, French et al found the proportion of patients in the pseudo-placebo group who met at least one of these Escape Criteria by Day 112 of monotherapy (the minimal duration of this phase in any of the studies) to be:

	N	Proportion Meeting Escape Criteria
Study 1	93	76.9
Study 2	74	77.2
Study 3	24	83.3
Study 4	32	87.5
Study 5	45	95.9
Study 6	46	93.2
Study 7	22	86.4
Study 8	55	74.9

In determining how best to combine these data to produce a single estimate of the proportion of patients meeting Escape Criteria, and in an attempt to determine the standard a new drug should have to meet to be considered effective, French et al considered several options:

1) Choose the lowest of the lowest bounds of the 95% confidence intervals for any of the 8 studies, and consider a new drug effective if the upper bound of the 95% confidence interval of the estimate for the new drug excludes this lower bound.
2) The data from the 8 studies could be combined, calculate the lower bound of the 95% confidence interval for the combined series, and consider the new drug effective if the upper bound of the estimate for the new drug excludes the lower bound of the confidence interval for the combined series.
3) Consider methods that include a measure of the variability in response seen in the 8 studies. The authors utilized a non-iterative random effects method to determine the combined exit rate and standard error, as well as a sensitivity analysis using a mixed effects model to calculate a restricted maximum likelihood estimate for the combined exit rate and standard error. To include a measure of increased conservatism, they calculated a 95% Prediction Interval (PI), which is an attempt to "bound how a single future study would behave...", in contradistinction to a confidence interval, which bounds the mean.

The sponsors chose to rely on the lower bound of the 95% PI for the combined estimate of the proportion of patients who met Escape Criteria as the bar that the upper bound of the 95% Confidence Interval (CI) of the exit rate for the new drug must exclude. The estimate of the combined exit rate calculated by the non-iterative mixed effects model was 85.1% with a lower bound of the 95% PI of 65.3%. They also calculated a lower bound of the 80% PI, which was 72.2%.

Dr. Ling et al have performed an independent analysis of these 8 studies.

In preparation for these analyses, we obtained from the authors the datasets they used in their analyses. In addition, Dr. Ling et al obtained additional data from the NDA databases for those studies that were submitted to an NDA (all except Study 4).

Although there were several discrepancies between the data used by the authors and Dr. Ling et al, she obtained results essentially identical to those of the authors when performing the analyses they performed.

An important additional analysis performed by Dr. Ling examined the appropriateness of combining the data from these 8 studies into a single estimate. Specifically, she performed a logistic model for escape with study as the main effect to examine the homogeneity of the studies; the p-value for the likelihood test was 0.018, suggesting that combining the data from these studies might be problematic.

Dr. Ling et al also performed other analyses of the historical data not performed by the authors, but that were specifically pertinent to the evaluation of the study of Lamictal XR. These will be discussed in relation to the discussion of that study, which begins below.

Lamictal XR-Effectiveness

As noted, the sponsor has submitted the results of a single trial, LAM30055. In this blinded, randomized, multi-national study, performed in patients currently receiving either valproate or a non-enzyme inducing AED were randomized to receive either Lamictal XR 300 mg/day or Lamictal XR 250 mg/day. Patients were entered into an 8 week baseline, followed by the addition of Lamictal over 6-7 weeks, then a 4 week background AED withdrawal phase (during which the Lamictal could continue to be increased), and a 12 week monotherapy phase.

Although the primary outcome described in the protocol was to be the proportion of patients in the 300 mg/day group who discontinued at any time after the initiation of withdrawal of the background AED, the Agency analysis considered the primary outcome to be the proportion of patients who met one of the following Escape Criteria, beginning at the initiation of AED withdrawal:

1) A doubling of the average monthly partial seizure frequency calculated starting the day prior to the study visit, and counting back 28 days
2) A doubling of the highest consecutive 2 day seizure frequency
3) Emergence of a new more severe seizure type
4) Clinically significant prolongation of generalized tonic-clonic seizures

A total of 226 patients were randomized; 113 to each dose group. A total of 94 (83%) and 79 (70%) of patients completed the study in the 300 and 250 mg/day groups, respectively. A total of 111/112 patients in the 300 mg/day group had only partial seizures, and 108/111 patients in the Lamictal 250 mg/day group had only partial seizures.

Baseline Partial Seizures/Week	Lam 300	Lam 250
Mean	3.3	4.3
Median	1.4	1.5

The sponsor's original analyses revealed only 6 or 7 patients per group who met Escape Criteria. However, examination of the data after the study was completed revealed a larger number of patients who met Escape Criteria. Specifically, the following results were obtained by the sponsor for the proportion of patients meeting Escape Criteria upon re-analysis:

Treatment	Proportion of those meeting Escape Criteria [95% CI]
Lamictal 300 mg/d	26/108 (24%) [16.0, 32.1]
Lamictal 200 mg/d	25/97 (26%) [17.1, 34.5]

Dr. Ling performed several additional analyses.

As noted above, it was unclear if, in the calculation of 28 day seizure frequency, previous sponsors used the "rolling" calculation approach. For the Lamictal dataset, Dr. Ling used this approach, which yielded an additional 3 escapes in the 300 mg/day group and 2 more escapes in the 250 mg/day group.

Regarding the Escape Criterion about the emergence of a new, more severe seizure type, the sponsor compared the seizures in the randomized phase to seizure types the patient might have experienced at any time in their lives. To be more conservative, Dr. Ling compared the seizures during treatment to those that had occurred during the Baseline phase. This resulted in 2 more escapes in the Lamictal 300 mg/day group, and 3 more in the Lamictal 250 mg/day group.

Surprisingly, no patients were reported to have experienced Escape Criterion 4, a clinically significant prolongation of generalized tonic-clonic seizures, raising the question of whether the number of patients who might have met this endpoint (acknowledging that it is frankly subjective) were under-reported. In the studies

comprising the historical control group, the rate of Criterion 4 escapes (though they were defined somewhat differently than in the Lamictal XR study) ranged from 4% to 45%. There was no obvious way to account for this discrepancy in the analysis.

Given the issues raised and discussed above, Dr. Ling performed several additional analyses, which are presented below.

Binomial Proportion including additional calculated escapes identified above (dropouts unrelated to Escape Criteria are considered completers, which was the approach taken by the sponsor):

Treatment	Lam 300	Lam 250
Prop Escape [95% CI]	31/108 (29%) [20.2, 37.2]	30/97 (31%) [21.7, 40.1]

Sensitivity (dropouts unrelated to Escape Criteria are considered escapes):

Treatment	Lam 300	Lam 250
Prop Escape [95% CI]	37/108 (34%) [25.3, 43.2]	37/97 (38%) [28.5, 47.8]

Worst Case (dropouts before AED withdrawal are considered escapes) :

Treatment	Lam 300	Lam 250
Prop Escape [95% CI]	41/112 (37%) [27.7, 45.5]	51/111 (46%) [36.7, 55.2]

None of the upper bounds for either dose in any analyses cross the lower bound of the 95% PI.

Examination of Study LAM30055 revealed several obvious differences between the data in that study and the data that comprise the historical control. The most obvious differences relate to the location of the study sites, and aspects of the Inclusion Criteria.

Regarding the study sites, Study LAM30055 was conducted in 7 countries (Argentina, Chile, Costa Rica, Korea, Russia, Ukraine, and the US). A total of 25% of the patients in this study were US patients. The studies used to create the historical control were done in the US, with a small number of patients from Canada. Dr. Ling examined the proportion of escapes in Study LAM30055 by region, the results of which are as follows:

Binomial Proportion (dropouts unrelated to Escape Criteria are considered completers):

Treatment	US	non-US
Prop Escape	19/50 (38%)	42/155 (27%)
[95% CI]	[24.5, 51.5]	[20.1, 34.1]

Sensitivity (dropouts unrelated to Escape Criteria are considered escapes):

Treatment	US	non-US
Prop Escape	25/50 (50%)	49/155 (32%)
[95% CI]	[36.1, 63.9]	[24.3, 38.9]

Worst Case (dropouts before AED withdrawal are considered escapes) :

Treatment	US	non-US
Prop Escape	31/56 (55%)	61/167 (37%)
[95% CI]	[42.3, 68.4]	[29.2, 43.8]

Only in the Worst Case scenario does the upper bound of the 95% CI for the US data cross the lower bound of the 95% PI.

The sponsor suggests that the major difference between the escape rate between US and non-US sites is attributable to an unbalanced use of valproate (valproate was the background AED in the US in about 20% of the patients, compared to about 80% in the non-US sites). However, as Dr. Ling has shown, the escape rates were very similar ***within*** region between patients who used valproate and those who used a neutral AED (about 38-40% in the US, and about 27-29% in the non-US sites).

As noted above, patients in LAM3005 were allowed to be on only one concomitant AED at the time of enrollment, whereas in 5 studies included in the historical control, patients could have been on 2 concomitant AEDs. For this reason, Dr. Ling re-calculated the historical control analysis using only those patients who were taking only one AED at the time of enrollment (in studies allowing up to 2 AEDs at the time of enrollment, the percent of patients taking 2 AEDs varied from 17% to 33%). This re-calculation yielded an estimated escape rate of 83%, with a lower bound of the 95% PI of 58.6%. The Sensitivity and Worst Case analyses for the US-only data fail the standard set by this re-calculated bar.

Another difference between the patients in Study LAM30055 and those in the historical control group was that about 80% of patients in the historical control group were receiving carbamazepine, an enzyme inducing AED, at enrollment, and Study LAM30055 excluded patients receiving enzyme-inducers. The authors conclude that there was no important difference between escape rates in patients in the historical control who withdrew from carbamazepine and those who had not been receiving carbamazepine, and this was confirmed by Dr. Ling. No other specific analyses were done to address the use of carbamazepine (or use of other enzyme-inducers) in the historical control and their exclusion in Study LAM30055.

Another issue addressed by Dr. Ling related to the baseline seizure rates in Study LAM30055 and the historical control cohort.

In the historical control cohort, 3 studies required patients to have at least 2 seizures/week, and 4 studies required that patients have at least 4 seizures/week. This resulted in median baseline seizure rates of between 1.4 and 2.5 seizures/week. In Study LAM30055, patients were required to have at least 2 seizures/week, which resulted in median seizure rates of 1.4 (300 mg) and 1.5 seizures/week (250 mg), which was closer to the lower end of the median ranges in the historical cohort. This raised the possibility that patients in this study may have been less likely to escape than patients in the historical cohort, given their fewer baseline seizure rates.

However, Dr. Ling examined the escape rate by baseline seizure rate in Study LAM30055. She found that patients with baseline seizure rates of between 2-4/week had an escape rate of 42% compared to an escape rate of 25% in patients with more than 4 seizures/week at baseline. This demonstrates that fewer baseline seizures did not predict a lower escape rate.

It is also instructive to compare the exit rate of the two treatment groups in this study with those of the active treatment arms in the studies that comprise the historical control. Recall in this regard that patients in this study were aware that they were receiving active drug; it is not entirely clear what the expectations of patients were in the previous studies, in which patients were randomized to either a dose of study drug believed to be effective, or one considered sub-therapeutic (though it has been pointed out by Dr. French that in those studies, patients were presumably under the impression that either treatment to which they could have been randomized would have some effect). In any event, the following chart presents the exit rates in the active arms of the previous 8 studies (recall that the exit rates in the Lamictal XR study were 29% and 30% for the 300 mg/day and 250 mg/day groups, respectively, when using the analyses used in the White Paper):

Active treatment Daily Dose	Exit Rate
Gabapentin 2400 mg	73%
Lamictal IR 500 mg	42%
Topamax 1000 mg	50%
Oxcarbazepine 2400 mg	61%
Oxcarbazepine 2400 mg	34%
Felbamate 3600 mg	14%
Felbamate 3600 mg	32%

The exit rate for the active arm in Study 4 was not available.

Safety

No new safety issues have been identified beyond those already known.

Advisory Committee Meeting

As noted above, because of the issues raised above, and the potential precedent-setting nature of an approval based on a historical control trial in this setting, the application was discussed at a meeting of the PCNS on March 10, 2011. The standing AC was supplemented with several epileptologists and statisticians.

There was general agreement, especially among the epileptologists, that for most clinical populations (including the type of patients enrolled in this study), placebo-controlled monotherapy trials would be either prohibitively difficult or unethical. Although there was a view expressed that there were some epilepsy syndromes in which a placebo might be acceptable, for the typical patients with partial onset seizures, placebo was considered unethical in a monotherapy study.

Importantly, there was also a general consensus that the approach taken by French et al in the construction of the historical control was appropriate, and that the historical control constructed could be used in this, and future studies, as a comparator, as long as those future studies were adequately designed and conducted.

Most of the discussion at the meeting centered on the differences between the sample studied in this trial, and the patients included in the historical control. In the end, although many discussants expressed significant discomfort in those differences (especially in the fact that only 25% of the patients in this study were domestic patients and in the differences between the baseline AEDs in the Lamictal XR and the historical control patients), the fact that the vast majority of

the sensitivity analyses performed by Dr. Ling continued to show statistically significant effects for both dose groups was considered reassuring. On the critical question of whether or not the sponsor had submitted substantial evidence of effectiveness for Lamictal XR as monotherapy in the treatment of patients 13 years and older with partial onset seizures, the committee voted 10 Yes, 2 No, with 1 abstention.

Critically, of the 10 members who voted Yes on this question, all of them agreed that, given the differences in the patient samples between the Lamictal XR study and those who constituted the historical control group, the fact that the IR formulation of Lamictal is approved as monotherapy heavily influenced their vote. Just as critically, they all agreed that, in a future study of similar design, if the study sample is **sufficiently similar to that constituting the historical control**, they might be able to conclude that such a study could provide evidence of effectiveness **in the absence of a previous monotherapy approval with a different formulation of the same moiety**.

It is also worth noting that despite the fact that patients were randomized to one of two doses, and that they were blinded to treatment assignment, there was general agreement that it would be inappropriate to consider this study blinded and randomized in the sense those words are commonly understood, because all parties involved were aware that all patients received active drug, and patients were not randomized to treatment vs control.

(b) (4) at the meeting, was the one abstention. His comments are worth noting.

(b) (4) made the point that in most therapeutic areas in which a placebo has been considered to be unethical, that fact shifts the clinical paradigm from placebo controlled superiority studies to active control non-inferiority designs. In most such cases, once it has been determined that placebo is unethical, this has been considered to imply that a simple showing of superiority to placebo is insufficient to establish effectiveness. That is, in these settings, some proportion of the effect of a standard treatment is considered essential to the approval of subsequent treatments. (b) (4) noted that if, in the epilepsy monotherapy setting, a simple superiority to placebo is still considered acceptable, despite the fact that the use of placebo in a trial would be unethical, he would endorse approval of this application, but that if it would be essential for a new treatment to preserve some portion of the effectiveness of a standard treatment (non-inferiority), he would not. For this reason, he abstained.

COMMENTS

The sponsor has submitted the results of a randomized, double-blind trial in which the primary comparison, for purposes of determining effectiveness, was the exit rate (as determined by reaching one of four Escape Criteria) in the Lamictal XR 300 mg/day group compared to a combined exit rate calculated from the control groups of 8 similarly designed trials conducted in the past. Extensive analyses demonstrate that Lamictal XR 300 mg/day and 250 mg/day met the pre-determined standard established for this approach; that is, the upper bound of the 95% CI for the estimate of the effect of Lamictal XR excludes the lower limit of the 95% PI calculated for the combined estimated historical exit rate.

The division has advised sponsors that, under certain circumstances, this proposed historical control approach may be acceptable. In particular, we have advised sponsors that, **in those cases in which an AED has already been found to be effective as adjunctive therapy on the basis of adequate and well-controlled trials** (as is the case with Lamictal XR), we would consider approving that AED for use as monotherapy on the basis of an historical controlled study of the sort conducted with Lamictal XR. Specifically, we have agreed that the standard applied in this case would be acceptable, if a single such trial was conducted. If a sponsor performed two such studies, we have agreed that the upper bound of the 95% CI around the estimate of the treatment effect would need to exclude the lower bound of the 80% PI of the historical control in both studies.

However, as discussed above, a comparison to a historical control raises numerous critical interpretive questions. Especially critical are the almost certain fundamental differences between the patients in the treated and the historical control groups, due to the absence of randomization, on factors known and unknown that may affect response to treatment, with the resultant very real possibility of the introduction of (unknowable) bias. In this case, our prior belief about the likelihood of Lamictal XR being effective as monotherapy is high (it is effective as adjunctive therapy and the immediate release Lamictal is known to be effective as monotherapy, albeit at a higher dose of 500 mg/day).

Our prior beliefs notwithstanding, we have seen that there are numerous differences between the patients enrolled in Study LAM30055 and those that constitute the historical control. In particular, almost all of the patients comprising the historical control group were US patients, whereas only about 25% of the patients in Study LAM30055 were from the US. All of the patients in Study LAM30055 were taking one concomitant AED prior to enrollment, whereas patients in the studies that comprise the control group were taking up to two concomitant AEDs. None of the patients in Study LAM30055 were receiving carbamazepine or other enzyme-inducing AEDs prior to enrollment, whereas about 80% of the historical control patients were being treated with carbamazepine.

Dr. Ling has performed numerous analyses to attempt to address some of these discrepancies, and the results of all but the most severe worst-case analyses are consistent with an effect of Lamictal XR.

Also, there were numerous differences in the design and conduct of the 8 studies that comprise the historical control (e.g., different durations of the withdrawal period, differences in the seizure types of the patients enrolled, differences in the definitions of the Escape Criteria, etc.) that have raised questions about not only whether the patients in Study LAM30055 were sufficiently similar to those in the control, but also about whether or not it is fundamentally appropriate to calculate a combined exit rate for the historical control.

All of these questions were discussed in detail at the PCNS AC meeting on 3/10/11. As described above, although the committee had reservations about this approach, they provided a strong endorsement of the conclusion that the study provided substantial evidence of effectiveness of Lamictal as monotherapy for partial onset seizures.

I agree. I acknowledge the shortcomings of this approach, and recognize that no analysis or set of analyses can completely overcome the fact that patients in this study were not randomized to a concurrent control, and that, therefore, we cannot be entirely confident that the patients in this study were sufficiently similar to those constituting the historical control. Nonetheless, I agree with the committee that French et al's approach to constituting the historical control is acceptable, and that the data in this study do, in fact, provide substantial evidence that Lamictal XR is effective as monotherapy in the treatment of partial seizures. In particular, despite the differences between the study sample and the patients in the historical control group, the overwhelming agreement of numerous sensitivity analyses with the primary analyses, the fact that Lamictal XR is effective as adjunctive therapy, and the fact that IR Lamictal is effective as monotherapy all argue, in my view, for concluding that Lamictal XR is effective as monotherapy.

This approach has been proposed, of course, because placebo controlled trials, the so-called gold standard, cannot be performed ethically. This raises the question of why a non-gold standard study should be accepted. That is, why should we accept a study with potentially significant methodological flaws because the "right" study cannot be done? It may be true, in this case, that the only study that is capable of being interpreted cannot be performed ethically. In such a case, the conclusion would be that no claim for which this was true could be granted.

Certainly, there can be cases in which this is true; that is, cases in which no claim can be granted for certain indications, because no ethical, interpretable, trial can be done. I do not believe that this is the case here, however. I believe, given the

context of a previous finding of effectiveness for the treatment in a related setting (in this case, adjunctive treatment for partial onset seizures), and in this particular setting (where the IR formulation has been found to be effective as monotherapy), the robust results of the current study, though obtained in a design that is not ideal, provide adequate reassurance that Lamictal XR is effective as monotherapy against partial seizures.

It should be noted that there are at least two issues related to the specific study done with Lamictal XR that no sensitivity analysis can address. Specifically, as noted earlier, the study cannot truly be considered to be a blinded study, given that everyone involved knew that patients were not only on an active drug, but also that patients were on one of two very similar doses. In addition, there were no Criterion 4 events, which, again as described above, was different from the experience in the pseudo-placebo groups that constituted the historical control. Although these issues cannot be dismissed, my view is that they do not undermine the conclusion that the data, for the reasons expressed above, support the conclusion that Lamictal XR is effective as monotherapy for partial onset seizures in patients 13 years old and older.

One final point.

As noted above, (b) (4) raised the very interesting question of whether or not, in this setting, the conclusion that placebo controlled trials are unethical argues for requiring active control, non-inferiority studies, for the reasons stated earlier.

Although the question is clearly pertinent, I do not believe that non-inferiority studies should be required. That is, I believe that any effect of an AED greater than placebo, in reasonably sized trials of the sort we typically see, is acceptable for a showing of effectiveness. In those settings in which placebo is considered ethical in epilepsy studies, namely in adjunctive treatment studies, placebo is required and used, and there is general agreement that the effect sizes seen in those studies that reach statistical significance are clinically meaningful. I believe the same reasoning is true in the monotherapy setting, and therefore I believe that a difference between drug and placebo (if placebo could be used) is adequate for approval. In this regard, to the extent that the historical control design is interpretable, I note that the historical control group, as previously described, is composed of groups treated not with placebo, but with "sub-therapeutic" doses of active drugs. These specific doses were chosen to prevent patients from experiencing major seizures or status epilepticus. It is possible (or perhaps likely), therefore, that these patients did experience some degree of seizure control. If this is true, this would make any difference seen between a new treatment and this historical control group "larger" than a simple difference between drug and placebo.

For these reasons, then, I will issue the attached Approval letter, with attached agreed-upon labeling.

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

/s/

RUSSELL G KATZ
04/25/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-115/S-006

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	4/25/11
From	Norman Hershkowitz, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	22115 (SN 0074)
Applicant	GlaxoSmithKline
Date of Submission	3/31/10
PDUFA Goal Date	4/30/11
Proprietary Name / Established (USAN) names	Lamictal XR/ lamotrigine extended-release tablets
Dosage forms / Strength	Extended-release tablets: 25 mg, 50 mg, 100 mg, 200 mg, and 300 mg
Proposed Indication(s)	Monotherapy in partial onset seizures in patients ≥ 13 years of age
Recommended:	Approval

1. Introduction/Background

Immediate release Lamictal is a sodium channel blocking anticonvulsant. It is approved, as adjunctive therapy for the treatment of partial seizures, primary generalized seizures, and seizures associated with Lennox Gastaut syndrome in patients ≥ 2years of age. It is also approved as monotherapy for the treatment of partial seizures in patients ≥ 16 years old. These indications were labeled as a result of conventional multiple-site, parallel-arm double-blinded studies. More specifically, the monotherapy indication was approved following a "conversion to monotherapy" trial design in patients who were receiving either phenytoin or carbamazepine. In that study patients were randomized so as to be converted from their present drug to receive either low dose of valproate (1,000 mg/day, referred to as a pseudo-placebo) or a target dose of lamictal (500 mg/day, divided bid). The conclusion of efficacy was based upon the number of patients whom meet exit criteria[1] (42% Lamictal and 69% of VA, $p<0.0012$ exited based on these criteria). An extended formulation of Lamictal (Lamictal XR) has recently been approved for the adjunctive treatment in partial and primary generalized tonic-clonic seizures in patients of ≥ 13 years old. The approval was based upon both the determination of this formulation similar bioavailability to the instant release formulation (IR) of Lamictal (Lamictal IR) and two conventional randomized, double-blinded, placebo-

[1] The criteria include: 1) doubling of average monthly seizure 1340 count, 2) doubling of highest consecutive 2-day seizure frequency, 3) emergence of a new 1341 seizure type (defined as a seizure that did not occur during the 8-week baseline) that is more 1342 severe than seizure types that occur during study treatment, or 4) clinically significant 1343 prolongation of generalized tonic-clonic (GTC) seizures.

controlled trials, one in each type of seizure disorder. The Sponsor is now submitting a trial for the approval of Lamictal XR in the monotherapeutic treatment of seizures of partial origin.

This trial being submitted, however, is not of a conventional nature. It utilizes a historical design proposed by Dr. Jacqueline French, an epileptologist, and her colleagues. Typically trials in the past performed to examine for monotherapeutic efficacy have consisted of a blinded parallel arm study comparing study drug to a low dose of the drug being studied or a low dose of another reference drug, referred to as a pseudoplacebo. The comparator dose was selected so as to not completely control seizure activity, but to presumably prevent serious seizure outcomes (e.g. status epilepticus). Over the past 10 years, however, the clinical epilepsy community has come to consider the use of a pseudoplacebo in studies as unethical. The question then remains as to what type of study would allow for an empirical determination of efficacy and dosage of an anticonvulsant drug in monotherapy trials. Dr. Jacqueline French, an epileptologist, and her colleagues observed that many of the past studies used to examine monotherapy utilized a similar design and recruited similar populations of patients. All such studies recruited patients who were already on anticonvulsants and were then to monotherapy arms of either study medication or a pseudoplacebo. Using data from 8 such studies she devised a statistical method to compare results modeled from these historical data to data acquired in the new studies, which uses a similar patient population and have a similar experimental design to the prior 8 studies. This theoretically should allow the performance of monotherapy trials without the need of a pseudoplacebo arm. The methodology of this procedure was first promulgated as a white paper and latter published in the literature.[2] This may called a "true historically" designed study.

This Division has never depended on historical design studies, although there are other Divisions that have used such studies for product approval (Oncology). Because of the difficulty in performing such studies the Division has agreed with the Sponsor that such a study may theoretically allow for approval and labeling in monotherapy. The Sponsor was I informed that the final approval, however, would have to await review of the application and discussion with experts in the form of an Advisory Committee.

2. CMC/Device

This product is already marketed. There are no CMC issues.

3. Nonclinical Pharmacology/Toxicology

There are no new major issues in this already marketed. There were some minor labeling issues for which the reader is referred to discussions in section 11 (Labeling).

[2] French JA, Wang S, Warnock B, Temkin N. Historical control monotherapy design in the treatment of epilepsy. *Epilepsia.* 2010; 54:1936-1943.

4. Clinical Pharmacology/Biopharmaceutics

There is no new data. Clinical pharmacology has previously concluded the similar bioavailability of this agent administered once daily with that of the immediate release formulation administered twice daily. It should be noted that Clinical Pharmacology (Dr. Ta-Chen Wu) assisted in the label review. They agreed with the pharmacokinetic assumption made in labeling. Most importantly they agreed with the assumptions made for patients already on metabolic inducers. This is pertinent as patients on such drugs were excluded in the present protocol and the dosing regimen had to be extrapolated.

5. Clinical Microbiology

Not Applicable.

6. Clinical/Statistical- Efficacy

Both the Medical Reviewer (Dr. Dinsmore) and Statistical Reviewer (Dr. Ling) performed a joint Statistical-Efficacy review.

As noted above, the foundation of the study was based upon the assumption that it was possible to compare results of the drug treated groups in this study to that of pseudoplacebo groups in 8 prior similar studies. In the methodology described by the originator of the technique (French et al, see above) a non-iterative random effects approach was utilized to compute a combined percent escape rate and standard error from the data of the pseudoplacebo groups from 8 prior studies. A 2-sided 95% prediction interval on the percent escape was calculated, based upon a projected sample size of 50 subjects and a pseudoplacebo escape rate of 80%. The final modeled lower 95% confidence interval range would then be compared to the upper 95% confidence range for the studied drug. If these did not overlap, efficacy was to be concluded.

The analysis performed by French et al (see above), was therefore analyzed by this Divisions consulting statisticians (Reviewer Xiang Ling and Team Leader Kun Jin). Permission was granted from the original Sponsor to use datasets for the pseudoplacebo control groups. These as well as those provided in the white paper were analyzed by this Division's statisticians. These statisticians were able to replicate efficacy criteria recommended in the work of French et al. (see below) using a Kaplan-Meir analysis (lower bond of 65.7% drop outs). A binomial estimate, not used by French et al, was however somewhat stricter (lower bond 62.7%). One issue raised in this analysis was that of the homogeneity of escape rates. A homogeneity test raised some concern that there may be to much heterogeneity escape rates to justify the pooling of all 8 pseudoplacebo groups.

Study Design

The present historical control study (study LAM30055) design consisted of an international, multicenter, double-blind (although both blinded groups consisted of active drug), randomized study. In it patients with "refractory" partial onset seizures who were ≧ 13 years of age were converted to monotherapy by randomizing them to 2 active treatment arms (250 and 300 mg qD, 1:1), a design similar to that of the studies analyzed in the Dr. French's analysis. Two-hundred and thirty patients were screened so as to enroll 164 patients in the trial. Patients who were screened for eligibility entered an 8 week baseline phase. If patients continued to meet eligibility criteria (based on background seizure activity) they were randomized and entered into the double blind conversion phase (10-11 weeks) , during which time lamictal was added and titrated up to the target dose and background AED is withdrawn. This is followed by the double-blind maintenance phase (12 weeks) during which patients are maintained on lamictal XR monotherapy.

The planned primary endpoint was the upper 95% confidence interval of the proportion of *any* subject in the 300 mg/day treatment group who prematurely discontinued at any time after starting withdrawal of background AED (the last 16 weeks of the double-blind phase). This was to be compared to the lower bond of the historical control rate (65.3%). A post-hoc primary endpoint was established to better reflect those used in Dr. French's analysis and was defined as the proportion of patients who met the following predefined withdrawal criteria, which was based upon those identified and described in Dr. French's analysis [3] (all references of change is in reference to the baseline period):

Escape criteria 1. Doubling of average monthly seizure frequency calculated as the sum of countable, partial seizures starting the day prior to the study visit and extending back 28 days
Escape criteria 2. Doubling of the highest consecutive 2-day seizure frequency
Escape criteria 3. Emergence of a new, more severe seizure type
Escape criteria 4. Clinically-significant prolongation of generalized tonic-clonic seizures

Secondary endpoints including proportion of subjects in the 250 mg/day treatment group who prematurely discontinue, time to discontinuation, percent change from baseline in seizure frequency and the percent seizure-free patients at the last visit.

Three analysis groups can be identified: 1) the white paper per protocol population that consisted of all subjects who took at least one dose of lamictal and began background drug withdrawal, 2) the ITT population that consisted of patients who took at least one dose of lamictal. 3) The per-protocol population that consisted of patients in item #1, but without major violation (this was the Sponsor's primary population analysis).

[3] This determination was made after completion of the study and correction of the white paper. These calculations had to be performed by the Sponsor after the completion of the study
This is generally deemed to be the appropriate endpoint.

A total of 226 subjects were randomized, with 113 in each dose group. Nineteen patients in the 300 mg/day group prematurely withdrew from the study, whereas 34 of the 250 mg group prematurely withdrew. Reasons for withdrawal in the primary treatment group (300 mg/day) included adverse events (4%), subject decided to withdrew from study (8%) and insufficient therapeutic response (5%). Other reasons in the 250 mg/day group included lost to follow up, protocol violation, and "other."

Demographic and Baseline Features

The mean age for the primary treatment group was 34 years age, with equal number of male and females studied. The majority of patients (86%) were Caucasian, with the remainder being of Asian (10%) and African in decent (4%). About 29% were categorized as having Hispanic ethnicity. The patients were largely enrolled from outside the United States with 75% coming Argentina, Chile, Costa Rica, Korea, Russian and Ukraine and the remainder coming from with in the US. It is important to note that historical pseudoplacebo comparator controls were almost fully of US origin (1 of the 8 studies also containing some Canadian patients). This will be discussed below. The majority of patients in the primary treatment groups had complex partial seizures (63%) followed by primary secondarily generalized (54%) and simple partial seizures (44%). The median seizure at baseline was 3.3/week, the mean age at seizure onset was 21 years of age and the mean duration of seizures was 14 years. Demographic values were similar in the low dose treatment group.

Results

Sponsor's Analysis

During the trial there were very few patients identified who escaped as a result of meeting some of the predetermined criteria which were based upon investigator impressions (criteria 3 and 4). As a result the Sponsor performed their own analysis. This analysis, performed by the Sponsor, is more appropriate analysis, and is presented in the table below ("calculated escapes") along with those based upon the analysis determined by the investigator ('investigator determined escapes"). As is apparent large number of additional escapes where identified by the Sponsor, which was not identified by the investigator, however the upper 95% confidence interval of this stricter analysis of the upper limits of the 95% CI (32.1%) for the 300 mg group is still well below the predetermined cut off value of 65.3%. Indeed all calculations for both dosage groups similarly met this criterion. The low rate of investigator identified escapes raises the issue of investigator bias, as there was no true blind (investigators understood that both arms were on drug) and whether there could have been a problem in investigator training. It is noteworthy that these rates were appreciated during the study and the Sponsor attempted to retrain investigators during the study.

Proportion of Subjects Meeting Escape Criteria (Sponsor Results for White Paper PP Population)

	LTG XR 300 mg/day	LTG XR 250 mg/day
Investigator Determined Escapes (based on CRF)		
n/N (%)	6/108 (6)	7/97 (7)
[95% CI]	[1.2, 9.9]	[2.1, 12.4]
Calculated Escapes		
n/N (%)	26/108 (24)	25/97 (26)
[95% CI]	[16.0, 32.1]	[17.1, 34.5]

Source: Sponsor ISE Table 2, 8, 11.

Agency Reviewers' Analysis

Identification of patients who met escape criteria and potential underreporting

The statistical reviewer uncovered a number of issues regarding the Sponsor's analysis of patients fulfilling the various escape criteria. They are as follows

Escape criteria 1 and 2: As some, but not all, white paper calculations used a rolling calculation of 28 day seizure frequency, which is the most conservative mean, the Division's statistical reviewer reevaluated criteria 1 using a rolling calculation. When this was done she identified 3 additional escapes using the 300mg group and 2 additional escapes in the 250 mg group. A similar calculation was performed for the criteria 2, 2 day seizure frequency. But, no additional escapes were identified.

Criteria 3: This criterion compares severity of seizures occurring during the study with those that the patient previously experienced. What is really meant by previous seizures varied from different studies in the white paper. In 4 studies the reference was that to the baseline, while others appeared to use a longer period for reference. The Sponsor, in their calculation used the baseline, which would be the most liberal. The Sponsor was requested to recalculate this using only the baseline period as reference. In doing so 2 more escapes were identified in the 300 mg group and 2 more in the 250 mg group.

Criteria 4: This criterion was the clinically significant prolongation of generalized tonic-clonic seizures. This was fully determined by the investigator. No cases were reported, which was well outside the experience from that of the white paper where anywhere from 4 to 45% of patients in the pseudo-placebo groups where categorized as having met this criteria. Dr. Dinsmore examined the adverse event profile and identified one case that may have fulfilled such a criterion. As this criterion was solely based on the investigators opinion and there was already evidence that investigators underreported events (see above), the statistical and clinical

reviewers believed that this low rate may have been an indication of underreporting, perhaps because of the absence of a true blind.

The statistical reviewer noted that the Sponsor's calculation treated patients who dropped out for reasons other then meeting escape criteria as treatment successes. However, the statistical reviewer noted that the white paper handled that data by censoring such data. To explore this Division's statistical reviewer performed a sensitivity analysis where such patients were treated as escapes [4] (referred to as the "white paper per protocol sensitivity analysis"). An additional sensitivity analysis was performed by the statistical reviewer that included all patients who dropped out who received test drug, even before background drug withdrawal (referred to as the ITT worst case scenario). These data, which includes the above noted additional criteria identified cases, are presented in the table below. These sensitivity analyses still resulted in a positive effect for both dosages (i.e. upper confidence values < 65.3%).

. **Proportion of Subjects Meeting Escape Criteria**

	LTG XR 300 mg/day	LTG XR 250 mg/day
White Paper PP Sensitivity Analysis		
n/N (%)	37/108 (34)	37/97 (38)
[95% CI]	[25.3, 43.2]	[28.5, 47.8]
ITT Worst Case Analysis		
n/N (%)	41/112 (37)	51/111 (46)
[95% CI]	[27.7, 45.5]	[36.7, 55.2]
The 95% prediction limit is 65.3% for all escapes. The 95% prediction limit is 58.6% for escapes in the subgroup of patients with 1 background AED (the subgroup will be mentioned later in the review).		

Comparability to white paper study population

An important element to the use of historical controls is the comparability between the study population and those of the historical control. The clinical reviewers compared different characteristic elements of the historical white paper population with those of study LAM30055. What follows is a point by point discussion of various pertinent characteristics of the two populations.

Background AEDs may indicate general degree of severity of underlying epilepsy and may result in a different propensity of withdrawal type seizures. Indeed the White Paper data suggested that patients on one background AED had fewer escapes than patients on two AEDs. Therefore the reviewers examined the comparability of background anticonvulsants. The percent of patients on two background AEDs in the historical control database varied between studies between 17% and 34%. LAM30055, however, only allowed patients on monotherapy to enter the trial. To examine this issue the statistical reviewer reanalyzed white paper data so

[4] This was similar to the Sponsor's secondary analysis of all cause discontinuation.

as to include only patients with single anticonvulsants. When this was performed a new revised lower limit of 58.6% was obtained. This still leaves the primary analysis and sensitivity analyses of both dosage groups exhibiting a statistically significant affect.

As noted above, a unique feature, at least by today's standards, of studies used in the white paper was that, with the exception of a few Canadian patients, it was performed wholly in the United States. It has not been routinely studied whether populations are comparable across different nations and cultures. This would be dependent on a number of factors including similarity of placebo effect, pharmacogenomic differences and standards of medical practice across nations, and cultures. LAM30055 was conducted in the US and 6 additional nations (Argentina, Chile, Costa Rica, Korea, Russian and Ukraine). A large part (75 %) of patients in this study was recruited outside the US. To examine this, the Division's statistical reviewer performed an analysis of the US patients in LAM30055. In order to increase the sample size patients in both dose groups were pooled. Of note the statistics reviewer identified that US patients, on average, met escape criteria at a higher rate then foreign patients. Nonetheless both the white paper PP and White paper sensitivity analysis appeared to exhibit a positive outcome with the upper 95% confidence interval being 51.5% and 63.9%. The ITT worst case scenario, however, was not positive, with the upper 95% confidence interval being 68.5%.

As a placebo effect between cultures and nations may be a pertinent issue the Sponsor was asked to explore this more thoroughly. The statistical reviewer noted that the Sponsor's exploration revealed that differences were inconsistent. Dr. Dinsmore, the clinical reviewer, notes upon examining the prior Lamictal XR study, which examined this drugs use as adjunctive treatment, that the placebo response in the US was notably larger then across other nations. However, another Lamictal XR study appeared to reveal a higher non-US placebo effect. This clinical analysis, however, is confounded by the fact that the non-US placebo groups in these prior studies were from very different nations. Generally it appeared that India demonstrated little placebo effect and South America a large placebo effect. Considering this variability and cross study comparison, I believe that such data may be difficult to definitively interpret. The clinical reviewer concludes that the use of a US psuedoplacebo comparator with a largely non-US treatment arm is not appropriate. I would, however, add that the analysis performed above in part supports efficacy. Nonetheless, it does detract somewhat from the interpretation of the present study.

Another baseline feature that was explored was that of the baseline seizure frequency, which may reflect upon the severity of the seizure disorder. The inclusion criteria and the actual baseline seizure frequency for Patients admitted to LAM30055 were in the lower range to that used in white paper. Thus, the median baseline seizure frequency for LAM30055 was 1.4 seizures per week for LTG 300 mg/d group and 1.5 for LTG 250 mg/d group, whereas the median seizure frequency in the white paper ranged from 1.4 TO 2.5 seizures per week. To explore this issue the statistical reviewer examined whether there was any relation in patients in the LAM30055 study between baseline seizure frequency and escape rate. If anything, the relationship was the reverse of whet was suspected. Therefore the statistical reviwer concluded this was not an issue.

Different partial seizure subtypes may have different sensitivity to therapeutic agents and perhaps a different natural history; thus, it is frequently thought that complex partial seizures are harder to control then other partial seizure subtypes. The statistical reviewer notes a notable difference in the distribution of seizures in LAM30055 and the pseudoplacebo controls used from the white paper. Thus, the statistics reviewer noted that there 83 to 95% of patients who exhibited complex partial seizures during the baseline period in subjects in 4 studies derived from the white paper for which data was available. This compared to approximately 62% of subjects in Study LAM30055. This was evaluated by demonstrating similar escape rates in both patients with CPS and without CPS in LAM30055.

Of note, no obvious age, sex or race differences in escape rates were noted.

A prior study (US 30/31), which examines the use of lamotrigine as an IR formulation, has been performed and served as the basis for the approval of the IR therapy in monotherapy. This study was similar in methodology (up and down titrations) except it performed superiority analysis of 500 mg/day, divided bid, of the lamotrigine to a pseudoplacebo (valproic acid at 1,000 mg/day). A number of analyses in this IR study were performed, including the evaluation of all patients who left the trial, those meeting escape criteria and a worst case analysis treating dropouts differently between the drug and pseudoplacebo control arm. All analyses, but the worst case scenario, was positive. This led to the labeling of this formulation for monotherapy, but at a higher daily dose.

In general the statistical reviewer noted the principal flaws in this study consisted of the subjective nature of some of the exit criteria (particularly #3 and #4), the absence of a concurrent control arm (allowing the randomization of known and unknown factors that may influence the study outcome) and absence of true blinding. Some of these were examined through a reanalysis by this Division through the various sensitivity analyses described above. These analyses were generally supportive of a conclusion of efficacy. Moreover the statistical reviewer notes that a significant effect was still detected even with a worst case scenario sensitivity analysis of the complete dataset.[5] In general the population differences between groups appeared not to markedly influence the results, with the one exception of the worst case scenario in the US patients. In conclusion the statistical reviewer notes that the data "seem to suggest some evidence of efficacy of LTG XR as monotherapy treatment of partial seizures. However, interpretability of these analysis results is undermined by the limitations of the historical control design..." Dr. Dinsmore, the medical reviewer expressed an opinion that there was adequate evidence to support approval of both studied doses for monotherapy of Lamictal XR of the treatment of partial onset seizures. I essentially agree as did the advisory committee. For further discussions see sections below.

[5] The worst case scenario analysis that separated out the US patients were however negative, but there was likely power loss in such an analysis

7. Safety

New safety data was provided consisting of the present pivotal efficacy trial (LAM30055, n=223) and for patients who continued into an open label extension of this trial (n=195). The Sponsor also included in this submission safety data from Lamictal IR monotherapy trials, which have already been reviewed by this Division as part of our previous action for the approval of monotherapy for the IR product, and some information on an ongoing trial in the elderly. Although, as pointed out by Dr. Dinsmore, monotherapy exposures for Lamictal XR was not great (e.g. total of 223 exposures with, 184 patients exposed for 6 months and only 2 patients exposed for 1 year or greater) this was more then made up for by Lamictal XR exposures in adjunctive studies. I would also add there is substantial experience of exposure of Lamictal IR in monotherapy trials, which tended to be at higher daily doses then that studied for XR.

One important caveat to the present new safety data base is that there was no placebo control; indeed, it is also questionable if one can consider study LAM30055 a truly blinded studied. As a result of both these factors definitive causality is difficult to determine.

No deaths were observed during treatment in the new monotherapy XR study database. One death was observed from hepatocellular cancer 9 months after drug withdrawal, which Dr. Dinsmore notes was clearly not a result of drug treatment.

Eight patients suffered from 10 serious adverse events in study LAM30055. Four of these events were related to seizures (e.g. seizure leading to head injury, seizure leading to an MVA, grand mal seizure and seizure with secondary generalization). Such events would not be unexpected in this population. One rash was labeled as an SAE. Serious rashes are presently labeled. The remainder of events (brain neoplasm, upper GI bleeding, and hepatic neoplasm (with background viral cirrhosis), as per Dr. Dinsmore, could not be attributed to drug. I agree. Four serious adverse events were observed in the open label phase, two related to accidents (unrelated to seizures) and 2 to seizures. None of these are necessarily unexpected in the background of the present disorder.

Dropout rates due to adverse event were 10% in the 250 mg/day group and 4% in the 300 mg/day groups in LAM30055. The most frequent reason for drop out was rash, as may be expected from the known adverse reactions of this drug, with 8 out of the 223 patients receiving either of the doses dropping out for this reason. Other reasons for dropping out could not easily be attributed to drug.

Common adverse events observed in this study were generally similar to those observed and attributed to drug in adjunctive and monotherapy of immediate-release lamotrigine and adjunctive treatment of Lamictal XR. Only 2 adverse events, nasopharyngitis and upper respiratory tract infection, were observed at a rate of $\geq$ 3% and not reported at a similar rate in previous studies. As noted above, because this study did not include a placebo control group, causality could not be established.

Dr. Dinsmore performed his own postmarketing analysis using the AERS database comparing the last year to a variety of previous years could not identify a new significant signal.

In summary, there are no new signals identified in the present database.

8. Advisory Committee Meeting

As the approval of an AED based upon historical controls would be a precedent, an Advisory Committee was convened.

The Committee discussed the ethics of performing a placebo control trial, as this was predominant reason for performing an historical control trial. They concluded that placebo control trials are unethical in the study of the patient population in this disorder. But, they also noted that placebo control trials may be possible in some subpopulations (patients admitted for seizure surgery evaluation) and other types of epilepsy for which there is no treatment,

In a vote the committee voted unanimously that historical control trials, like the one performed, can be acceptable under the specific circumstances in which the drug is already known to be effective as adjunctive treatment. There was some concern of regarding heterogeneity of the historical pseudo-control groups in the French et al analysis and some of the committee members expressed concern about combining all escape criteria into one analyzable statistic.

The committee agreed that it is important to match the study population use in historical control trial with a number of features of the pseudo-placebo controls historical comparator. Thus, it is important to match demographics, initial concomitant antiepileptic drugs, differences in conversion methods, temporal trends in response, and dropouts. Some of these were not well matched in the present study. In particular the present study had few US participants and had few patients dropping out as a result of criteria #4. One of the statisticians referred to the publication by Stuart Pocock (Journal of Chronic Disease, 1976), who described a number of criteria that historical control study should meet[6]. Although not specifically discussed, while some Pocock;s criteria are met, not all were met in the present study.

[6] Although not specifically discussed Pocock's criteria require that the historical control groups meets the following conditions: I) must have received a precisely defined standard treatment which must be the same as the treatment for the randomized controls, 2) must have been part of a recent clinical study which contained the same requirements for patient eligibility, 3) the methods of treatment evaluation must be the same, 4) the distributions of important patient characteristics in the group should be comparable with those in the new trial, 5) the previous study must have been performed in the same organization with largely the same clinical investigators, 6) there must be no other indications leading one to expect differing results between the randomized and historical controls. For instance, more rapid accrual on the new study might lead one to suspect less enthusiastic participation of investigators in the previous study so that the process of patient selection may have been different.

The Advisory Committee generally agreed that issues of the comparability between the present study and those used in the historical control studies with regard to a number of factors were problematic. These factors included potential for bias due to the fact that all patients are receiving active treatment (i.e. the study was not truly blinded), potential bias due to under-reporting of study endpoints (probably related to the lack of a true blind), number of background AEDs, the comparability of exit criteria in this study and in the historical control, percent of United States (US) data vs. foreign data. Some of these were explored in the Division's sensitivity analyses.

In a question as to whether the "sponsor submitted substantial evidence of effectiveness for Lamictal XR as monotherapy for the treatment of partial seizures" 10 members voted yes, 2 voted no and 1 abstained. All those who voted yes noted that the fact that Lamictal IR was approved for monotherapy was critical to their affirmative vote.

In view of the concerns about the comparability of the present trial to those used in the historical controls the Advisory Committee was asked, if the trials were more comparable would they have required another monotherapy trial to be positive. They noted that had there been an adequate match between active and historical control groups they would have recommended approval, even in the absence of another study.

9. Pediatrics

The present study contained 32 pediatric patient (≤ 16 years of age), which is over 13% of the total population. Historical control studies included 14 patients (5 additional patients were 17 years of age). Analysis in the white paper revealed no age effect. Logistic statistical analysis did not observe age as a factor in the effect in study LAM30055. Although one may argue that the power of such analyses is probably low. Importantly labeling for adjunctive dosing is identical for adults and children 13 to 16 years of age for both the IR and XR population. All of these factors indicate that there is adequate evidence for these studies to allow labeling in children 13 to 16 years of age.

The sponsor requests a partial waiver from conducting a study evaluating conversion to monotherapy with LAMICTAL in pediatric patients with partial seizures age 1 month to 16 years who are receiving therapy with a single antiepileptic drug. The sponsor believes that conducting such a trial would not be feasible for ethical reasons as there is an absence of a suitable comparator group. This reviewer completely agrees with this. A waiver was previously granted for expansion of the monotherapy indication language for the IR formulation of Lamictal for same for this reason when the Sponsor requested the division to reexamine the requirement to fulfill a previous PREA commitment to perform studies on the conversion from valproic acid to Lamictal monotherapy[7]. The reasons given for this waiver were: 1) conducting a placebo-controlled trial would not be feasible due to ethical considerations, and historical control studies are not possible due to the lack of suitable historical data. This waiver should also apply for the present study

[7] This requirement was requested before the epilepsy community concluded that such studies were unethical

As per our policy we are waiving the pediatric study requirement for ages birth up to 1 month because the necessary studies are impossible or highly impracticable, as there are too few children in this age group with the disease to study.

10. Other Relevant Regulatory Issues

DSI examined three sites in the pivotal trial, one in the US, one in the Ukraine and one in the Argentine. The Argentine site was found lacking in that: 1) there was failure to report adverse events in two patients there, 2) incorrect total daily doses (lower then iy should have been)of study drug for a five week period, 3) proper medication dosing records were not kept on all subjects, 4) randomization was assigned without waiting for a fax of the "randomization confirmation form. As both groups won, it is unlikely that this error would affect the final results. Nonetheless, an analysis excluding this site was study positive. Other issues that describe problems in the performance of this study can be found in the section on efficacy.

Dr. Dinsmore, the Medical reviewer, reviewed the financial disclosure information acceptable. *This section would include:*

11. Labeling

For details of the final label the reader is referred to the label. Three predominant issues were raised during the labeling, these were as follows:

- Because enzyme inducer AEDs were not permitted during the study, labeling of dosing regimen and schedule for these was based upon experience with the IR and an understanding of the interaction of such drugs and Lamictal XR metabolism. Clinical Pharmacology (Dr. Ta-Chen Wu) provided input on this and agreed to the final labeling (see above).
- The adverse event section provided more of a qualitative, than quantitative, description of adverse reactions as there was no placebo group.
- The pregnancy section of the label was updated. While this was mostly format in nature, the Pharm Tox team leader (Lois Freed) examined some additional new animal data, the information of which was included in the label.

12. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

There is a consensus, which includes the statistical reviewer, medical reviewer, the Division Director (Russell Katz) and our advisory Committee that there is reason to approve Lamictal XR for the monotherapeutic treatment of partial onset seizures for both studied doses. While the historical control trial was not ideal for many reasons, as described above, a number of

factors mitigated these problems. Thus, the statistics reviewer demonstrated that a statistically significant effect was observed in all, but the absolutely most strict (worst case scenario), sensitivity analyses performed to correct for these study insufficiencies. Moreover, Lamictal IR had previously been approved for monotherapy, albeit at a higher dose. The dose studied for Lamictal XR was lower and similar to the dose used in adjunctive treatment. It is noteworthy that for drugs used as both adjunctive and monotherapeutic treatment, the dosages used frequently overlaps.

- Risk Benefit Assessment

Lamotrigine has been marketed for a number of years. No new risks have been identified in the present application. The XR preparation may increase the ease of dosing with the potential to increase compliance.

- Recommendation for Postmarketing Risk Management Activities

All lamotrigine products have the requirement for the distribution of a MedGuide. This was originally a result of the need to inform patients of the potential suicidality risk for all anticonvulsants. Other important information, however, such as that of serious skin reactions, are included in the MedGuide. The MedGuide is distributed in the form of REMS (e.g. requiring a scheduled REMS evaluation). Up to recently all MedGuides had to be approved as a REMS. The process has now changed, so that MedGuides may be distributed outside of a REMS. Both OSE and this Division have come to the consensus that, short of a compelling reason, although a MedGuide is necessary for anticonvulsant products, they need not be part of a REMS. Therefore, in the process of this review a decision was made to maintain the MedGuide, but not to include it under a REMS. The Sponsor has agreed to this. The Division is maintaining the MedGuide bit withdrawing the REMS requirement.

- Recommendation for other Postmarketing Study Commitments

None.

- Recommended Comments to Applicant

None.

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/s/

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NORMAN HERSHKOWITZ
04/25/2011

Reference ID: 2938159

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-115/S-006

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	22115
Priority or Standard	Standard
Submit Date(s)	3/31/2010
Received Date(s)	3/31/2010
PDUFA Goal Date	1/31/2011
Division / Office	DNP
Reviewer Name(s)	Steven T. Dinsmore
Review Completion Date	
Established Name	Lamotrigine
(Proposed) Trade Name	Lamictal XR
Therapeutic Class	Anticonvulsant
Applicant	GSK
Formulation(s)	XR = extended release
Dosing Regimen	Oral, once daily
Indication(s)	Conversion to monotherapy
Intended Population(s)	Adults and Children age 13 and above receiving treatment with a single AED

Template Version: March 6, 2009

Reference ID: 2937647

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

There is adequate support for approval of Lamictal XR for use in conversion to monotherapy for patients ≥13 years of age who are receiving treatment with a single AED. The recommended target dose is 300mg daily, although the 250mg/day dose remained superior to the pseudoplacebo, this dose was not the protocol directed primary efficacy endpoint.

It is also noted that advisory committee was convened on March 10, 2011 to advise on the validity of the historic controlled methodology of the pivotal study LAM30055 and the adequacy of this study to support the efficacy of LAMICTAL XR monotherapy. The committee agreed that historic control methodology utilized by French et al. is an acceptable method and the majority agreed that the sponsor submitted substantial evidence of effectiveness for Lamictal XR as monotherapy treatment.

1.2 Risk Benefit Assessment

Lamotrigine has established efficacy in epilepsy treatment and the immediate release form is currently approved for conversion to monotherapy in patient's receiving treatment with a single AED. Availability of the extended release form would be of benefit to those patients currently taking Lamictal XR who are candidates to switch to monotherapy. There is no new risk related to the active ingredient that has not already been identified by the extensive experience with immediate release lamotrigine. Additional benefit may be anticipated from greater ease of compliance with a Lamictal XR monotherapy dosing program.

This application was supported by study LAM30055 where a dose of 300mg/day Lamictal XR compared to historic control was the primary endpoint. This dose is lower than the approved monotherapy dose for LTG IR of 500mg/day (250mg twice a day). The data from study LAM30055 reveal that the escape rate for both LTG XR 300mg and 250mg is less than the lower bound prediction interval in both of the sensitivity analysis performed by the FDA statistician. In addition the sponsor provides additional support by the observation that LTG IR at 150mg / day has shown efficacy similar to CBZ 600mg/day, LTG IR dose was also chosen in a study where LTG IR was given concurrently with background EIAEDs during transition to LTG IR monotherapy. In the conversion interval, when the effective dose of lamotrigine approximated 250mg/day, superiority over the pseudoplacebo treatment arm was observed. Overall the efficacy findings of study LAM30055 and the supportive arguments by the sponsor indicate the 250mg to 300mg/ day dose are adequately effective as monotherapy treatment.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Medication guide dispensed with each LAMICTAL prescription with REMS assessment using a survey of patient understanding of serious LAMICTAL risks at 18 months, 3 years and 7 years.

1.4 Recommendations for Postmarket Requirements and Commitments

none

2 Introduction and Regulatory Background

2.1 Product Information

LAMICTAL® (lamotrigine, LTG), a phenyltriazine anticonvulsant, was first approved in the United States (US) in December 1994 (New Drug Application [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 also 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. More recently, LAMICTAL was approved for primary generalized tonic-clonic (PGTC) seizures in September 2006 in adults and pediatric subjects (2-16 years of age).

An extended-release (LTG XR) formulation of lamotrigine (NDA 22-115; LAMICTAL Extended-Release Tablets) is currently approved for use as adjunctive therapy of partial seizures and PGTC seizures in patients thirteen years and older. The current application seeks approval of LTG XR for conversion to monotherapy in subjects ≥13 years of age with partial seizures at target maintenance doses of 250mg to 300mg / day

2.2 Tables of Currently Available Treatments for Proposed Indications

This topic has been fully covered in the application for Lamictal XR for adjunctive treatment of primary generalized tonic-clonic seizures (NDA 22509)1

1. Dinsmore S. Medical Officer Review, NDA22509. Product: Lamictal XR, Indication: Oral, once daily adjunctive treatment for primary generalized tonic clonic (PGTC) seizures. 1/28/2010

2.3 Availability of Proposed Active Ingredient in the United States

Lamotrigine is approved in the US as immediate release and extended release forms for several indications noted in section 2.1

2.4 Important Safety Issues with Consideration to Related Drugs

Lamotrigine (LAMICTAL, 3,5-diamino-6-(2,3-dichlorophenyl)-as-triazine) is a phenyltriazine and is chemically unrelated to other marketed anitiepileptic drugs (AEDs). The precise mechanism(s) by which lamotrigine exerts its anticonvulsant effects is unknown. In vitro pharmacologic studies suggest that lamotrigine inhibits voltage sensitive sodium channels thereby stabilizing neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (primarily glutamate and aspartate).

Neurobiology of-Modulation of the gating of brain sodium channels is believed to account, at least in part, for the ability of several other AEDs to protect against generalized tonic-clonic and partial seizures. These AEDs include phenytoin, carbamazepine, oxcarbazepine and zonisamide, and possibly felbamate, topiramate and valproate[2].

Although lamotrigine may share sodium channel action with several other anticonvulsants the chemical moiety is unrelated and there is no overlap of major unique safety issues with these other sodium channel modulators. There is overlap in the common anticonvulsant adverse effects.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The unique regulatory issue of this submission is the absence of an internal control. The drug recipient test group of the pivotal trial for this submission is compared to an historical control group. This historic control method is fully discussed in section 6. On July 24, 2009 there was a teleconference between the FDA and representatives of GlaxoSmithKline to discuss GSK plans for this sNDA (use of Lamictal XR for conversion to monotherapy). GSK proposed use of an historic control devised based on a White Paper by French et.al. At this meeting the FDA stated "a single clinical study using a historic control could potentially be sufficient to support approval for monotherapy of partial onset seizures after having previously been determined to be effective by adequate and well controlled clinical trials for adjunctive treatment. Lamictal XR has been approved as adjunctive therapy in adults with partial seizures. Therefore, a single clinical study using a historic control might be sufficient to support approval of LTG XR for conversion to monotherapy in adults with partial seizures.

2 Rogawski MA, Löscher W. The Neurobiology of Antiepileptic Drugs. Nature Reviews Neuroscience 2004;5(7):553-564.

Whether the recently completed study LAM30055 will be adequate to support approval will be a review issue at the time of NDA submission"

No SPA for this development plan was submitted.

2.6 Other Relevant Background Information

The historic control monotherapy methodology presented in the White Paper and in the published version, "Historical control monotherapy design in the treatment of epilepsy"[3] springs from a concern that patient safety is compromised in the traditional path to approval for monotherapy. Most approvals for monotherapy have been achieved using a trial design known as the "pseudo-placebo withdrawal to monotherapy study", which assigns treatment resistant patients to receive study drug or a suboptimal maintenance dose of a safe and effective active drug. Those in the pseudoplacebo arm of the study are at risk of breakthrough seizure.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The reviewer is concerned about two patients with SAEs identified in the LAM30055 study report (Table 26) and the summary of clinical safety (Table 24) (SCS). In both cases a traumatic event was apparently the primary reason for the designation of "serious" adverse event. In Patient #62 the event was "trauma craniocerebral", in the second case, patient # 810 the event was "possible concussion". In both cases the underlying cause of these traumas was a seizure. The causative basis of seizure was not indicated in the discussion section or tables of non-lethal serious adverse events. This is a deficiency in an anticonvulsant study where knowledge of the frequency of epilepsy related adverse events is always important.

The fields from the serious adverse events section of the case report forms for both patients are shown below. The relationship of the trauma to seizure is noted in the "general narrative comment" field. It should be intuitive in the construction of a study report or summary of clinical safety for an anticonvulsant study that involvement of a seizure in a serious adverse event should be prominent in discussion or included in the table of serious adverse events.

Patient ID 62:

3 French JA, Wang S, Warnock B, Temkin N. Historical control monotherapy design in the treatment of epilepsy. Epilepsia 2010;51(10):1936-1943

FIELD 4a: Serious Adverse Event- trauma craniocerebral
FIELD 5: Specify the reason for considering this an SAE-
Is life-threatening Requires hospitalization or prolongation of existing hospitalization
FIELD 12: General narrative comments: head injury as a result of seizure; hospitalization

Patient 810:

FIELD 4a: Serious Adverse Event- Possible Concussion
FIELD 5: Specify the reason for considering this an SAE-
Requires hospitalization or prolongation of existing hospitalization
FIELD 12: General narrative comments: Subject was in a motor vehicle accident while having a seizure. He was admitted into the hospital because of a possible concussion, and the seizure.

3.2 Compliance with Good Clinical Practices

The sponsor identified a site with systematic protocol violations. A site in Costa Rica, #27083 was not using the study drug prescription forms and was not properly maintaining the bulk drug accountability log. Return of used drug by subjects was also not being recorded consistently. In addition placebo which was used as blinding instrument to balance pill count was no used in a consistent manner. As a result, dosing errors may have occurred for some subjects, including errors during the period of dose escalation. Because the record keeping did not a allow GSK to pinpoint problems with specific subjects, it was decided to exclude all data from all subjects at this site from the per protocol analysis but data from this site was retained in the ITT analysis.

Our statistical reviewer was appraised of that the sponsor retained site 027083 in the ITT analysis and was asked to re-analyze the efficacy results of the ITT population with this site removed. She found that with this site removed the ITT population analysis still remained below the lower bound of the prediction interval.

Three sites for DSI inspection from study LAM30055 were selected, one from the Ukraine due to a large influence on the primary outcome measure, a second from the US, representing the largest US enrollment and with 2 protocol violations and the third from Argentina, also with a large influence on the primary outcome measure.

The Argentine site was found to have several protocol violations and study site procedural violations. For two patients there was failure to report adverse events. An additional two patients received incorrect total daily doses of study drug for a five week period. In each case the dose was lower than protocol directed dosing. Proper medication dosing records were not kept on all subjects. Randomization was assigned without waiting for a fax of the "randomization confirmation form". Due to concerns about reliability of data from this site the statistical reviewer was requested to perform a

sensitivity analysis of LAM30055 efficacy results with this site excluded. The statistical reviewer found that the study results were not changed by exclusion of this site.

3.3 Financial Disclosures

None of the investigators in study LAM30055 had disclosable financial interests at initiation of their study participation. The sponsor does note that 12 (2.4%) of investigators did not have financial disclosure update information available when needed for documentation at the time of this NDA. The sponsor does note that "based on information available internally, none of the clinical investigators listed below had disclosable interests.

Reviewer comment: According to the sponsor the absent information is update information with no conflict present for these investigators initially. Although 21 CFR part 54 requires update of financial disclosure during the study and up to 1 year after completion for investigators whose disclosure status changes to meet disclosure requirements, this section does not require spontaneous re-update of information. In the event that any of these 12 investigators had an unreported change in status with potential influence, their influence will be limited because none are principle investigators and there is not more than one of these investigators at a site.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

N/A for this application

4.2 Clinical Microbiology

N/A for this application

4.3 Preclinical Pharmacology/Toxicology

No new non-clinical data have been generated for LTG XR.

4.4 Clinical Pharmacology

The PK and drug interactions of LTG, administered as the IR tablet has been well established (NDA 20-241, approved December 1994). These data are summarized in the prescribing information for LTG XR [LAMICTAL XR Extended-Release Tablets Package Insert, 2009]. No further PK or drug interactions studies were conducted to support this application.

4.4.1 Mechanism of Action

N/A

4.4.2 Pharmacodynamics

N/A

4.4.3 Pharmacokinetics

N/A

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1 Table of White Paper Monotherapy Trials Including LAMICTAL IR (study 30/31) and LAMICTAL XR (study LAM30055)

Study[1]	N	Mean Age (years) (range)	Gender (%, M/F)	Study Locations	Race (%) (White/Black/ Other)
1	94	35 (14-63)	54:45	US, Canada	NA
2 (US 30/31)	80	36 (14-71)	40:60	US	69/14/18
3	24	35 (NA)	38:63	NA	83/4/13
4	32	NA	NA	NA	NA
5	45	35 (18-53)	53:47	US	87/--/13
6	46	36 (11-66)	41:59	US	NA
7	22	38[2] (18-62)	NA	US	NA
8	55	35 (17-67)	36:64	NA	85/9/5
LAM30055 300 mg/day	112	34 (13-80)	50:50	US, Latin America, Ukraine, Russia, Korea	86/4/10
250 mg/day	111	33 (13-59)	59:41		86/4/10

5.2 Review Strategy

Create as discussion unfolds

5.3 Discussion of Individual Studies/Clinical Trials

Pivotal Study LAM30055

This was a double-blind, randomized, historic-control study comparing the premature discontinuation rate for 2 doses of LTG XR (300 and 250mg/day) to an historic escape rate determined from aggregated pseudoplacebo data [French, 2005]. The purpose of the study was to demonstrate the effectiveness of a lower monotherapy lamotrigine dose than the currently-approved 500mg/day in subjects with partial epilepsy who were receiving AED monotherapy with VPA or a non-enzyme inducing AED (non-EIAED) but were still experiencing partial seizures. The study used a conversion to monotherapy design in which eligible subjects had LTG XR added to their current therapy (background AED) followed by gradual withdrawal of the background AED.

Screen and Baseline

Subjects who met eligibility requirements during screening entered an 8-week, non-interventional Baseline Phase to establish a 28-day baseline seizure frequency. Adequately documented historic seizure data and AED dosing information could be substituted for up to the first 4 weeks of baseline data with approval from GSK.

The baseline seizure frequency criterion was ≥4 partial seizures with ≥1 seizure occurring in each 28-day interval of the 8-week Baseline Phase. Subjects who did not meet this criterion (Baseline Failures) were allowed to enter the Continuation Phase for up to 24 weeks, if clinically appropriate.

Double Blind Treatment Phase

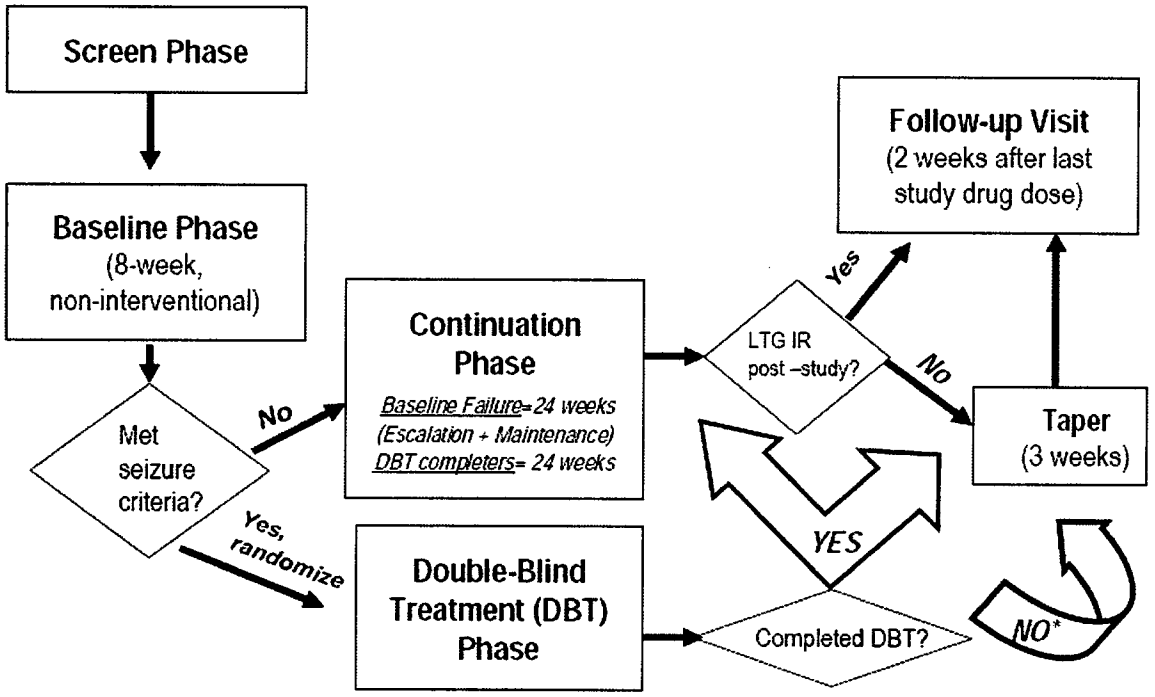
Subjects who met the baseline seizure criterion entered the Double-Blind Treatment Phase and were randomized (1:1) to receive LTG XR at either 300mg or 250mg given once daily. During the Conversion Phase, subjects underwent escalation to the LTG XR target dose and gradual withdrawal of the background AED. Subjects started the 12-week Monotherapy Phase when withdrawal of the background AED was complete.

No new AEDs could be added during the Baseline or Double-Blind Treatment Phases. Chronic benzodiazepine use for epilepsy management was prohibited, but acute benzodiazepine use as rescue medication was allowed with restrictions.

Continuation Phase

All enrolled subjects could participate in the open-label Continuation Phase, if appropriate. The Continuation Phase consisted of up to 24 weeks of additional monotherapy with LTG XR to allow for gathering additional, long-term safety information.

Figure 1 LAM30055 Study Design Schematic



Unless approval is given by GSK Medical Monitor

Abbreviations: DBT = double-blind treatment; LTG = lamotrigine; IR = immediate-release; GSK = GlaxoSmithKline

Figure 2 LAM30055 LTG Escalation and Background VPA taper schedule (Subjects on background VPA)

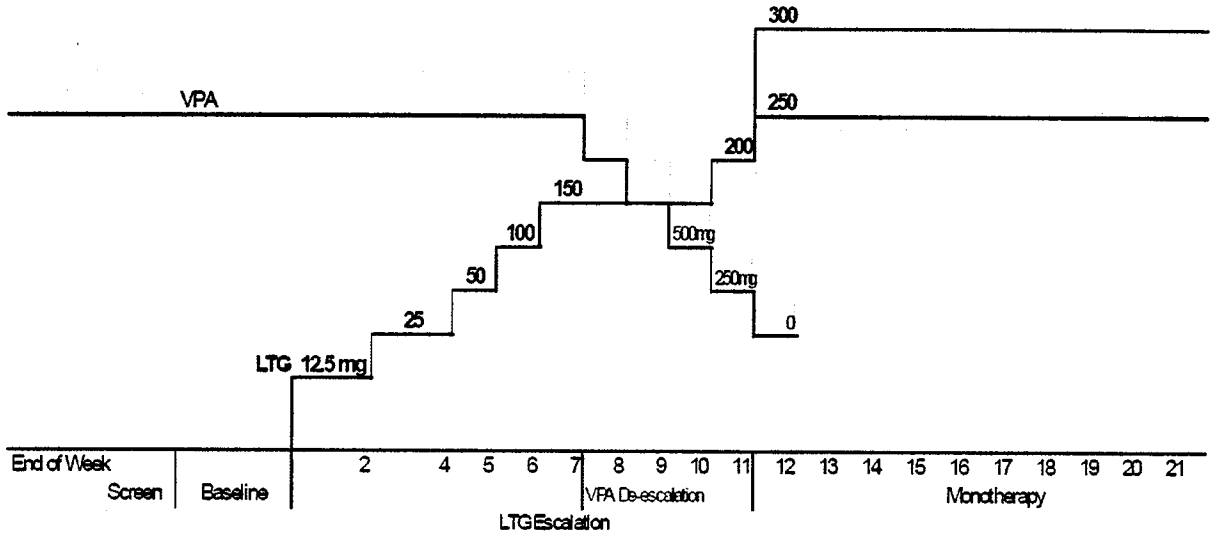
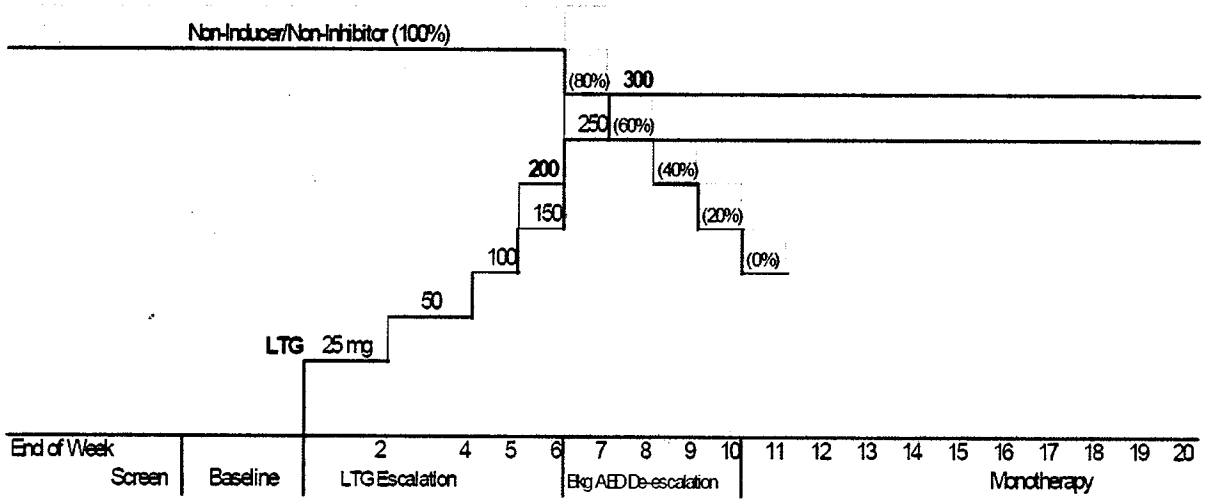


Figure 3 LAM30055 LTG Escalation and Background AED taper schedule (Subjects receiving neither VPA nor an EIAED)



Study Population

Inclusion Criteria

1. Male or female ≥ 13 years of age
2. Confident diagnosis of epilepsy with partial seizures for at least 24 weeks prior to baseline phase
3. documented history of partial seizures and the investigator had judged that the subject was likely to have at least 4 partial seizures during the 8 week baseline phase.

4. had experienced at lest 4 partial seizures (i.e., simple or complex partial seizures with or without secondary generalization) during an 8 week prospective baseline phase with at least one partial seizure occurring during each 4 week period. Note: with prior authorization from GSK, retrospective data could take the place of up to the first 4 weeks of the baseline phase for subjects providing reliable documentation of the following

a. a complete daily seizure diary that included the number, and type (i.e., simple or complex partial seizures with or without secondary generalization) of seizures experienced each day for up to 28 consecutive days immediately prior to the prospective Baseline Phase.
b. stability of prescribed dosages of background AED.
c. compliance with background AED.

All subjects permitted to use retrospective baseline data must have completed a minimum of 4 weeks (i.e., 28 days) of the prospective Baseline Phase. The retrospective plus the prospective Baseline Phases must equal the 56 consecutive days prior to start of dosing with study drug.
5. Was currently receiving AED monotherapy treatment with a stable regimen for at least 4 weeks prior to starting the Baseline Phase.
6. Was able and willing to maintain an accurate, complete, written daily seizure diary, or had a parent/caregiver who was able and willing to maintain an accurate, complete, written daily seizure diary for the entire duration of the study.
7. was able to comply with dosing of study drugs, background AED, and all study procedures.
8. Understood and signed written informed consent, or had a parent or a legally authorized representative who had done so, prior to the performance of any study assessments.
9. If female, and of childbearing potential, was using an acceptable form of birth control, to include one of the following: * see appendix 9.4.1

Exclusion Criteria

1. Exhibited any primary generalized seizures (e.g., absence, myoclonic, primary generalized tonic-clonic seizures).
2. Had status epilepticus within the 24 weeks prior to, or during, the Baseline Phase.
3. Was taking an EIAED (e.g., carbamazepine, phenytoin, phenobarbital, primidone) or was taking more than 1 background AED.
4. Was currently taking lamotrigine or had previously had an adequate trial of lamotrigine.
5. Was currently taking felbamate.
6. Was using hormone therapy.
7. Was abusing alcohol and/or other substance(s).
8. Had taken an investigational drug within the previous 30 days or planned to take an investigational drug anytime during the study.

9. Was receiving chronic treatment with any medication that could have influenced seizure control.
NOTE: Use of benzodiazepines was allowed as rescue medication, limited to 2 acute uses during each of the baseline, conversion and monotherapy phases.
10. Was currently following the ketogenic diet.
11. Was using vagal nerve stimulation
12. Was planning surgery to control seizures during the study.
13. Was pregnant, breastfeeding, or planning to become pregnant during the study or within the 3 weeks after the last dose of study drug.
14. Was suffering from acute or progressive neurological disease, severe psychiatric disease, or severe mental abnormality that was likely to interfere with the objectives of the study.
15. Had any clinically significant cardiac, renal, hepatic condition, or a condition that affected the absorption, distribution, metabolism or excretion of drugs.

6.1.2 Demographics

Table 2 LAM30055 Study Demographics

Demographic Characteristic	LTG XR 300mg/day N=112	LTG XR 250mg/day N=111
Age (years)		
Mean (SD)	33.8 (14.33)	32.9 (12.60)
Range	13-80	13-59
Age Group (years), n (%)		
<16	10 (9)	7 (6)
16-65	100 (89)	104 (94)
>65	2 (2)	0
Gender, n (%)		
Female	56 (50)	66 (59)
Male	56 (50)	45 (41)
Ethnicity, n (%)		
Hispanic/Latino	33 (29)	30 (27)
Not Hispanic/Latino	79 (71)	81 (73)
Race, n (%)		
African American/African Heritage	5 (4)	4 (4)
Asian - East Asian Heritage	11 (10)	11 (10)
White - Arabic/North African Heritage	0	2 (2)
White – White/Caucasian/European Heritage	**96 (86)**	**94 (85)**
National Origin		
US	28 (25%)	28 (25%)

Ukraine	33 (29%)	27 (24%)
Russia	15 (13%)	20 (18%)
Argentina	14 (12%)	13 (12%)
Korea	11 (10%)	11 (10%)
Costa Rica	7 (6%)	9 (8%)
Chile	5 (4%)	5 (4%)

Demographic characteristics were comparable between the treatment groups with the exception of fewer females in the LTG XR 300mg/day group (50%) relative to the LTG XR 250mg/day group (59%). Mean age was 33.8 and 32.9 years, respectively, and the majority of subjects in both treatment groups were 16 to 65 years, not Hispanic/Latino, and of White – White/Caucasian/European Heritage, table 2.

National Origin: A total of 226 subjects (n = 113 per treatment group) were randomized from 7 countries. The majority of these subjects were randomized in the Ukraine (29% [LTG XR 300mg/day] and 24% [LTG XR 250mg/day]), the US (25% for both groups), and the Russian Federation (13% and 18%, respectively). The remaining subjects were randomized in Argentina (12% for both groups), Korea (10% for both groups), Costa Rica (6% and 8%, respectively), and Chile (4% for both groups), table 2 above. Finally, subjects were randomized at a total of 57 sites with no single site randomizing more than 7% of all subjects..

6.1.3 Subject Disposition

Table 3 LAM30055 Subject Disposition

	LTG XR 300mg/dayN =113	**LTG XR 250mg/dayN =113**
Completion status, n (%)		
Completed study[1]	94 (83)	79 (70)
Prematurely withdrawn	19 (17)	34 (30)
Reason for premature withdrawal, n (%)		
Adverse event (AE)	4 (4)	10 (9)
Lost to follow-Up	0	4 (4)
Protocol violation	0	4 (4)
Subject decided to withdraw from the study	9 (8)	8 (7)
Insufficient therapeutic response	6 (5)	7 (6)
Other, specify[2]	0	1 (<1)

1. A subject was considered to have completed the study if (s)he completed the Baseline, Conversion and Monotherapy Phases of the study.
2. Other, specify = Subject 130 withdrew due to pregnancy

Fewer subjects were prematurely withdrawn from the LTG XR 300mg/day group (17%) relative to the LTG XR 250mg/day group (30%). This difference was due to fewer subjects in the 300mg/day group who were discontinued due to AE(s), lost to follow-up, and discontinued with protocol violations. The most common reason for withdrawal from the 300mg/day group was "subject decided to withdraw from the study" (8%). For the 250mg/day group, AE was the most frequent cause for withdrawal (9%).

Study 30/31

Introduction

Study 30/31 was the pivotal trial for approval of Lamictal IR for conversion to monotherapy in patients with partial seizures. This study represents two studies, 30 and 31 which were combined due to slow enrollment. They were combined prior to breaking the blind in order to ob tin one study with the required sample size. These studies were of identical design. The primary objective of the study was to compare the efficacy and safety of Lamictal monotherapy 500mg/day to valproate monotherapy 1000mg/day in adult outpatients. Efficacy was based on the proportion of patients who discontinued treatment due to meeting escape criteria. Study 30/31 was also study number 2 of the White Paper Table 1) whose valproate treatment arm contributed to the aggregate pseudoplacebo group of the White Paper.

Study 30/31 is included as a supportive efficacy study in this sNDA. The design of study 30/31 was similar to study LAM3005. A full description of study 30/31 may be seen in the review of efficacy p43.

6 Review of Efficacy

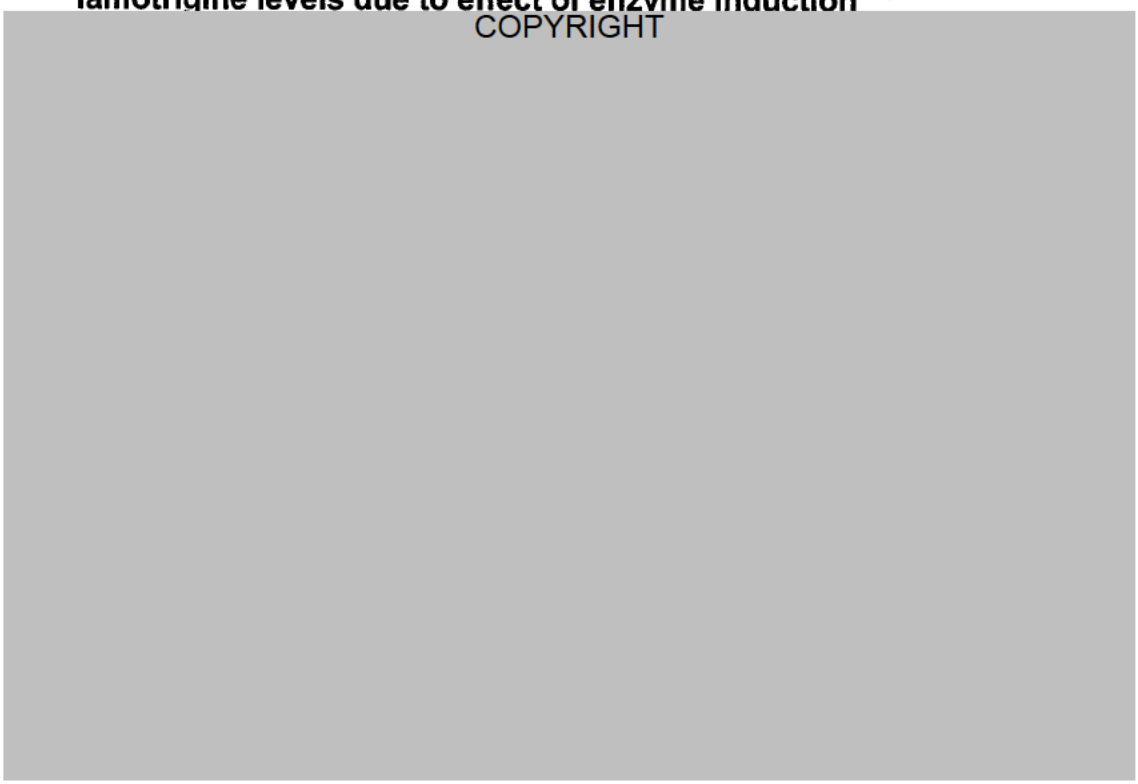
6.1 Analysis of Clinical Information Relevant to Dosing Recommendations

The sponsor has requested an indication for 250mg/day to 300mg/day for use in conversion to monotherapy at a dose of 250mg/day to 300mg/day in patients ≥ 13 year of age with partial seizures who are receiving treatment with a single AED. There is some contrast between this dose and the approved dose of LAMICTAL IR for conversion to monotherapy which is 500mg/day. In addition the approved dose for LAMICTAL IR as adjunctive therapy for patients on enzyme induction neutral AEDs is 300mg/day to 400mg/day.

The sponsor supports this lower target therapeutic range with the results of study LAM30055 discussed in section 6.1, the combined statistical & Clinical Review of Efficacy. The historical control design of this study was accepted unanimously by an advisory committee meeting (section 9.3). The results of of the study were accepted as substantial evidence of effectiveness for Lamictal XR as monotherapy were also accepted by the committee.

The sponsor indicates the choice of Lamictal XR dose in study LAM30055 is supported by the observation that a separation was seen between Lamictal IR and patients on pseudoplacebo (VPA 1000mg/day), between weeks 4 and 10, during and following the conversion interval from enzyme inducing AEDs (carbamazepine & phenytoin). During this interval, although the patient is on 500mg /day of Lamictal IR, the effective dose is approximately 250mg due to the 2 fold increase in metabolism of lamotrigine caused by enzyme induction (figure 4). Addition support for the dose of 250mg/day and 300mg/day in study LAM30055 is provided by a double blind study of lamotrigine monotherapy 150mg/day compared to carbamazepine 600mg/day. In this study In addition lamotrigine IR at a median dose of 150mg has demonstrated effectiveness similar to carbamazepine in an active comparator study[4].

Figure 4 Kaplan-Meier distribution curve of time to escape showing separation of Lamictal IR from Pseudoplacebo during interval of depressed lamotrigine levels due to effect of enzyme induction[5]



Reviewer Comment: The choice of Lamictal XR dose for study LAM30055 is lower than Lamictal IR monotherapy based on pharmacokinetic observations of the

4 Bodie MJ, Richens A, Yuen AWC. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. The Lancet 1995;345:476-479.
5. Gilliam F, Vasquez B, et al. An active-control trial of lamotrigine monotherapy for partial seizures. Neurology1998;51:1018-1025.

conversion phase of study 30/31 and an active comparator trial of lamotrigine and carbamazepine in newly diagnosed seizures. This choice was supported by the outcome of study LAM30055 as discussed in section 6.1 and 9.3.

6.1 Combined Statistical & Clinical Review of Efficacy

6.1.1 Executive Summary

Statistical Reviewer Summary

This supplemental New Drug Application (sNDA) consisted of a single pivotal clinical study (Study LAM30055) evaluating conversion to monotherapy with LTG XR in subjects 13 years of age and older with partial seizures using an historical control from the White Paper (see French et al, Epilepsia 20106 for the published version of the White Paper). The use of historical control for monotherapy was mainly due to ethical and clinical consideration. However, due to lack of internal control, Study LAM30055 suffered from the common problems that usually arose in historical controlled trials, such as potential bias, non-comparability of treatment groups to the historical control, and difficulty in interpreting efficacy results.

Specifically, in this study, there was potential bias due to under-reporting of escapes. The investigator-reported escape rate was about 6%, compared to about 30% calculated escapes rate based on seizure data, and 42% reported rate for LTG IR in Study US30/31. In addition, none met escape criterion #4 in this study compared to up to 45% in the historical controls; and post-hoc evaluation of criterion #4 events could not be performed due to the subjective nature of this criterion. Another source of bias came from the handling of dropouts. The sponsor counted dropouts as completers which biased for treatment success.

The study population in Study LAM30055 was not comparable to those in the historical control studies. Study LAM30055 had approximately 75% of subjects enrolled outside US while all of the subjects in the historical control database were enrolled in US. A higher proportion of subjects at US sites met Escape Criteria compared to non-US sites. In addition, Study LAM30055 allowed one background AED while most White Paper studies allowed two background AEDs. The White Paper data suggested that patients with one background AED had fewer escapes than patients with two AEDs.

To make an attempt to adjust for biases, the reviewer conducted analyses which

(1) calculated escapes according to more stringent Escape Criteria used in some of the White Paper studies

6 J. French, S. Wang, B. Warnock and N. Temkin: Historical control monotherapy design in the treatment of epilepsy. Epilepsia 1-8, 2010

(2) included dropouts as treatment failures in the analyses of the White Paper Per Protocol population and the ITT population,
(3) compared to a subgroup of historical control subjects who were on one background AED (consequently the 95% prediction limit changed to 58.6%, from the original 65.3%).

With above adjustments, LTG XR monotherapy remained superior to the historical controls for both dose groups. For the subgroup of US subjects pooled from the two dose groups, with adjustments (1) and (2), LTG XR monotherapy remained superior to the historical controls except in the ITT worst case analysis. With additional adjustment (3), LTG XR failed to show superiority in the White Paper PP sensitivity analysis or the ITT worst case analysis.

The potential bias due to under-reporting of criterion #4 events was not accounted for in above analyses. It was uncertain how to adequately assess this potential bias.

In summary, the data seemed to suggest some evidence of efficacy of LTG XR as monotherapy treatment of partial seizures. However, interpretability of these analysis results was undermined by the limitations of the historical control design and the problems described above; thus, it was uncertain that the efficacy of LTG XR as monotherapy treatment of partial seizures was conclusive based on this study.

Clinical Reviewer Summary

This submission represents a novel pathway for approval by using an historical control method to demonstrate efficacy of Lamictal XR for use in conversion to monotherapy. Previously approval for monotherapy has been gained through a clinical trial design known as the "pseudo-placebo withdrawal to monotherapy study" which assigns treatment resistant patients to receive study drug or a suboptimal maintenance dose of a safe and effective active drug. Development of the historical control methodology has been motivated by the danger of the "pseudo-placebo" which allows patients to participate in a study arm which is intrinsically sub-therapeutic.

To use an historical control method a study is required to have design features which allow comparability between a current study and the historical control studies. Key criteria are similarity of study design, population, evaluation criteria and analysis plan. Study LAM30055 met this requirement in the elements of conversion to monotherapy, study endpoint and analysis plan; however there was notable divergence in the study population. The first point of divergence was in the composition of the historical control population which was approximately 100% of US patients while LAM30055 was only 25% US. The second divergence was in the allowed number of background AEDs prior to monotherapy conversion. Six of the 8 historical control studies allowed 2 baseline AEDs whereas LAM30055 allowed only one AED for eligibility. In addition to these disparities a difference in study endpoint profile emerged. In the calculation of the White Paper prediction interval and the Lamictal XR monotherapy endpoint confidence interval

both were based on percent of patients meeting any of 4 escape criteria; however the Lamictal Study had no criteria # 4 escapes where the historical control studies had escapes due to criteria # 4 ranging from 4% to 45%. In addition the Lamictal XR monotherapy study had lower rates of escape reporting across all criteria.

The statistical reviewer identifies the sources of bias which include different methods of calculating escapes between the Lamictal XR study and the White Paper studies, treatment of dropouts, medical (1 or 2 background AEDs) and regional differences in the study population and under reporting of escapes, especially problematic in Criteria 4. The statistical approach to compensate for the bias was to perform a recalculation of escapes using more stringent criteria which included dropouts as treatment failures and reanalyzed the historical control (White Paper) dataset using only those patients on a single background AED. There was no clear approach to compensate for the divergence in escape criteria # 4 between the Lamictal XR study and the White Paper studies.

A recalculation of the White Paper prediction interval lower bound based on the population taking only 1 AED yielded a value of 58.6%. Both the 300mg/day and 250mg/day dose groups of the Lamictal XR monotherapy study retain superiority to this threshold in all adjustments to the White Paper escapes (table 12). The US subset of the Lamictal XR monotherapy study retains superiority only in the least conservative White Paper per protocol analysis (table 13).

If the White Paper methodology is accepted as a valid platform for historical control comparison and the population is restricted to 1 background AED, the resultant lower bound of the pseudoplacebo group prediction interval is 58.6%. All analysis for overall LAM30055 populations in both dose groups remain superior to this White Paper lower bound. The US subset remains superior only in the White Paper per protocol analysis. The US subset is small and not powered to independently test for significance, therefore this finding in isolation does not supersede the overall study results.

Clinical Reviewer Conclusion

There is adequate support for approval of Lamictal XR for use in conversion to monotherapy for patients ≥13 years of age who are receiving treatment with a single AED. The recommended target dose is 300mg daily, although the 250mg/day dose remained superior to the pseudoplacebo, this dose was not the protocol directed primary efficacy endpoint.

6.1.2 Introduction

Overview

Lamotrigine extended–release (LTG XR) formulation is currently approved as adjunctive treatment of partial seizures and primary generalized tonic clonic seizures in subjects ≥13 years of age. LTG Immediate-release (IR) was initially approved for adjunctive use and was later demonstrated to also be effective as monotherapy following conversion from add-on therapy with a single enzyme-inducing antiepileptic drug (EIAED).

This supplemental New Drug Application (sNDA) consisted of a single pivotal clinical study evaluating conversion to monotherapy with LTG XR in subjects 13 years of age and older with partial seizures using an historical control (referred to as Study LAM30055 subsequently in this document). The study used a conversion to monotherapy design in which eligible subjects with refractory partial seizures had LTG XR added to their current background antiepileptic drug (AED) (valproate or a non-enzyme inducing AED) followed by gradual withdrawal of the background AED and 12 weeks of monotherapy.

Approximately 230 male or female ≥13 years of age with seizures uncontrolled (≥2 per 28 days) by AED monotherapy were enrolled to randomize 164 subjects to the two dosing groups in a 1:1 ratio. The primary treatment comparison evaluated the proportion of subjects who discontinue LTG at 300 mg/d (pre-specified) / meet Escape Criteria (post-hoc) during the last 16 weeks of treatment with LTG compared to an historical pseudo-placebo control rate.

The historical control dataset was the aggregated data from eight monotherapy studies. All of these studies utilized a "pseudoplacebo", either a sub-therapeutic dose of an active drug or a low dose of study drug, and efficacy was based on the proportion of patients who exited the studies as a result of predefined Escape Criteria related to worsening of seizures. In the White Paper, French et al proposed that using the lower bound of the 95% prediction interval (PI) based on the combined percent escape rate (65.3%) for a single study or the lower bound of the 80% PI based on the combined escape rate (72.2%) for 2 studies. Specifically, the upper 95% confidence limit of the test group was compared to the lower prediction limit of the aggregated historical data. Non-overlap indicated a determination that the treatment was efficacious. FDA agreed in principle to accept their use as control during a meeting with GSK on September 08, 2005.

The previous study US 30/31 of LTG IR (immediate-release) was provided as a supportive study. It had a similar design to Study LAM30055 but used a low dose as internal pseudoplacebo. Study US 30/31 supported approval of LTG IR for conversion to monotherapy and was one of the eight studies from which the historical control endpoint was derived.

Clinical Reviewer Comment

History of Lamictal and Lamictal XR Pertaining To the Current Application

LTG Immediate-release (IR) was initially approved for adjunctive use in December 1994 and was later demonstrated to also be effective as monotherapy following conversion from add-on therapy with a single enzyme-inducing antiepileptic drug (EIAED) and approved for this use in December 1998. Lamictal XR was approved in May of 2009 for adjunctive therapy of partial seizures and in January 2010 as adjunctive therapy for primary generalized tonic-clonic. This background has provided extensive experience in the use and effectiveness of lamotrigine.

A clinical pharmacology review was performed for the submission of Lamictal XR for adjunctive therapy of partial seizures[7]. In the evaluation of proposed conversion dose from lamotrigine IR to Lamictal XR the reviewed examined the lamotrigine steady state relative bioavailability in 3 groups of patients receiving different concomitant AEDs (enzyme inducers, inhibitors and neutrals). The reviewer found the following:

- The steady-state mean trough concentrations for Lamotrigine XR were equivalent to or higher than those of lamotrigine IR depending on concomitant AED.

- A mean reduction in the lamotrigine Cmax by 11-29% was observed for lamotrigine XR compared to lamotrigine IR resulting in a decrease in the peak to trough fluctuation in serum lamotrigine concentrations.

- The fluctuation index was reduced by 17% in patients taking enzyme-inducing AED, 34% in patients taking VPA and 37% in patients taking neutral AEDs.

- Lamotrigine XR and lamotrigine IR regimens were almost similar (6% decrease) with respect to mean AUC(0-24ss), apart from patients receiving EIAEDs, where the relative bioavailability of lamotrigine XR was approximately 21% lower than for lamotrigine IR.

Table 4 Bioavailability of LAMICTAL XR and LAMICTAL IR

7 Tandon V. Clinical Pharmacology/Biopharmaceutics Review, NDA22115, Product: Lamictal XR, Indication: Adjunctive therapy for partial onset seizures with or without generalization in patients ≥ 13 years. 9/6/2007

PK parameter	AED Group	Ratio XR:IR	90% CI
AUC(0-24)/Total Daily Dose	Overall	0.90	0.84 – 0.98
	Induced	0.79	0.69 – 0.90
	Neutral	1.00	0.88 – 1.14
	Inhibited	0.94	0.81 – 1.08
Cmax/Total Daily Dose	Overall	0.82	0.76 – 0.90
	Induced	0.71	0.61 – 0.82
	Neutral	0.89	0.78 – 1.03
	Inhibited	0.88	0.75 – 1.03
Cτ/Total Daily Dose	Overall	1.04	0.98 – 1.10
	Induced	0.99	0.89 – 1.09
	Neutral	1.14	1.03 – 1.25
	Inhibited	0.99	0.88 – 1.10

There were however some outlier subjects taking enzyme inducing AEDs with a more marked reduction in AUC and Cmax. In the case of AUC there were two subjects, one with a 57% reduction, the second with a 70% reduction. In the case of Cmax there were three subjects with a range in reduction from 45% to 77%.

These observations offer some support for an expected similarity in performance between Lamictal IR (immediate release), already approved for conversion to monotherapy based on study 30/31, and Lamictal XR. Although those on inducers fell outside of the bioequivalence boundary, this is not relevant to use in monotherapy except in the transition phase where in proposed labeling Lamictal XR is maintained at a higher dose (500mg/day) until two weeks after the completion of background AED withdrawal and is then reduced to a target dose of 250mg to 300mg / day.

There is a robust history of Lamictal XR use, as shown in the table below representing the interval from May 29, 2009 to July 24, 2010. There were [redacted] (b) (4) mg (the equivalent of [redacted] (b) (4) 200mg tablets) of Lamictal XR sold in the US in this interval, not including start up kits, freely provided drug or samples[8].

Table 5 Lamictal XR distribution data

DISTRIBUTION DATA NDA 022-115; LAMICTAL XR EXTENDED-RELEASE TABLETS May 29, 2009 to July 24, 2010				
Description	**NDC Code**	**Domestic Sales**	**Domestic Free Issues**	**Domestic Samples**
LAMICTAL XR TABLETS 25MG 30s	0173075400	[redacted] (b) (4)		
LAMICTAL XR TABLETS 50MG 30s	0173075500			

8 Lamictal Annual Report covering 7/25/09 through 7/24/10

		(b) (4)
LAMICTAL XR TABLETS 100MG 30s	0173075600	
LAMICTAL XR TABLETS 200MG 30s	0173075700	
LAMICTAL XR TABLETS 25MG/50MG STARTER KT	0173075800	
LAMICTAL XR TAB BLUE DE KIT 25MG/50MGSPL	0173075860	
LAMICTAL XR TABLETS 50MG/100MG/200MG KIT	0173075900	
LAMICTAL XR TAB GREEN DE KIT 50/100/200	0173075960	
LAMICTAL XR TABLETS 25MG/50MG/100MG KIT	0173076000	
LAMICTAL XR TAB ORANGE DE KIT 25/50/100	0173076060	

Data Sources

The data files are located in the following directory:
\\Cdsesub1\evsprod\NDA022115\0024\m5\datasets\lam30055-double-blind\analysis
\\Cdsesub1\evsprod\NDA022115\0050\m5\datasets\lam30055-double-blind\analysis\datasets
\\Cdsesub1\evsprod\NDA022115\0052\m5\datasets

The study reports are located in the following directory:
\\Cdsesub1\evsprod\NDA022115\0024\m5\53-clin-stud-rep\535-rep-effic-safety-stud\monotherapy\5351-stud-rep-contr\lam30055-double-blind

6.1.3 Statistical Evaluation

Evaluation of Efficacy

Study LAM30055

The study was initiated on 16 May 2006, and completed double-blind phase on 06 May 2008. The original protocol (dated 19 December 2005) was amended twice (19 January 2006, 30 August 2006) with both amendments applying to all study sites. There were no changes to study conduct implemented with either amendment. SAP was dated 19 December 2007.

Study Design (see 5.3)

This was an international, multicenter, double-blind, randomized study of 2 doses (300 and 250 mg/day) of lamotrigine extended-release (LTG XR) tablets comparing the

premature discontinuation rate for each dose to an historical escape rate (65.3%) determined from aggregated pseudo-placebo data. The purpose of the study was to demonstrate the effectiveness of a lower monotherapy dose of LTG XR than the currently approved 500 mg/day of LTG IR.

The study used a conversion to monotherapy design in which eligible subjects with refractory partial seizures had LTG XR added to their current background antiepileptic drug (AED) (valproate or a non-enzyme inducing AED) followed by gradual withdrawal of the background AED and 12 weeks of monotherapy. Subjects who completed the Treatment phase or met Escape Criteria were allowed to enter the Continuation phase. Study phase and duration was shown in Table 6. Approximately 230 male or female ≥13 years of age with partial epilepsy with seizures uncontrolled (>=2 per 28 days) by AED monotherapy were enrolled to randomize 164 subjects to the two dosing groups in a 1:1 ratio.

Table 6. Study Design

Phase	Duration
Screen	<2 weeks
Baseline	8 weeks[1]
LTG XR escalation	6-7 weeks [2]
Background AED withdrew and continuation of LTG XR escalation	4 weeks
Monotherapy	12 weeks
Optional Continuation Phase	24 weeks
Taper-Follow-up or Conversion to immediate release	~2 weeks ~3 days
Total (maximum)	59 weeks

1. With approval from GSK, up to the first 4 weeks of Baseline may be retrospective
2. Differs based on background AED and escalation schedule for LTG-XR

Efficacy Measures

Efficacy measures were variables derived from seizure information that were monitored through subject diary and evaluated at each study visit. Subjects recorded the number of seizures, by seizure type, as well as duration of episodes of innumerable seizure activity in their daily diaries. Site personnel transcribed the daily seizure information from the diary into the electronic Case Report Form (eCRF).

The planned primary endpoint was the proportion of subjects in the 300 mg/day treatment group who prematurely discontinued at any time after starting withdrawal of background AED.

A "completer" was defined as a subject who completed the Baseline, Conversion and Maintenance Phases of the study. In all other cases, the subject was considered to have prematurely discontinued.

Post-hoc primary endpoint was the proportion of subjects meeting pre-defined efficacy Escape Criteria. These criteria were the occurrence of any of the following compared to Baseline:

1. doubling of average monthly seizure frequency calculated as the sum of countable, partial seizures starting the day prior to the study visit and extending back 28 days
2. doubling of the highest consecutive 2-day seizure frequency
3. emergence of a new, more severe seizure type
4. clinically-significant prolongation of generalized tonic-clonic seizures

This post-hoc primary endpoint was one of the original secondary endpoint but transitioned to primary endpoint as discussed in Efficacy Analysis. Other secondary endpoints were:

- Proportion of subjects in the 250 mg/day treatment group who prematurely discontinue
- Time to discontinuation
- Percent change from Baseline in seizure frequency
- Percent seizure-free at last visit

Statistical Analysis Methods

Analysis Population

Per Protocol (PP)
All subjects randomized to treatment who took at least one dose of study medication and began withdrawal of the background AED, excluding those with major protocol violations. The planned primary efficacy analysis was based on the PP population.

Intent-to-Treat (ITT)
All subjects randomized to treatment who took at least one dose of study medication.

White Paper Per Protocol
All subjects randomized to treatment that took at least one dose of study drug and began withdrawal of the background AED. This population was defined post-hoc in order to make a direct comparison with the White Paper. This was the primary population for this review.

Efficacy Analyses

The planned primary treatment comparison in study LAM30055 evaluated the proportion of subjects who discontinued LTG at 300 mg/d during the last 16 weeks of treatment with LTG XR compared to an historical pseudo-placebo control rate. This pre-specified primary endpoint of 'all-cause' discontinuation was based on the way Study US 30/31 data was analyzed as part of the aggregation of 8 studies included in the

historical database. After completion of the double-blind phase of LAM30055, it was learned that the analysis of US 30/31 in the 2005 version of the White Paper was incorrect. US 30/31 data were subsequently re-analyzed utilizing only escape data. In response to this, data from LAM30055 were analyzed post-hoc focusing only on subjects who met Escape Criteria. Since this was the endpoint used in the White Paper, the Escape Criteria analyses was referred as post-hoc primary analysis.

As the sponsor found that the Escape Criteria were not correctly applied at study sites (e.g., subjects who met an Escape Criterion were not discontinued), daily seizure data in the database were evaluated against the Escape Criteria (1, 2, and 3) to identify additional escapes following completion of the trial.

The estimated proportion and confidence interval were calculated using binomial distribution. Subjects who dropped out due to reasons other than meeting Escape Criteria were included in Sponsor's analyses as having successfully completed the treatment.

Patient Disposition, Demographic and Baseline Characteristics

A total of 226 subjects (113 per treatment group) were randomized from 7 countries. Three of the 226 randomized subjects did not receive study drug and were not included in ITT Populations (1 subject in each treatment group decided to withdraw, and 1 subject [250 mg/day] had a protocol violation). The PP Population included 93 subjects in the LTG XR 300 mg/day group and 81 subjects in the LTG XR 250 mg/day group. The White Paper PP Population, which did not exclude subjects with major protocol violations, included 108 subjects in the LTG XR 300 mg/day group and 97 subjects in the LTG XR 250 mg/day group. The most common reason for withdrawal from the LTG XR 300 mg/day group was "subject decided to withdraw from the study" (8%). For the LTG XR 250 mg/day group, AE was the most frequent cause for withdrawal (9%), see Table 7.

Table 7 Subject Disposition

	Number (%) of Subjects	
	LTG XR 300 mg/day	**LTG XR 250 mg/day**
Population		
Randomized	113	113
Safety	112 (>99)	111 (98)
Intent-to-Treat (ITT)	112 (>99)	111 (98)
Per Protocol (PP)	93 (82)	81 (72)
White Paper PP	108 (96)	97 (86)
Subject Disposition (Randomized Subjects)		

	Number (%) of Subjects	
	LTG XR 300 mg/day	LTG XR 250 mg/day
Completed study	94 (83)	79 (70)
Prematurely withdrawn	19 (17)	34 (30)
Met Escape Criteria[1]	28/112 (25)	25/111 (23)
Reason for premature withdrawal		
Adverse event	4 (4)	10 (9)
Lost to follow-up	0	4 (4)
Protocol violation	0	4 (4)
Subject decided to withdraw from the study	9 (8)	8 (7)
Insufficient therapeutic response[2]	6 (5)	7 (6)
Other, specify[3]	0	1 (<1)

1. Includes post-hoc escape determination.
2. Escapes based on the CRF, does not include the post-hoc escape determination.
3. Other, specify = Subject 130 withdrew due to pregnancy.

Source: Sponsor ISE page 23.

The majority of subjects in both treatment groups were 16 to 65 years and of White – White/Caucasian/European heritage (Table 8).

Table 8 Study LAM30055 Demographics

Demographic Characteristic	LTG XR 300 mg/day N=112	LTG XR 250 mg/day N=111
Age (years)		
Mean (SD)	33.8 (14.33)	32.9 (12.60)
Range	13-80	13-59
Age Group (years), n (%)		
<16	10 (9)	7 (6)
16-65	100 (89)	104 (94)
>65	2 (2)	0
Gender, n (%)		
Female	56 (50)	66 (59)
Male	56 (50)	45 (41)
Ethnicity, n (%)		
Hispanic/Latino	33 (29)	30 (27)
Not Hispanic/Latino	79 (71)	81 (73)
Race, n (%)		
African American/African Heritage	5 (4)	4 (4)
Asian - East Asian Heritage	11 (10)	11 (10)
White - Arabic/North African Heritage	0	2 (2)
White - White/Caucasian/European Heritage	96 (86)	94 (85)

Source: Sponsor ISE page 26.

Most subjects in both treatment groups had only partial seizures at Baseline. The median Baseline seizure frequency (number of partial seizures/week) over the entire Baseline was 1.4 for the LTG XR 300 mg/day group and 1.5 for LTG XR 250 mg/day group. Seizure history at Baseline was similar for the two treatment groups with a mean age of 20.5 and 18.7 years, respectively at first seizure, and a mean of 14.3 and 15.2 years, respectively for duration of epilepsy (**Error! Reference source not found.**.)

Baseline Characteristic	LTG XR 300 mg/day N=112	LTG XR 250 mg/day N=111
Baseline Seizure Type[1], n (%)		
A (simple partial seizures)	49 (44)	53 (48)
B (complex partial seizures)	71 (63)	67 (60)
C (partial seizures evolving to secondarily generalized seizures)	60 (54)	59 (53)
D5 (primary generalized)[2]	1 (<1)	1 (<1)
Partial seizures only (A, B, or C)	111 (>99)	108 (97)
Both partial and generalized seizures	1 (<1)	1 (<1)
Baseline Seizure Frequency per Week - All Partial Seizures Entire Baseline		
Mean (SD)	3.3 (8.21)	4.3 (10.59)
Median (Range)	1.4 (0.5-69.9)	1.5 (0.5-67.0)
Age at First Seizure (years)		
Mean (SD)	20.5 (13.81)	18.7 (12.72)
Median (Range)	16.5 (1-76)	16.0 (1-49)
Duration of Epilepsy (years)		
Mean (SD)	14.3 (11.61)	15.2 (11.25)
Median (Range)	12.0 (2-67)	13.0 (1-55)

Data Source: CSR LAM30055 DB, Table 6.9, Table 6.10, Table 6.11

1. Subjects may have reported more than one seizure type.
2. One subject in each group (Subject 271 and Subject 1111) reported a history of D5 seizures prior to the Screen Visit. Neither subject experienced a primary generalized seizure in the 8 weeks prior to screen. Subject 271 experienced D5 seizures during the study; Subject 1111 did not.

Source: Sponsor ISE page 27.

Sponsor's Efficacy Results

Planned Analyses Results

Primary efficacy endpoint

The proportion of subjects who discontinued at any time after starting withdrawal (not including calculated escapes) of the background AED in Study LAM30055 was 12% for the LTG XR 300 mg/day group in the PP Population, with a 95% upper limit of 18.4%. However, this analysis was not considered primary analysis for regulatory evaluation as this was not the way the White Paper analyzed the pseudo-placebo data.

Secondary efficacy endpoints
The proportion of subjects who discontinued at any time after starting withdrawal (not including calculated escapes) of the background AED was 16% for the LTG XR 250 mg/day group in the PP Population.

The proportion of subjects in the PP Population who met Escape Criteria (not including calculated escapes) was 4% for the LTG XR 300 mg/day group and 6% for the LTG XR 250 mg/day group.

Response to treatment, as measured by seizure frequency, showed a greater than 50% reduction in both treatment groups for the entire treatment period. Reduction in seizure frequency was evident in the Conversion phase and increased during the Monotherapy phase. During LTG XR monotherapy, the majority of subjects showed a ≥50% reduction in all partial seizure frequency at both 300 mg/day (64.0%; 57/89) and 250 mg/day (56.6%; 43/76) in the PP Population. Additionally, 24.7% (22/89) of subjects in the 300 mg/day group and 10.5% (8/76) of subjects in the 250 mg/day group became seizure-free.

Table 9. Summary of Planned Analyses (PP population)

	LTG XR 300 mg/day N=93	**LTG XR 250 mg/day N=81**
Percent of subjects who discontinued		
n/N (%)	11/93 (12)	13/81 (16)
[95% CI]	[5.3, 18.4]	[8.1, 24.0]
Percent of subjects meeting Escape Criteria		
n/N (%)	4/93 (4)	5/81 (6)
Percent change from Baseline in weekly seizure frequency[1]		
Conversion Phase, n	93	81
Median (range)	45.5 (-124.5-100.0)	50.2 (-168.6-100.0)
p-value[2]	<0.0001	<0.0001
Monotherapy Phase, n	89	76
Median (range)	67.4 (-100.0-100.0)	59.4 (-635.0-100.0)
p-value[2]	<0.0001	0.0150
Entire Treatment Period, n	93	81
Median (range)	54.8 (-124.5-100.0)	52.2 (-221.3-100.0)
p-value[2]	<0.0001	<0.0001
Categorical change in seizure frequency		
Conversion Phase, n	93	81
≥50% reduction, n (%)	43 (46.2)	41 (50.6)
Seizure-free (100% reduction), n (%)	5 (5.4)	6 (7.4)
Monotherapy Phase, n	89	76
≥50% reduction, n (%)	57 (64.0)	43 (56.6)
Seizure-free (100% reduction), n (%)	22 (24.7)	8 (10.5)

	LTG XR 300 mg/day N=93	LTG XR 250 mg/day N=81
Entire Treatment Period, n	93	81
≥50% reduction, n (%)	54 (58.1)	42 (51.9)
Seizure-free (100% reduction), n (%)	3 (3.2)	4 (4.9)

1. Positive number means a decrease in seizure frequency
2. Paired t-test

Source: Sponsor ISE Table 5 & 6.

Post-hoc Analyses Results

The post-hoc primary analysis was the percent of subject meeting Escape Criteria in the White Paper population. While the trial was ongoing, the sponsor evaluated a random sample of subjects for correct application of the Escape Criteria and identified a number of errors (e.g., some patients met an Escape Criterion but were not discontinued). As a result, remedial training of study site personnel and monitors was undertaken. Following completion of the study, the analysis of escapes showed that the number of subjects who met pre-defined Escape Criteria was surprisingly small: only 6 to 7 subjects in each group were discontinued due to meeting Escape Criteria (Table 10).

Post-hoc evaluation of the seizure data led to reclassification of many subjects as escapes (i.e., having met Escape Criteria) (Table 10). The proportion of subjects who met calculated Escape Criteria was 24% for the LTG XR 300 mg/day group and 26% for the LTG XR 250 mg/day group. The upper 95% confidence limit did not overlap the lower 95% prediction limit (65.3%) from the historical pseudo-placebo control data for both groups.

Table 10. Proportion of Subjects Meeting Escape Criteria (Sponsor Results for White Paper PP Population)

	LTG XR 300 mg/day	LTG XR 250 mg/day
Investigator Determined Escapes (based on CRF)		
n/N (%)	6/108 (6)	7/97 (7)
[95% CI]	[1.2, 9.9]	[2.1, 12.4]
Calculated Escapes		
n/N (%)	26/108 (24)	25/97 (26)
[95% CI]	[16.0, 32.1]	[17.1, 34.5]

Source: Sponsor ISE Table 2, 8, 11.

Reviewer's Results

Use of an historical control requires that the study design, study population, efficacy evaluation and analyses are consistent with the historical pseudo-placebo studies, which is the focus of the review.

Evaluation of the Escape Criteria

Escape Criterion #1: doubling of average monthly seizure frequency

The White Paper mentioned that "it was unclear if this was done on a rolling basis in all cases. Discussion with the companies involved has determined that the statistical **methodology may have varied from trial to trial".**

In Study LAM30055, the sponsor calculated the average monthly seizure frequency as the sum of countable, partial seizures starting the day prior to the study visit and extending back 28 days. As calculating the highest seizure frequency for *any* consecutive 28 days was more stringent and was used for some of the White Paper studies, the reviewer used this method for Study LAM30055. Three additional subjects in each group were identified to have met this Escape Criterion, resulting in 3 more escapes for the LTG XR 300 mg/day group and 2 more escapes for the LTG XR 250 mg/day group (one subject in the 250 mg/day group met multiple Escape Criteria).

Escape Criterion #2: doubling of the highest consecutive 2-day seizure frequency.

In study LAM30055, the highest consecutive 2-day seizure frequency was calculated for the 28 days prior to each visit. The reviewer calculated the highest consecutive 2-day seizure frequency for the *whole treatment phase*. One more subject the LTG XR 300 mg/day group was identified to have met this Escape Criterion but resulting in no additional escapes as this subject met Escape Criterion #1 already.

Escape Criterion #3: emergence of a new, more severe seizure type

In the White Paper, this criterion varies among studies: occurrence of a single generalized seizure if none had occurred in the previous 6 months (Study 6), within two years of study entry (Study 1), during Baseline **(Studies 3, 5, 7, 8), and "emergence of a** more severe seizure type (which would include generalized seizure).

The criterion in the study **LAM30055 Protocol was 'emergence of a new, more severe seizure type compared to the Baseline'. However,** the sponsor calculated the escapes by comparing the seizure types during the Double-Blind Phase to the seizure types the subject had in their lifetime history. The reviewer requested that the sponsor re-calculate the escapes using Baseline period for comparison. Two more escapes were identified for LTG XR 300 mg/day group and three more escapes were identified for LTG XR 250 mg/day group.

Escape Criterion #4: clinically-significant prolongation of generalized tonic-clonic seizures

The data suggested that none of the subjects met this criterion (Table 11). The escapes based on this criterion were solely evaluated by the sites/investigators. The sponsor did not perform the re-calculation due to the subjective nature of this criterion. It was recognized the investigators tended to under-report escapes for criteria 1, 2 and 3. Therefore, there was concern that the escapes due to this criterion were also under-reported.

In addition, the criterion #4 in the study LAM30055 may be more restrictive than the White Paper criterion, which was "prolongation or worsening of seizure duration or frequency considered by the investigator to require intervention." Some events may be considered escapes according to the White Paper criteria, but not by the Study LAM30055 criteria. The medical reviewer examined the adverse event database and identified a patient who may have met Escape Criteria according to the White Paper criterion: subject 255 required intervention in the form of hospital admission.

Furthermore, Study US 30/31 was for LTG IR (with an internal control) and the Escape Criteria were defined the same as Study LAM30055. There were 10% subjects in the LTG IR group who met criterion #4 vs 4% for the pseudoplacebo. Other White Paper studies tended to have a large percentages of subjects meeting criterion #4 (19%, 17%, 11%, 7%, 45% and 29% for study 1, 3, 5, 6, 7, 8, respectively).

Therefore, there was serious concern about the bias due to potential under-reporting of escapes for criterion #4.

Table 11. Percentage of Subjects Meeting Each Criterion

Criterion	LTG XR 300 mg/day	LTG XR 250 mg/day
Criterion #1	12/108 (11)	19/97 (20)
Criterion #2	20/108 (19)	18/97 (19)
Criterion #3	8/108 (7)	7/97 (7)
Criterion #4	0	0

* Numbers are n/N (%).
* Patients may meet more than one criterion.
Source: FDA reviewer.

Statistical Analysis of the Proportion of Subjects Meeting Escape Criteria

The post-hoc primary analysis by the sponsor estimated the binomial proportion of subjects meeting Escape Criteria. The analyses were conducted for White Paper PP Population in order to make a direct comparison with the White Paper. Subjects who dropped out due to reasons other than meeting Escape Criteria were treated as treatment successes. However, the White Paper used Kaplan-Meier estimate of the proportion, in which subjects who dropped out for other reasons were censored. The

estimated binomial proportion will be smaller than the Kaplan-Meier estimate due to the different ways of handling dropouts.

The reviewer conducted a sensitivity analysis in which subjects who dropped out for other reasons were considered treatment failures/escapes. This way the estimated binomial proportion will be larger than the Kaplan-Meier estimate. This was also the **planned primary analysis of 'all-cause' discontinuation.**

To deal with potential bias due to conducting an essentially open-label study (all patients were on potentially effective test drug), a worst case analysis was conducted by the reviewer in which ITT subjects who dropped out before the background AED withdrawal were also considered escapes.

None of the upper 95% confidence limits generated by all of these analyses are greater than the White Paper 95% prediction limit for escapes (65.3%) from the historical pseudo-placebo control data (Table 12).

Table 12. Proportion of Subjects Meeting Escape Criteria

	LTG XR 300 mg/day	LTG XR 250 mg/day
White Paper PP		
n/N (%)	31/108 (29)	30/97 (31)
[95% CI]	[20.2, 37.2]	[21.7, 40.1]
White Paper PP Sensitivity Analysis		
n/N (%)	37/108 (34)	37/97 (38)
[95% CI]	[25.3, 43.2]	[28.5, 47.8]
ITT Worst Case Analysis		
n/N (%)	41/112 (37)	51/111 (46)
[95% CI]	[27.7, 45.5]	[36.7, 55.2]
The 95% prediction limit is 65.3% for all escapes. The 95% prediction limit is 58.6% for escapes in the subgroup of patients with 1 background AED (the subgroup will be mentioned later in the review).		

*Includes calculated escapes (none met escape criterion #4)
Source: FDA reviewer.

Clinical Reviewer Comment

Study LAM30055 had no escapes due to category #4. This raises a concern of under reporting of escapes. One escape was identified in the adverse event dataset which fits the more general category 4 of the white paper. The observation of no criteria 4 escapes prompts a closer examination of the parity of escape criteria between study LAM30055 and the White Paper composite criteria. The individual criteria are captured for each study and shown in appendix 1. The White Paper creates a composite criteria 3 and 4 which acceptably captures criteria 3 and 4 of the 8 White Paper studies;

however as can be seen in the "matching" column of the table (appendix 1), 5 of 7 studies where the data is available do not have strict 1:1 matching with the criteria of LAM30055. Criteria 1 and 2 best approximate a clear 1:1 mapping between the Lamictal XR monotherapy study and the White Paper studies but the distinction is blurred for criteria numbers 3 and 4 which confounds a clear statistical solution to this bias.

Evaluation of the Study Population

Background AED

Most White Paper studies allowed two background AEDs. The percent of subjects receiving two background AEDs ranged between 17% and 34%. Enzyme-inducing antiepileptic drugs (EIAEDs) such as carbamazepine (CBZ) were often the background AED from which subjects were converted. Study LAM30055 allowed one background AED and excluded subjects taking EIAEDs. The White Paper indicated that withdrawal from CBZ did not increase the likelihood of escape, which was confirmed by the reviewer.

The White Paper data suggested that patients on one background AED had fewer escapes than patients on two AEDs. For patients on one background AED, the estimated percent escape is 83.0% with a lower prediction limit of 58.6%. Comparing to this limit, both groups remained superior to the historical pseudo-placebo.

Clinical Reviewer Comment

The LAM30055 design allowed patients only on stable monotherapy to enter the trial. As noted above, this design is divergent from White Paper studies which allowed up to two background AEDs. There is a potential for the population on stable monotherapy to be less refractory than those requiring polytherapy. Those on two AEDs may be more prone to escape events. The statistical reviewer has reanalyzed the White Paper dataset with modifications which restricted analysis to patients on one background AED. When compared to the revised 58.6% lower bound prediction interval the upper 95% CI of both the 300mg/day and 250mg/day dose groups of study LAM30055 remain superior to the pseudoplacebo group (table 12).

Regional Comparisons

Study LAM30055 was conducted in 7 countries (Argentina, Chile, Costa Rica, Korea, Russian, Ukraine and US) with approximately 75% of subjects enrolled outside the US. In contrast, virtually all of the subjects in the historical control database were enrolled in the US. Table 13 showed the percent escape by region (US vs non-US). Due to the small size in the US, the two dose groups (300 mg/d and 250 mg/d) were pooled. A higher proportion of subjects at US sites met Escape Criteria compared to non-US sites. The proportion of US subjects meeting Escape Criteria remained superior to the historical control except for the ITT worst case analysis. When comparing to the

prediction limit for subgroup of patients with one background AED, LTG XR did not show superiority over the historical pseudo-placebo for the US population in the White Paper PP sensitivity analysis or the ITT worst case analysis (Table 13).

Table 13. Proportion of Subjects Meeting Escape Criteria by Region

	US	Non-US
White Paper PP		
n/N (%)	19/50 (38)	42/155 (27)
[95% CI]	[24.5,51.5]	[20.1,34.1]
White Paper PP Sensitivity Analysis		
n/N (%)	25/50 (50)	49/155 (32)
[95% CI]	[36.1,63.9]	[24.3,38.9]
ITT Worst Case Analysis		
n/N (%)	31/56 (55)	61/167 (37)
[95% CI]	[42.3,68.4]	[29.2,43.8]
The 95% prediction limit is 65.3% for all escapes. The 95% prediction limit is 58.6% for escapes in the subgroup of patients with 1 background AED.		

* Includes calculated escapes (none met escape criterion #4)
Source: FDA reviewer.

The sponsor stated that the regionally unbalanced use of VPA was the most likely reason for the regional difference in escape percentage at US compared to non-US sites. Approximately 80% patients were receiving VPA as the background AED at non-US sites compared to about 20% at the US sites. The escape percentage was lower in subjects who transitioned from VPA vs neutral AEDs.

The above argument was not convincing in the reviewer's opinion. As shown in Table 14, the escape rates were similar between VPA and neutral AEDs within each region. The escape rate was higher at US compared to non-US sites for each type of background AEDs.

Table 14. Region and Background AED Comparisons (White Paper PP)

	US		Non-US	
	Neutral AEDs	VPA	Neutral AEDs	VPA
n/N (%)	15/40 (38)	4/10 (40)	9/31 (29)	33/124 (27)
[95% CI]	[22.5,52.5]	[9.6,70.4]	[13.1,45.0]	[18.8,34.4]

* Includes calculated escapes (none met escape criterion #4)
Source: FDA reviewer.

The Agency requested the Sponsor to establish the comparability of placebo escape rate among the regions. The Sponsor provided US vs non-US placebo rates for recent

LAMICTAL adjunctive studies, and conducted literature review of analysis of placebo response by region for various indications. While there may be regional differences in placebo response, the data was limited and the regional differences were inconsistent (sometimes higher in the US, sometimes non-US).

Clinical Reviewer Comment

As noted above in study LAM30055 25% of subjects were recruited from US sites while 75% were from non-US or Western European sites. This raises two concerns, first that study LAM30055 may not be generalizable to the US population. Second is the concern that the LAM30055 study population may not be comparable to the White Paper pseudoplacebo population which is 100% North American.

The concern of generalizability to the US population is addressed first. There is uncertainty about the comparability of US to foreign clinical trial sites, especially those that are non-North American, non-Western European sites. There may be differences between the US and foreign sites based on differences in practice of medicine, cultural framework of heath care, the level of investigator and staff training at non-US sites and pharmacogenomic differences in the studied population[9].

There is a suggestion of differences between US and Non-US populations in prior Lamictal XR trials. In study LAM0034 a placebo controlled trial of Lamictal XR for treatment of partial seizures, which was composed of approximately 40% US sites, the efficacy subset analysis of US sites did not reach a threshold of significance. This raised a concern that efficacy within the study as a whole was driven by the foreign data. In study LAM00036, a placebo controlled trial of Lamictal XR in primary generalized tonic-clonic seizures; the placebo response of the US sites was notably larger than in the non-US sites. In another placebo controlled study (LAM40097) of Lamictal XR in primarily generalized tonic-clonic seizures the findings were reversed with a placebo response in the non-US sites which was larger than the US placebo response rate. The reversal in placebo response rate between studies LAM0036 and LAM40097 suggests non-systematic variation in the placebo response between studies, a favorable observation, which at face value poses less of a challenge to the generalizability of foreign data to the US. The situation may be more complex. In study LAM40097 the non-US placebo treatment patients were all from South America whereas in study LAM0036 only 16% of 62 non-US, placebo treated patients were from South America and the remainder were from Germany, Russia, Ukraine, Malaysia, and India. The majority were from India. Therefore it may be postulated that there is a higher placebo response in the South American cohort which was diluted, in this second case, by the larger numbers of European and Asian patients. In conclusion, regional differences in placebo response cannot be ruled out by the reversal of placebo response observations in studies LAM100036 and LAM40097.

9 Glickman SW, McHutchinson JG, et.al. Ethical and Scientific Implications of the Globalization of Clinical Research. NEJM 2009;360(8):816-823.

In the current study, LAM0035, there is a divergence in the escape rate between the US and non-US patient groups. The upper 95% CI of the US subset was below the original White Paper lower CI of the prediction interval (65.3%) for the White Paper PP analysis and the White Paper sensitivity analysis (table 13), Subsequently following a reanalysis of the White Paper with only patients on one background AED included, the statistical reviewer has found the US subset breaches the resulting modified White Paper lower bound of 58.6% in both the ITT worst case analysis and the White Paper sensitivity analysis (table 13). This observation is again suggestive of a different population behavior in the US and non-US cohorts.

The sponsor analysis explained this difference as, quite plausibly, due to imbalance in treatment with valproic acid (VPA) as a background anticonvulsant agent. In order to further investigate this possibility the statistical reviewer has performed an analysis of the LAM30055 escape rate by background AED type, either VPA or enzyme induction neutral. The US and non-US escape rates were extracted. This analysis revealed that within region the background AED is not associated with a difference in escape rate (table 14). This observation undermines the proposition that difference in the proportion of patients entering the study with VPA as a background AED is responsible for the difference in US vs non-US escape rate. The cause of this difference remains unexplained but underscores the concern that non-US cohorts may not be generalized to the US population.

Is the LAM0035 treatment population appropriately paired with the historical control (pseudoplacebo group)? The first point of examination again is related to the US, non-US composition of the study population. The aggregate pseudoplacebo group derived in the White Paper is a very close approximation to a 100% US sample while study LAM30055 is 75% non-US. To be a valid placebo for LAM30055 it must be accepted that the non-US treatment component of the study (LAM30055) and the US pseudoplacebo will behave as homogenous groups in response to treatment. Based on the discussion of differences in placebo response and escape rate between US and non-US groups, adequate parity does not appear to be present for the composite pseudoplacebo cohort to act as a placebo comparator for study LAM30055.

Baseline Seizure Frequency

In the White Paper studies, the minimum number of Baseline seizures required for randomization ranged from at least 2 seizures per 4 weeks (3 studies) to at least 4 seizures per 4 weeks (4 studies). The median Baseline seizure frequency ranged between 1.4 and 2.5 seizures per week. Study LAM30055 required at least 2 seizures per 4 weeks of Baseline. The median Baseline seizure frequency was 1.4 seizures per week for LTG 300 mg/d group and 1.5 for LTG 250 mg/d group, which is at the lower end of the range of the White Paper studies.

Table 15 showed that the escape rate was 42% for subjects with Baseline seizure frequency less than 4 per 4 weeks and 25% for subjects with Baseline seizure frequency of at least 4. The escape rate was higher for the subset of patients with 2-4 seizures per 4 weeks at Baseline. Therefore, there was no evidence that the relatively low Baseline seizure frequency in Study LAM30055 led to lower escape rate.

Table 15. Escape Rate by Baseline Seizure Frequency (White Paper PP)

	2- 4 Seizures per 4 weeks	At Least 4 Seizures per 4 weeks
n/N (%)	25/59 (42)	36/146 (25)
[95% CI]	[29.8,55.0]	[17.7,31.6]

* Includes calculated escapes (none met escape criterion #4)
Source: FDA reviewer.

Clinical Reviewer Comment

There is variability in the eligibility requirement for baseline seizure frequency among the White Paper studies. As noted by the statistical reviewer in the above section on baseline seizure frequency. Three White Paper studies had an eligibility of 2 seizures per four weeks and 4 studies had a requirement of 4 seizures per four weeks with a resulting range of 1.4 to 2.5 seizures per week at baseline, in the White Paper pseudoplacebo group. Study LAM30055 required 2 seizures per 4 weeks with a resulting median of 1.4 seizures / week. This places study LAM30055 at the lowest end of the White Paper pseudoplacebo baseline seizure frequency. This observation raises the possibility that the two populations are not matched. The lower baseline seizure frequency rate of the LAM30055 population may be represent a more stable population, physiologically inclined toward more stable epilepsy and lower escape rate. In order to test this hypothesis, the statistical reviewer examined the escape rate by baseline seizure frequency. The escape rate was found to be higher in those with a lower baseline seizure frequency. This finding, although counterintuitive, indicates the difference in baseline seizure rate between the White Paper pseudoplacebo group and the LAM30055 treatment group does not reduce the study validity.

Baseline Seizure Types

Data on the distribution of simple partial (SP), complex partial (CP) and secondarily generalized tonic-clonic (SGTC) seizure subtypes at Baseline were available from 4 of the 8 historical studies. There were 83 to 95 percent of the subjects in these 4 studies having CP seizures during Baseline compared to approximately 62% of subjects in Study LAM30055.

Table 16 showed that the escape rate was higher for the subset of patients without CP in Study LAM30055. Therefore, there was no evidence that the lower percentage of subjects with CP in Study LAM30055 contributed to the lower escape rate.

Table 16. Escape Rate by Baseline seizure Type (White Paper PP)

	Subjects without CP	Subjects with CP
n/N (%)	27/77(35)	34/128(27)
[95% CI]	[24.4,45.7]	[18.9,34.2]

* Includes calculated escapes (none met escape criterion #4)
Source: FDA reviewer.

Clinical Reviewer Comment

There is a notable difference in the baseline seizure type of study LAM30055 and in 4 studies of the White Paper pseudoplacebo group where this information is available. Those patients with complex partial seizures comprised 83 to 95 percent of the White Paper studies whereas 62% of patients in study LAM30055 had complex partial seizures. In order to determine if this difference of seizure type distribution would influence escape rate in a direction that would favor the success of study LAM30055, the statistical reviewer performed an analysis of the escape rate according to baseline seizure type. The sample from LAM30055 was analyzed. This revealed that patients with complex partial seizures had a lower escape rate. Study LAM30055 had a smaller proportion of CP seizures than the White Paper pseudoplacebo group, thus this difference in background seizure type does not bias toward success of study LAM30055.

Supportive Study (LTG IR) – US 30/31

The previous study US 30/31 which used the LTG IR formulation was the basis for the LTG IR monotherapy indication at a dose of 500 mg/day. Study US 30/31 was one of the eight studies from which the historical control endpoint was derived.

US 30/31 was combined from two studies US 30 and US 31 due to slow enrollment. The design of Study US 30/31 was similar to Study LAM30055 consisting of an 8-week Baseline phase followed by randomization to one of two treatment groups (LTG IR, 500 mg/day or pseudo-placebo valproic acid (VPA), 1000 mg/day). There was an 8-week Conversion phase from background AED monotherapy to either LTG IR or VPA comprised of 4 weeks of escalation of LTG IR or VPA followed by 4 weeks of withdrawal of the background AED. Twelve weeks of monotherapy followed and a Continuation phase was provided by roll-over to another study. Unlike Study LAM30055 which excluded subjects taking EIAEDs, Study US 30/31 included only subjects taking an EIAED as their background monotherapy.

Subject disposition was presented in Table 17. A total of 156 subjects were randomized. The ITT Population which consisted subjects randomized to treatment who received at least one dose of the assigned treatment included 76 subjects in the LTG IR group and 80 subjects in the VPA group. The PP Population of subjects who met Escape Criteria or completed 12 weeks of monotherapy (i.e., completers; differently from Study LAM30055 PP) included 50 subjects in the LTG IR group and 64 subjects in the VPA group. More subjects in the LTG IR group than the VPA group prematurely discontinued the study (34% vs 20%, respectively) for reasons other than having met Escape Criteria, primarily due to a higher occurrence of AEs (20% vs 8%, respectively).

Table 17. Subject Disposition (All Randomized Subjects: Study US 30/31)

	Number (%) of Subjects	
	LTG IR	**VPA**
Population		
Randomized	76	80
Intent-to-Treat (ITT)	76	80
Per Protocol (PP)	50	64
Completion status		
Completed study	28 (37)	13 (16)
Met Escape Criteria	22 (29)	51 (64)
Prematurely withdrawn	26 (34)	16 (20)
Reason for premature withdrawal		
Adverse event (AE)	15 (20)	6 (8)
Protocol violation	2 (3)	4 (5)
Subject decided to withdraw from the study	4 (5)	2 (3)
Insufficient therapeutic response	5 (7)	3 (4)
Death	0	1 (1)

Source: Sponsor ISE Table 16.

The primary measure used to evaluate efficacy was the proportion of subjects meeting Escape Criteria (escapes) after the start of AED taper in the PP Population. A secondary measure used to evaluate efficacy was the proportion of escapes in the ITT Population. In this analysis, subjects who prematurely discontinued from the study and did not meet Escape Criteria were analyzed in two ways. In the first analysis, both LTG IR and VPA dropouts were also counted as escapes. This analysis was post-hoc and was labeled the ITT analysis. In the second ITT analysis, LTG IR dropouts were counted as escapes while VPA dropouts were counted as completers. This analysis was labeled the worst case analysis. An additional analysis was conducted on the ITT Population by the agency during the review of the LTG IR monotherapy sNDA that added subjects withdrawing due to inadequate response to those who met Escape Criteria (FDA Drug Approval Package; NDA 20-241/S003 and NDA 20-764/S001, approved 14 December 1998). The worst case analysis revealed no statistically

significant difference between LTG and VPA. Other analyses showed that LTG was superior (Table 18).

Table 18. Proportion of Subjects Meeting Escape Criteria (Study US 30/31)

	Number n/N (%) of Subjects	
	LTG IR	**VPA**
US 30/31 PP Population[1]	22/50 (44)	51/64 (80)
ITT	48/76 (63)	67/80 (84)
ITT worst case analysis	48/76 (63)	51/80 (64)
ITT Agency[2]	32/76 (42)	55/80 (69)

1. Different from the PP population is Study LAM30055.
2. Subjects who escaped were defined as meeting Escape Criteria or withdrawing due to an inadequate response. Subjects withdrawing due to AEs were not counted as escapes.

Source: Sponsor ISE Table 19-21.

6.1.4 Findings in Special/Subgroup Populations

Gender, Race and Age

Table 19 showed the subgroup analysis results for age, gender and race subgroups for Study LAM30055. Majority of the patients are 16 years old or older (92%), White (87%), female (53%). The escape rate was consistent across the race subgroups, but appeared higher in young (<16 years) and old (>=55 years) male patients. Logistic regressions indicated that there was no effect of age or gender on the escape rate.

Table 19. Escape Rate by Gender, Race and Age in Pooled Treatment Group (Study LAM30055 White Paper PP)

	Subgroups	**n/N (%)**	[95% CI]
Gender	Female	27/109 (25)	[16.7,32.9]
	Male	34/96 (35)	[25.8,45.0]
Race	White - White/Caucasian/European Heritage	53/178 (30)	[23.1,36.5]
	Asian - East Asian Heritage	6/19 (32)	[10.7,52.5]
	African American/African Heritage	2/6 (33)	[-4.4,71.1]
Age	Less than 16	8/17 (47)	[23.3,70.8]
	16 - 55	45/171 (26)	[19.7,32.9]
	55 or Greater	8/17 (47)	[23.3,70.8]

Source: FDA reviewer.

6.1.5Summary and Conclusions

Statistical Issues and Collective Evidence

The formulation and dosage of LTG were different in the pivotal study LAM30055 and the supportive study US 30/31. The main differences in study design between the two studies were (1) Study US 30/31 was placebo-controlled but Study LAM30055 was not; (2) Study US 30/31 was conducted in the US while Study LAM30055 was conducted in 7 countries with approximately 75% of subjects enrolled outside the US; (3) and Study US 30/31 included only subjects taking an EIAED as their background monotherapy but Study LAM30055 excluded subjects taking EIAEDs. The study results were presented in Table 20. The proportion of subjects meeting Escape Criteria was lower in Study LAM30055 than Study US 30/31. The identified issues were discussed below.

Table 20. Summary of Escape Rate by Study

	LAM30055[1]		US 30/31	
	LTG XR 300 mg/day	LTG XR 250 mg/day	LTG IR	VPA
White Paper PP	31/108 (29, 37.2)	30/97 (31, 40.1)		
White Paper PP Sensitivity Analysis[2]	37/108 (34, 43.2)	37/97 (38, 47.8)		
ITT Worst Case Analysis[2]	41/112 (37, 45.5)	51/111 (46, 55.2)	48/76 (63)	51/80 (64)
Study US 30/31 PP (Completer Analysis)	31/102 (30)	30/90 (33)	22/50 (44)	51/64 (80)
ITT[3]	33/112 (29)	30/111 (27)	32/76 (42)	55/80 (69)
The 95% prediction limit is 65.3% for all escapes. The 95% prediction limit is 58.6% for escapes in the subgroup of patients with 1 background AED.				

*Numbers are: n/N (%, confidence upper bound%) or n/N (%)
1.Includes calculated escapes (none met escape criterion #4)
3.LTG dropouts were counted as escapes while VPA dropouts were counted as completers.
2.Subjects who escaped were defined as meeting Escape Criteria or withdrawing due to an inadequate response. Subjects withdrawing due to other reasons were counted as treatment successes.

Post-hoc Analyses

The analyses of the pivotal trial Study LAM30055 were altered post-hoc in the following aspects.

The primary endpoint and analysis population were changed to reflect the analysis of the White Paper. This post-hoc change did not seem to be a concern since this analysis could be viewed as pre-specified in the White Paper.

While the trial was ongoing, the sponsor evaluated a random sample of subjects for correct application of the Escape Criteria and identified a number of errors (e.g., some patients met an Escape Criterion but were not discontinued). As a result, remedial training of study site personnel and monitors was undertaken. Following completion of the study, planned analysis of escapes showed that the number of subjects who met pre-defined Escape Criteria was surprisingly small. Only about 6% of the subjects met Escape Criteria compared to 42% in Study US 30/31 (Table 21). Therefore, to correct errors by sites/investigators, seizure data were evaluated post-hoc leading to reclassification of many subjects as 'escapes' (Table 20).

Table 21. Escapes As Determined by Investigator (ITT Population)

LAM30055		US 30/31	
LTG XR 300 mg/day	LTG XR 250 mg/day	LTG IR 500 mg/day	VPA
6/112 (5)	7/111 (6)	32/76 (42)	55/80 (69)

* Numbers are n/N (%).
* Subjects who escaped were defined as meeting Escape Criteria or withdrawing due to an inadequate response, as determined by investigator.

Potential Biases

It is well known that trials with internal control provide greater assurance than afforded by comparison to historical controls. The absence of an internal control arm is of particular concern when the primary endpoint is adverse outcome and involves subjective evaluation. In epilepsy monotherapy trials, dropouts, under-reporting seizures/escapes, etc, could bias toward treatment success and undermine the validity of the trial.

In Study LAM30055 subjects who dropped out for reasons other than meeting Escape Criteria were treated as completers in the sponsor's analysis, which biased toward treatment success (analysis for White Paper PP population). The White Paper used Kaplan-Meier estimate of the proportion, in which subjects dropped out due to other reasons were censored. This gives a higher estimated escape rate. The reviewer conducted a sensitivity analysis which included dropouts as treatment failures. This was also the planned primary endpoint of 'all-cause' discontinuation. To deal with potential bias due to conducting an essentially open-label study (all patients were on potentially effective test drug), a worst case analysis was conducted by the reviewer in which ITT subjects who dropped out before the background AED withdrawal were also considered escapes. The results remained positive for those analyses (Table 20).

The bias from under-reporting escapes was present in Study LAM30055. This bias was corrected to some extend by performing the post-hoc calculation of escapes using seizure data. However, there was no criterion #4 events reported and it was difficult to identify such events post-hoc due to the subjective nature of this criterion. Of the White Paper studies, Study US 30/31 was designed most comparable with Study LAM30055. Study US 30/31 had 10% subjects in the LTG IR group who met criterion #4 and 4% in the pseudo-control group. Other White Paper studies tend to have a large percentage (19%, 17%, 11%, 7%, 45% and 29% for study 1, 3, 5, 6, 7, 8 pseudo-control group, respectively). The criterion #4 in the LTG studies may be more restrictive than the White Paper criterion. Some events may be considered escapes according to the White Paper criteria, but not by the Study LAM30055 criteria. Therefore, comparing the Study LAM30055 escape rate with the combined escape rate due to all 4 criteria from the White Paper studies may bias towards treatment success. However, it was uncertain how to adequately assess the potential bias due to under-reporting criterion #4 events.

Population Comparability

Study LAM30055 had approximately 75% of subjects enrolled outside the US while all of the subjects in the historical control database were enrolled in the US. A higher proportion of subjects at US sites met Escape Criteria compared to non-US sites. The comparability of the US and non-US subjects was not established. The result for the US subgroup was positive except for the ITT worst case analysis (Table 13).

The White Paper data suggested that patients on one background AED had fewer escapes than patients on two AEDs. For patients on one background AED, the estimated percent escape is 83.0% with a lower prediction limit of 58.6%. In comparison to this limit, both LTG dose groups remained superior to the historical pseudo-placebo. However, LTG XR failed to show superiority for the US subgroup in the White Paper PP sensitivity analysis or the ITT worst case analysis (Table 13).

Conclusions and Recommendations

In summary, the data seem to suggest some evidence of efficacy of LTG XR as monotherapy treatment of partial seizures. However, interpretability of these analysis results is undermined by the limitations of the historical control design; thus, it is uncertain that the efficacy of LTG XR as monotherapy treatment of partial seizures is conclusive based on this study.

Clinical Reviewer Comments

The sponsor analysis revealed an unexpectedly low escape rate prompting re-evaluation of seizure data to create "calculated escapes". The proportion of subjects meeting escape criteria based on this analysis was 26/108 (24%) with lower and upper bound of 95% confidence intervals of 16% and 32.1% respectively for the 300mg /day

group. The statistical reviewer notes that the sponsor analysis conducted for the White Paper per protocol population is based on the binomial proportion of subjects meeting escape criteria. The reviewer indicates that the White Paper used Kaplan-Meier estimate of the proportion in which subjects who dropped out for other reasons were censored. This results in a larger estimate of escapes. The statistical reviewer also created two additional analysis of the proportion of subjects meeting escape criteria, these three analysis methods are defined for as follows:

- White Paper Per Protocol: White Paper per protocol population where Kaplan-Meier estimate of the proportion in which subjects who dropped out for other reasons were censored.

- White Paper Sensitivity Analysis: Subjects who dropped out for reasons other than meeting escape criteria were considered escapes.

- ITT Worst Case: ITT subjects who dropped out before the background AED withdrawal were also considered escapes.

The results of study LAM30055 based on these analysis may be seen intable 12. Based on the White Paper 95% prediction limit of 65.3% all of the 300mg/day or 250mg/day upper 95% confidence intervals in addition to the US subset where the White Paper per protocol and sensitivity analysis remain superior to this threshold (table 13).

Comparability of the White Paper and LAM 30055 study populations reveals difference in two elements of composition; region and number of background anticonvulsant drugs allowed at study entry. The White Paper is derived from an almost 100% US population while study LAM30055 is 75% non-US.

In 6 the 8 White Paper studies where the data is available the participants were on 2 background AEDs at entry while study LAM30055 required background monotherapy for eligibility. The statistical reviewer has found that the White Paper data indicate that patients with one background AED had fewer escapes than patients with two AEDs. An analysis of the White Paper pseudoplacebo population on only 1 background AED is performed and reveals a Kaplan Meier escape rate of 83% with a lower bound prediction interval of 58.6%. The overall study LAM30055 results were not changed based on the statistical reviewer escape groups oftable 12. The US subset results did lose superiority to the White Paper sensitivity analysis (table 13)

From within the White Paper studies there was only one non-US study site which was located in Canada. Study LAM30055 has only a 25% US composition. As discussed in the section on regional comparisons, the non-US results may not be generalizable to the US. The small US subset of LAM30055 was not designed to be a stand alone comparator to the White Paper pseudoplacebo composite.

The most valid modification for comparing study LAM30055 to the White Paper pseudoplacebo composite group appears to be restriction to those participants on 1 AED. It is not clear that those on 1 AED are a distinct population from those on 2 AED; however the statistical reviewer examined the White Paper data and found fewer escapes among those on 1 AED. Therefore those in the White Paper on 1 AED are most suited to compare to the study population of LAM30055.

The use of an historical control comparator is a novel methodology. There are multiple components of the White Paper pseudoplacebo aggregate which present a challenge to confidence in this approach as a valid comparator to study LAM30055. The populations are different across time and region. The span of the pseudoplacebo population ranges from approximately 1992 to 2001. In the oldest White Paper study the pseudoplacebo patients will be almost a generation older than the study population of LAM30055. The regional divergence is discussed above. The variation in mapping of escape criteria between the Lamictal XR monotherapy study and the White Paper studies are features which point to insufficient uniformity between studies to act as a pooled comparator. There are also features which support the validity of this aggregate pseudoplacebo group. First, in every study the pseudoplacebo escape rate was larger than the active therapy escape rate and in 6 of 7 studies where the data is available; the active therapy was statistically superior to the pseudoplacebo arm (see appendix 2). The common core feature of all 8 White Paper trials was a study endpoint of patient exit (escape) rate.

Additional support for efficacy is provided by the bioequivalence data on Lamictal IR and XR presented in the Clinical Pharmacology review of Lamictal XR (adjunctive therapy in partial seizures)10. This data provides an expectation that this extended release form of Lamictal will perform similarly to Lamictal IR which is approved for conversion to monotherapy. Conceptual support for efficacy of Lamictal XR monotherapy is provided by the established effectiveness of Lamictal XR for treatment of partial and primary generalized tonic-clinic seizures.

Summary

If the White Paper is accepted as a valid platform for historical control comparison, modified by restricting the population to those on 1 background AED, then the resultant lower bound of the pseudoplacebo group prediction interval is 58.6%. All analysis subsets for study LAM30055 populations in both the 300mg/day and 250mg/day dose groups remain superior to this (58.6%) White Paper lower bound. The US subset remains superior only in the White Paper per protocol analysis derived by the statistical reviewer. The US subset is small and not powered to independently test for significance, therefore this finding in isolation does not supersede the overall study results.

10 Tandon V. Clinical Pharmacology/Biopharmaceutics Review, NDA22115, Product: Lamictal XR, Indication: Adjunctive therapy for partial onset seizures with or without generalization in patients ≥ 13 years. 9/6/2007

Conclusion

There is adequate support for approval of Lamictal XR for use in conversion to monotherapy for patients ≥13 years of age who are receiving treatment with a single AED. The recommended target dose is 300mg daily, although the 250mg/day dose remained superior to the pseudoplacebo, this dose was not the protocol directed primary efficacy endpoint.

7 Review of Safety

Safety Summary

From Protocol LAM30055

Definition of an AE

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.

Note: An AE can therefore be 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, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

Examples of an AE **include**:

- **Significant or unexpected worsening or exac**erbation of the condition/indication under **study. See Section 10.3, "Lack of Efficacy", for additional** information.
- **Exacerbation of a chronic or intermittent** pre-existing condition including either an increase in frequency and/or intensity of the condition.
- **New conditions detected or diagnosed after** investigational product administration even though it may have been present prior to the start of the study.
- **Signs, symptoms, or the clinical** sequelae of a suspected interaction.
- **Signs, symptoms, or the clinical sequelae** of a suspected overdose of either investigational product or a concurrent medication (overdose per se should not be reported as an AE/SAE).
- **Significant failure of expected pharma**cological or biological action. See Section 10.2.1, **"Disease-Related Events and/or** Disease-Related Outcomes Not **Qualifying as AEs or SAEs" for additional information.**

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety grouping for the sNDA is comprised of the subjects in the double blind phase of study LAM30055, also the principle efficacy study.

An additional panel of studies provides supportive safety information. This panel includes an open label phase of study LAM30055 as well as clinical studies conducted with lamotrigine IR. The lamotrigine IR studies include five controlled and four uncontrolled studies and are collectively referred to as "Completed Monotherapy Studies"

The five controlled, lamotrigine IR monotherapy studies include the pivotal monotherapy study (US 30/31), four monotherapy studies in newly diagnosed subjects (UK 49, UK 74, UK 89, and UK 106). The four uncontrolled studies include: one conversion to monotherapy study (UK 105) and three continuation trials (UK115, UK 111, UK 112), table 18, Study Grouping.

Table 22 Study Grouping

Study Grouping	Studies
Principal Efficacy Study	double-blind Treatment Phase of Study LAM30055
Long-term Continuation Data	open-label Continuation Phase of Study LAM30055
Supportive Efficacy Study (LTG IR)	double-blind Treatment Phase of Study US 30/31
Completed Monotherapy Studies (LTG IR)	double-blind Treatment Phase of Study US 30/31 double-blind Treatment Phase of Study UK 49 double-blind Treatment Phase of Study UK 89 double-blind Treatment Phase of Study UK 74 open-label, controlled Treatment Phase of Study UK 106 open, conversion to monotherapy Study UK 105 open Continuation Study UK 115 open Continuation Study UK 111 open Continuation Study UK 112
Ongoing Clinical Study of LAMICTAL XR	Open-label, monotherapy and adjunctive therapy in elderly subjects, Study LEP105972

A table of the characteristics of the individual studies contributing to the safety information is provided below (table 23). This table contains a brief description of the type of study for each study number.

Table 23 Study Characteristics and Data Provided

Study Number	Status of Study	Type of Study	Number of Subjects in Safety Population	Information Provided	GSK CSR Document Number
Phase III Studies					
LAM30055 (double-blind Phase)	Complete	Efficacy and safety (conversion to monotherapy, partial seizures), 22 to 23 weeks blinded	223	All safety data	RM2008/00412/01
LAM30055 (open-label Phase)	Complete	Efficacy and safety (conversion to monotherapy, partial seizures), 24 weeks open-label	195	All safety data	RM2009/00139/01
US 30/31	Complete	Efficacy and safety (conversion to monotherapy, partial seizures), 12 weeks blinded, double-blind, compared to VPA	76	All safety data	NDA 20-241/S003, approved 14 December 1998
UK 49/UK 89	Complete	Efficacy and safety, partial seizures and generalized tonic-clonic seizures, LTG monotherapy compared to CBZ	131	All safety data	NDA 20-241/S003, approved 14 December 1998
UK 74	Complete	Efficacy and safety, double-blind, partial seizures with or without secondarily generalized tonic-clonic seizures and primary **generalized tonic –clonic** seizures, LTG monotherapy compared to PHT	85	All safety data	NDA 20-241/S003, approved 14 December 1998
UK 106	Complete	Efficacy and safety, open-label, partial or generalized tonic-clonic seizures, LTG monotherapy compared to CBZ	230	All safety data	NDA 20-241/S003, approved 14 December 1998
UK 105	Complete	Efficacy and safety, open-label, 16 weeks add on to 1 AED, 12 weeks AED withdrawal, 12 weeks LTG monotherapy	345	All safety data	NDA 20-241/S003, approved 14 December 1998
UK 115	Complete	Safety and efficacy, open-label continuation for subjects who completed UK 49, UK 89 or UK 74.	52 (from UK 49/UK 89 and UK 74)	All safety data	NDA 20-241/S003, approved 14 December 1998
UK 111	Complete	Safety and efficacy, open-label continuation for subjects who completed, or withdrew for a seizure, from UK 106.	67 (from UK 106)	All safety data	NDA 20-241/S003, approved 14 December 1998

UK 112	Complete	Safety and efficacy, open-label continuation for subjects who completed UK 105.	135 (from UK 105)	All safety data	NDA 20-241/S003, approved 14 December 1998
Ongoing Studies (Synopses Only)					
LEP105972	Ongoing	Safety and tolerability of adjunctive and monotherapy in elderly subjects with epilepsy	110	Pregnancies, deaths, withdrawals due to AEs, and SAEs	m2.7.6

7.1.2 Categorization of Adverse Events

In order to capture most accurately the definitions of adverse events in the studies contributing to the safety dataset of this sNDA the following definitions of adverse events are taken directly from the Sponsor's **Summary of Clinical Safety**.

Definition of an Adverse Event

Study Number	Definition of an AE
LAM30055	An AE was defined as any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a
LEP105972	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.
Completed Monotherapy Studies: US 30/31, UK 49, UK 89, UK 74, UK 106, UK 105, UK 112, UK 115, UK 111	An AE was any undesirable medical experience/event occurring to a subject during participation in the study, whether or not the experience/event was considered related to the investigational drug.

Definition of a Treatment Emergent Adverse Event
TEAEs in this CSS are defined as any event that increased in intensity from the Baseline Phase or had an initial onset during the Treatment Period. The TEAE definition is consistent with that used for the Completed Monotherapy Studies (LTG IR).

Definition of Serious adverse events:

In studies LAM30055 and LEP105972 an SAE was defined as 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 outpatient 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

Study US 30/31 and in the Completed Monotherapy Studies-

an SAE was defined as any AE that suggested a significant hazard, contraindication, side effect, or precaution. This included, but was not limited to, any experience that was fatal, life-threatening, permanently disabling, or required or prolonged inpatient hospitalization. Malignancy, overdose of the study drug, or congenital anomaly (in offspring) were also reported as SAEs. Note that these studies were conducted prior to the change in definition of an SAE.

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

In this novel application the primary objective was to demonstrate in a single study, the efficacy of lamotrigine extended-release (LTG XR) at 300mg/day compared to pooled historic pseudoplacebo data. There is no group of phase II/III studies with placebo

control for pooling. The completed Monotherapy study group is a pooled data group; however the pooling only provides total adverse events for the lamotrigine IR treatment group. There is no contrast to the active comparator provided. Each of the studies had a different active comparator.

7.2 Adequacy of Safety Assessments

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

Exposure

Lamictal XR exposure in controlled and open label monotherapy trials does not meet the guidelines in ICH E1A, however there is extensive experience with the use of Lamictal XR approved and marketed for adjunctive therapy in partial and primary generalized tonic clonic seizures.

In monotherapy trials of Lamictal XR there have been only 2 patients exposed for 1 year at the time of submission and 184 patients exposed for 6 months. There were 177 patients exposed for 32 weeks.

Exposure to Lamictal XR in clinical trials as adjunctive therapy was more extensive and fulfilled the ICH E1A guidelines for exposure to **assess clinical safety. In the "All Clinical Studies Grouping" 662 subjects were treated.** A total of 558 subjects were exposed to lamotrigine XR for 24 weeks, and 270 subjects for 52 weeks. The safety data package for NDA 22509 provides this data. This submission included the studies of Lamictal XR in partial seizures, primarily generalized tonic clonic seizures and monotherapy, LAM100034, LAM100036 and LAM30055 respectively.

Dose

LAM30055: the Lamictal XR dose in this study was equally divided on randomization between 300mg/day and 250mg/day, 83% and 70% of patients in these dose groups completed the double blind treatment phase respectively.

LAM100036 & LAM100034: The Maintenance Lamictal target dose in these studies were 200mg/day for patients on concomitant VPA, 500mg/day for patients on enzyme inducing AEDs and 300mg/day for patients taking AEDs other than VPA or enzyme inducing anticonvulsant medications.

Demographics

In study LAM30055 mean age is very close in the 250mg/day and 300mg/day groups and are found to be 32.9 years and 33.8 years respectively. In the 300mg dose group sex is divided equally with 50% male and female. In the 250mg dose group there were 59% females and 45% females. Racial distribution is largely caucasian/European in both the 250mg and 300mg dose group at 85% and 86% respectively. There were 4% African American in both groups and 10% east Asian heritage in both treatment groups, table 24.

Table 24 LAM30055 Demographic Characteristics

	LAM30055	
Demographic Characteristic	**LTG XR 300 mg/day N=112**	**LTG XR 250 mg/day N=111**
Mean (SD)	33.8 (14.33)	32.9 (12.60)
Range	13-80	13-59
Female	56 (50)	66 (59)
Male	56 (50)	45 (41)
African American/African Heritage	5 (4)	4 (4)
Black	NA	NA
Asian - East Asian Heritage	11 (10)	11 (10)
Asian (Indian)	NA	NA
Asian (Oriental)	NA	NA
White - Arabic/North African Heritage	0	2 (2)
White – White/Caucasian/European Heritage	96 (86)	94 (85)
White	NA	NA
Other	NA	NA

7.2.2 Explorations for Dose Response

Common Adverse events by study dose: The most common adverse events, occurring in at least 5% of patients were more frequent in the 250mg than the 300mg dose group. In the any adverse event category 53% of the 300mg / day group experienced an adverse event and 61% of the 250mg / day group experienced an adverse event. The individual events are shown in table x , section 7.4.1 (common adverse events).

Common adverse events by study phase: In the 300mg/day treatment group 5 of 7 adverse events that reached a frequency threshold of occurrence in greater than 5% of patients, occurred more commonly in the conversion interval of the study and two had a marginal predominance in the monotherapy phase of the study. The five which were more common in conversion were headache, dizziness, Nausea, and rash. Nasopharyngitis and nausea occurred with greater frequency in the monotherapy treatment interval. In the 250mg/ day treatment group 5 of 7 adverse events which a frequency threshold of occurrence in greater than 5% of patients, occurred more

commonly in the conversion interval of the study and two event terms had a marginal predominance in the monotherapy phase of the study. The five occurring more commonly in the conversion interval were dizziness, Nasopharyngitis, nausea, somnolence, and rash. The two adverse event terms more common in monotherapy phase were headache and insomnia, both by only small margins.

Serious adverse events occurred with greater frequency in the lower dose arm of Lamictal treatment. There were 3 (3%) SAEs in the Lamictal XR 300mg/day treatment group compared with 5 (5%) in the Lamictal XR 250mg group. Two of the SAEs in each dose group were related to seizures.

Reviewer Comment: counter to intuition the lower dose Lamictal XR group had a greater occurrence of common adverse events and SAEs (serious adverse events) than the 300mg/day group. Two each of the serious adverse events were related to seizures which is a concern in monotherapy treatment. The timing of these epileptiform adverse events will be explored further in section 7.3.2 (nonfatal Serious Adverse Events)

7.2.3 Special Animal and/or In Vitro Testing

None performed for this submission

7.2.4 Routine Clinical Testing

Routine clinical testing is attenuated in Study LAM30055 due to the extensive prior experience with the active pharmaceutical ingredients. Only a physical examination and full neurologic exam are scheduled at baseline and the end of monotherapy treatment phase, table 21. Clinical laboratory parameters, vital signs, and ECGs, are not monitored during the course of the study as noted in the sponsor statement in the Clinical summary of Safety, see below.

"Clinical laboratory evaluations were not conducted prospectively in Study LAM30055. Because of the extensive database of clinical laboratory data from adjunctive studies with LTG-IR, including the absence of laboratory findings in the previous conversion to monotherapy study with LTG (Study US 30/31), clinical laboratory tests were performed at screening only to confirm eligibility. Additionally, for a drug product that is so well characterized, the absence of a control arm within the study would minimize the interpretability and value of laboratory data." (p 67 CSC)

Table 25 LAM30055 Study Timeline and Activities Schedule

LAM30055		Screen	Baseline		Conversion Phase			Maintenance Phase			Continuation	Taper/ Follow-up[1]
Category	Event				Escalation		Withdrawal of Bkg AED	Monotherapy				
	Visit	V1	V2[2]	V3	V4	V5	V6	V7	V8	V9[3]	V10-12	V13
	Week (approximate)	(≤2 weeks)	Base Wk 4	Base Wk 8[4]	Treat Wk 4[4]	Treat Wk 6/74	Treat Wk 10/114	Treat Wk 14/15[4]	Treat Wk 18/19[4]	Treat Wk 22/23[4]	Continuation Wks 4, 12 and 24	
Eligibility	Informed Consent	x										
	I/E Criteria	x										
	Demography	x										
Safety	Medical & Seizure History	x										
	Physical Exam	x								x		
	Urine Pregnancy Test	x										x
	Full Neurological Exam	x								x		
	Hemat/Clinical Chemistry/Urinalysis	x										
	Adverse Events		x[5]	x[5]	x	x	x	x	x	x	x	x
Treatment	Study Drug Dispensing, Accountability and Compliance			x	x	x	x	x	x	x	x[6]	x

LAM30055		Screen	Baseline		Conversion Phase			Maintenance Phase			Continuation	Taper/ Follow-up[1]
Category	Event				Escalation		Withdrawal of Bkg AED	Monotherapy				
	Visit	V1	V2[2]	V3	V4	V5	V6	V7	V8	V9[3]	V10-12	V13
	Week (approximate)	(≤2 weeks)	Base Wk 4	Base Wk 8[4]	Treat Wk 4[4]	Treat Wk 6/74	Treat Wk 10/114	Treat Wk 14/15[4]	Treat Wk 18/19[4]	Treat Wk 22/23[4]	Continuation Wks 4, 12 and 24	
	Concurrent AEDs/Compliance and Concurrent Medications	x	x	x	x	x	x	x	x	x	x	x
Efficacy	Seizure Counts		x	x	x	x	x	x	x	x	x	x
Pharmacokinetic	LTG Serum Levels					x[7]		x[7]				
Pharmacogenetic	Blood Sample			x[8]								

1 Assessments 2 weeks after total discontinuation of study medication
2 This visit may be omitted if historic baseline data are used.
3 or premature discontinuation
4 Actual weeks will vary depending on use of historic baseline and background AED
5 SAEs only
6 Additional visits at Continuation Weeks 8 and 16 for dispensing and accountability only
7 Trough sample (Pre-dose)
8 Optional and may be obtained at any visit after Visit 2

Reviewer Comment: due to the extensive background experience with the active pharmaceutical ingredient as noted in 7.2.1 (Exposure), the attenuated clinical monitoring schedule is a reasonable course of action.

7.2.5 Metabolic, Clearance, and Interaction Workup

This section has been addressed in the prior submission of Lamictal XR for partial seizures (NDA 22115). Dr. Kapcala indicates in his safety review that the clinical pharmacology review of the submission concluded that the evaluation was adequate.

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 no deaths during the conduct of the double blind phase of the principal efficacy study LAM30055. There was one death 9 months after withdrawing prematurely from the double blind phase of the study due to hepatocellular cancer. This was in patient 254, a 57 year old male who was reported to have moderate alcoholic cirrhosis and viral cirrhosis 105 days after the start of Lamictal XR. The viral cirrhosis and alcoholic liver disease are clearly not due to Lamictal XR but elevate the risk of hepatocellular carcinoma. This death is confounded by the concomitant liver disease of viral and alcoholic cirrhosis and is very unlikely related to the treatment with Lamictal XR. This death was also reviewed for the submission of NDA 22509.

There were no deaths in the open label continuation of LAM30055. There was one death in the IR monotherapy study, US 30/31, study period April 7, 1994 to August 7, 1996. This occurred in patient 30-1-1039 a 22 year old white male randomized to receive valproic acid pseudoplacebo. After 36 days of treatment with VPA in addition to concomitant phenytoin the patient was found dead and a diagnosis of SUDEP was rendered. This event was reviewed for approval of Lamictal IR for use as monotherapy, NDA 20241

7.3.2 Nonfatal Serious Adverse Events

Table 26 Serious Adverse Events in Lamictal XR studies and Lamictal IR monotherapy studies

Study	SAE %	
LAM30055	250mg = 5% (5)	300mg = 3% (3)
30/31 lamotrigine monotherapy	5% (4) -76 patients randomized to LTG	
All completed monotherapy studies	5.4% (47)	
LAM100034 & LAM100036 pooled	3%	
LEP105972 (planned enrollment n=170)	11.8% (based on planned completed enrollment of 170 patients)	

Principal Efficacy Study – LAM30055

In the double blind phase of Study LAM30055 there were 10 serious adverse events which occurred in 8 subjects. 3 (3%) patients in the 300mg Lamictal XR group and 5 (5%) patients in the Lamictal XR 250mg group reported serious adverse events. Two subjects in each group reported two SAEs. The subject number, brief demographics, study phase at onset, and indication of study drug withdrawn (yes/no) are presented in table 27.

Table 27 Subject Listing of all Serious Adverse Events, LAM30055 DB phase

Subject #:Demographics	Preferred term (Verbatim text)	Study Phase at Onset	Background AED if onset during Conversion	Study Drug With-drawn (Yes/No)	Days on Mono-therapy
Lamictal XR 300mg / day group					
807: 24y/F/White	Brain neoplasm (Brain tumor)	Conversion	Pregabalin	Yes	
522: 14y/M/White	Grand mal convulsion (Acute seizure exacerbation [generalized tonic-clonic]) 105 days after lamotrigine	Monotherapy	---	No	105 (31 days on mono-therapy)
	Respiratory failure (Ventilator failure) -diastat	Monotherapy	---	No	
62: 25y/M/White	Head injury (Trauma craniocerebral) seizure day 28 with head trauma, still on background AED	Conversion (day 28 up titration of LTG, BKG unchanged)	Valproate	No	
Lamictal XR 250mg/day group					
810: 29y/M/African American	Concussion (Possible concus[s]ion) Seizure while driving with MVA, during monotherapy, day 141	Monotherapy	---	No	141 (64 days on mono-therapy)
821: 42y/F/White	Upper GI hemorrhage (Upper GI bleed)	Monotherapy	---	No	
223: 33y/F/Asian	Pyrexia (Fever)	Conversion	Oxcarbazepine	Yes	
	Rash (skin rash)	Conversion	Oxcarbazepine	Yes	
254: 56y/M/Asian	Hepatic neoplasm malignant (Hepatocellular cancer)	Monotherapy		Yes	
255: 52y/M/Asian	Partial seizures with secondary generalization (Partial seizures evolving to secondarily generalized seizures) recurrent seizures at initiation of background AED dose reduction.	Conversion (taper of BKG med, day 3 of 80%)	Oxcarbazepine	No	

*shaded rows represent seizure related adverse event

Four of the 8 serious adverse events involved convulsive activity (patients 522, 62, 810, 255). Two occurred during conversion phase (patient 62, 255) and two during monotherapy phase (810, 522). The epileptic events on monotherapy occurred when the patients were on Lamictal XR therapy alone for 31 days (patient 522) and 64 days (patient 810). In two cases the seizure events occurred during the conversion phase. In one case the event occurred during Lamictal XR dose escalation (patient 62) while background AED therapy remained unchanged. In the second case (patient 255) the subject was on the 3rd day of background dose reduction at 80% of original dose. In this second case the reduction of the background AED may be implicated in the seizure event.

There was one SAE of rash, which is in boxed warning in proposed labeling. The remaining three SAEs, brain neoplasm, upper GI bleeding, and hepatic neoplasm (with background viral cirrhosis) were not likely related to study drug treatment.

LAM30055 Open Label Phase

Four subjects (2%) experienced 5 SAEs during the open label continuation phase of Study LAM30055. During this phase all subjects are receiving Lamictal XR 300mg daily.

One patient tripped, fell and suffered a Periorbital hematoma, there was no apparent seizure. A second patient (62) had a seizure during the night and fell 15 days after beginning open label Lamictal XR, the patient suffered closed head injury. A third patient was struck by a motor vehicle when stepping off of a bus. The fourth patient was a baseline failure subsequently enrolled into open label therapy, approximately 7 weeks after beginning Lamictal XR treatment the patient developed status epilepticus and was hospitalized. The patient's baseline AED was Trileptal which had been reduced from 2400mg a day to 600mg a day by the time of the status epilepticus event. This event may have been related to background AED withdrawal.

Reviewer Comment: The percent of SAEs is comparable among the Lamictal XR studies and between the Lamictal XR and Lamictal IR monotherapy studies. The composition of SAEs differs between Study LAM30055 and Study 30/31 (Lamictal IR monotherapy study). In Study LAM30055 there were 4 SAEs due to seizure or seizure related traumatic injury while in Study 30/31 (Lamictal IR monotherapy) there were no SAEs due to seizure. In study LAM30055 two of the seizure related SAEs occurred in conversion phase while two were in monotherapy phase. The event of primary interest is the seizure during monotherapy in the 300mg/day treatment group which raises concern of that 300mg/ day may be an insufficient dose for monotherapy, especially in light of the absence of epilepsy related SAEs in study 30/31. This case was counted as an escape and therefore contributes to the efficacy analysis which mitigates this concern. The remainder of the convulsive events occurred either in the low dose, 250mg/day group, or while the background therapy was maintained.

Of the remaining 4 SAEs no causality can be established for the two cases of neoplasm or the GI bleed. The remaining case of rash is currently an adverse event in labeling.

7.3.3 Dropouts and/or Discontinuations

Table 28 Study Withdrawals in Lamictal XR and Lamictal IR monotherapy studies

Study	Dropout %	
LAM30055	250mg = (11)10%	300mg = (4) 4%
30/31 lamotrigine monotherapy	20%	
All completed monotherapy studies	13.4 %	
LAM100034 & LAM100036 pooled	5%	
LEP105972 (planned enrollment n=170)	13.5% (based on planned completed enrollment of 170 patients)	

The discontinuation rate in study LAM30055 was greater in the 250mg treatment arm, 11 cases (10%) compared to the 300mg / day treatment arm, 4 cases (4%). In the 250mg, lower dose group, breakthrough due to seizure is a concern however only one case was due to a seizure, 7 were due to rash, which is counterintuitive in this lower dose group.

The discontinuation rate is notably lower in study LAM30055 compared to the Lamictal IR monotherapy studies but in the 250mg /day group, the rate is somewhat greater than the Lamictal XR studies in partial (LAM00034) and primary generalized tonic clonic seizures (LAM00036). The 300mg / day group discontinuation rate is comparable to the Lamictal XR studies in partial and primarily generalized seizures, table 29. This comparability mitigates concern of a unique safety signal in the use of Lamictal XR in monotherapy.

Among those who discontinued Lamictal XR in both the 300mg and 250mg / day treatment group, 8 discontinued due to rash and 4 of these patients were on concomitant valproic acid. Two patients discontinued due to neoplasm, one due to **Arthralgia, one due to anxiety, one due to dizziness – nausea, one due to simple partial** seizures and one due to Hand-foot-and-mouth disease.

Table 29 Listing of TEAEs Leading to Withdrawal for the Principal Efficacy Study – LAM30055

Lamictal XR 300mg / day group (n= 113)					
Subject #	**AGE**	**RACE**	**SEX**	**Preferred Term**	**Serious Y/N**
8	34	White	F	Anxiety	N
318	36	White	M	Joint swelling	N

Lamictal XR 300mg / day group (n= 113)					
Subject #	**AGE**	**RACE**	**SEX**	**Preferred Term**	**Serious Y/N**
				Arthralgia	N
633	45	African American	F	Rash	N
807	24	White	F	Brain neoplasm	Y
Lamictal XR 250mg / day group (n=113)					
9	49	White	M	Dizziness	N
				Nausea	N
16	19	White	F	Rash	N
71	51	White	F	Rash	N
112	24	White	M	Rash	N
153	22	White	F	Rash	N
154	43	White	F	Rash	N
220	36	Asian	F	Rash	N
223	33	Asian	F	Pyrexia	Y
				Rash	Y
254	56	Asian	M	Hepatic neoplasm malignant	Y
301	27	African American	M	Simple partial seizures	N
805	39	White	F	Hand-foot-and-mouth disease	N

Reviewer Comment: The dropout rate for the 300mg / day group is similar to the dropout rate of Lamictal XR studies from the application packages for use of Lamictal XR as adjunctive therapy. The dropout rate for the 250mg / day group is notably higher. The reason for this elevated dropout rate in the low dose group is unclear. Only one case was due to seizure which is the intuitive reason which might be expected to occur in a lower dose group. The most frequent reason for dropout in the 250mg / day group is rash which is less expected in a low dose group. Three of the seven patients who developed rash were on concomitant valproic acid which may explain an increased likelihood of rash in approximately 40% of the patients that developed rash in the 250mg / day group. The projected dropout rate (study in progress) for study LEP105972 (Lamotrigine Extended-Release in Elderly Patients with Epilepsy) is the highest of all Lamictal XR studies. This is explainable due to the expected increased sensitivity of the elderly population.

Overall the dropout rate in studies of Lamictal XR is lower than Lamictal IR monotherapy studies.

7.3.4 Significant Adverse Events

Skin Rash

Serious skin rash is the most threatening adverse effect in the use of Lamictal. This risk is well defined and present in a boxed warning. In this section the frequency of rash in

study LAM30055 is compared with the occurrence of rash in study 30/31 and the completed monotherapy studies.

Principal Efficacy Study – LAM30055

In Study LAM30055, rash was reported by 4 (4%) subjects in the 300 mg/day LTG XR group and 12 (11%) subjects in the 250 mg/day LTG XR group. Most TEAEs of rash were judged to be reasonably attributable to study drug in both treatment groups. Additionally, rash led to withdrawal of 1 (<1%) subject in the 300 mg/day LTG XR group and 7 (6%) subjects in the 250 mg/day LTG XR group. During the long term continuation phase of study LAM30055 two subjects reported rash.

Study 30/31

10 (13%) subjects in the Lamictal IR treatment group experienced rash and 6 (7.5%) in the pseudoplacebo (VPA) group. One of the cases in the Lamictal IR group was diagnosed as Stevens-Johnson Syndrome. 8 of the 10 rashes in the Lamictal IR group were considered mild to moderate intensity while 2 sere considered severe. Eight of the rashes in the Lamictal IR group occurred during treatment transition, which is the most likely interval of onset. Six patients in the Lamictal IR group and 1 in the pseudoplacebo (VPA) group discontinued due to the rash. All serious rashes and rash leading to discontinuation in the Lamictal IR group occurred during treatment transition phase of the study.

Completed Monotherapy Studies (Lamictal IR, including study 30/31)

Of the 868 unique subjects exposed to LTG IR in the Completed Monotherapy Studies, **117 (13%) reported an AE classified as "all rash" (rash, pustular rash, macular papular** rash, urticaria, Stevens-Johnson Syndrome, and vesicular bullous rash). Most (100/117, 85%) of the rashes were mild to moderate in intensity. Seventeen rashes on LTG IR were considered severe, 8 were SAEs, and 53 lead to discontinuation of LTG IR.

Reviewer Comment: The frequency of rash in study LAM30055 is at a maximum in the 250mg/day group. At this maximum the frequency is less than the frequency in the Lamictal IR monotherapy trials. No SJS or TEN developed in study LAM30055.

SUDEP

There were no deaths in study LAM30055. In the completed IR monotherapy studies there were 7 deaths, 4 were on study medication, 3 were on a comparator AED. Among those on Lamictal IR two were classified as SUDEP. These events both occurred during stable monotherapy dosing for 300 days in one case and 355 days in the second. There was a SUDEP case in the VPA arm of study 30/31 which occurred approximately 1 month after the addition of the VPA pseudoplacebo. This latter case supports the ethical concern of pseudoplacebo which was put forward in the White Paper, see section 2.6

7.3.5 Submission Specific Primary Safety Concerns

none

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Principal Efficacy Study – LAM30055

A total of 53% (59) of patients in the 300mg / day Lamictal XR group and 61% (68) of patients in the 250mg / day group experienced an adverse event. The most common AEs for the LTG XR 300 mg/day group were headache (26%), dizziness (11%), nasopharyngitis (6%), and nausea (5%). The most common AEs for the LTG XR 250 mg/day group were headache (28%), rash (11%), dizziness (9%), nasopharyngitis (6%), insomnia (5%), nausea (5%), and somnolence (5%). The incidence of AEs was similar between the 2 treatment groups with the exception of rash and insomnia which were less common with LTG XR 300 mg/day (4% and 0%, respectively) relative to LTG XR 250 mg/day (11% and 5%, respectively), table 30.

Table 30 Most Common (Reported by At Least 5% of Subjects in Either Treatment Group) Treatment-Emergent Adverse Events (Safety Population: Study IAM30055)

	LTG XR 300 mg/day N=112	LTG XR 250 mg/day N=111
Any AE, n (%)1	**59 (53)**	**68 (61)**
Preferred Term, n (%)		
Headache	29 (26)	31 (28)
Dizziness	12 (11)	10 (9)
Rash	4 (4)	12 (11)
Nasopharyngitis	7 (6)	7 (6)
Nausea	6 (5)	6 (5)
Somnolence	5 (4)	6 (5)
Insomnia	0	5 (5)

Adverse Events by Study Phase at Onset

Adverse events overall were more common during the Conversion Phase relative to the monotherapy phase for both the 300mg/day and 250mg / day treatment groups. The preferred terms which were most frequent during the Conversion Phase for both

treatment groups were dizziness, somnolence, rash, and nausea. There was no consistent trend seen in the incidence related to study phase for headache, n nasopharyngitis, or insomnia. The incidence of AEs was consistently lower for the LTG XR 300 mg/day group relative to the 250 mg/day group regardless of study phase at onset.

Study 30/31

A total of 63 subjects (83%) in the LTG group and 69 subjects (86%) in the VPA group (low dose active control- pseudoplacebo) reported AEs.

The five most commonly reported AEs in the Lamictal IR treated group in this study were dizziness (24%), nausea (18%), headache (17%), asthenia (14%), and tremor (11%).

Completed Lamictal IR Monotherapy Studies

A total of 605 (69.7%) subjects on LTG reported AEs some time during the course of treatment. The five most commonly reported AEs were headache (16.7%), asthenia (13.6%), "all rash (13.5%), dizziness (12.7%), and nausea (9.1%).

Reviewer Comment: Study LAM30055 had fewer total adverse events than the immediate release studies, 53% , compared to 83% in study 30/31 and 69.7% in the pooled Lamictal IR monotherapy studies. The profile of adverse events which occurred in at lease 5% of patients was similar. In study LAM30055 headache was the most frequent at 26% compare to 13% in study 30/31 and 17% in all pooled IR monotherapy trials. In Study LAM30055 there was a 6% frequency of Nasopharyngitis in the 300mg/day group whereas this adverse effect did not occur at a rate greater than 5% in either study 30/31 or the pooled IR (immediate release) monotherapy studies. Dizziness and nausea were less frequent in LAM30055 compared to study 30/31 or the pooled IR monotherapy studies.

7.4.2 Laboratory Findings

Clinical laboratory evaluations were not conducted prospectively in Study LAM30055. Because of the extensive database of clinical laboratory data from adjunctive studies with LTG-IR, including the absence of laboratory findings in the previous conversion to monotherapy study with LTG (Study US 30/31), clinical laboratory tests were performed at screening only to confirm eligibility- agreed upon at teleconference with sponsor on July 24, 2009.

7.4.3 Vital Signs

Vital signs and ECG data were not collected prospectively during treatment in Study

LAM30055. Because of the extensive database of vital signs and ECG data from adjunctive studies with LTG-IR, including the absence of safety findings in the previous conversion to monotherapy study with LTG (Study US 30/31), vital signs and ECG were performed at screening only to confirm eligibility- - agreed upon at teleconference with sponsor on July 24, 2009.

7.4.4 Electrocardiograms (ECGs)

ECG not collected prospectively - agreed upon at teleconference with sponsor on July 24, 2009.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies submitted in this application.

7.4.6 Immunogenicity

Lamotrigine is a small molecule however 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 study LAM30055 the frequency of rash has been less than in Lamictal IR study 30/31 seen to be 11% (11% in 250mg/day group and 4% in 300mg/day group) 13% respectively. In study 30/31 one case developed into Stevens-Johnson syndrome whereas non in study LAM30055 developed Stevens-Johnson syndrome or Toxic Epidermal Necrolysis.

7.5 Other Safety Explorations

This safety dataset for efficacy supplement for Lamictal XR is composed of pivotal clinical trial LAM30055, legacy Lamictal IR monotherapy trials, and ongoing trial LEP105972. All but ongoing study LEP105972 were reviewed in NDA22509 (**LAMICTAL® XR™ (lamotrigine)** Extended-Release Tablets for Adjunctive Treatment of Primary Generalized Tonic-Clonic Seizures), therefore NDA22509 is referenced for this section.

7.5.1 Dose Dependency for Adverse Events

See section 7.5 opening statement

7.5.2 Time Dependency for Adverse Events

See section 7.5 opening statement

7.5.3 Drug-Demographic Interactions

See section 7.5 opening statement

7.5.4 Drug-Disease Interactions

See section 7.5 opening statement

7.5.5 Drug-Drug Interactions

See section 7.5 opening statement

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 (normal birth), 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

There were 32 patients in enrolled in the age range 13 to 17 inclusive. Twenty of the pediatric age range subjects experienced 65 adverse events. One pediatric patient suffered an SAE; none were withdrawn from the study. The subject (522), who experienced the SAE, noted in table 23, suffered an exacerbation of seizures and developed respiratory failure, possibly due to a Diastat treatment.

Table 31 Adverse events in the pediatric population of study LAM30055

Perferred term	Frequency	Percent of All AE
Headache	29	44.6
Nasopharyngitis	3	4.6

Nausea	3	4.6
Pharyngitis	3	4.6
Abdominal pain upper	2	3.1
Rash	2	3.1
Rhinitis allergic	2	3.1
Seasonal allergy	2	3.1
Abdominal pain	1	1.5
Alopecia	1	1.5
Amnesia	1	1.5
Bronchitis	1	1.5
Cough	1	1.5
Diarrhoea	1	1.5
Dysmenorrhoea	1	1.5
Epistaxis	1	1.5
Gastrooesophageal reflux disease	1	1.5
Grand mal convulsion	1	1.5
Muscle spasms	1	1.5
Pain in extremity	1	1.5
Pharyngotonsillitis	1	1.5
Respiratory failure	1	1.5
Tachycardia	1	1.5
Tonsillitis	1	1.5
Tremor	1	1.5
Upper limb fracture	1	1.5
Vomiting	1	1.5

Table 32 Adverse events in the pediatric population of study LAM30055 by dose group

	LTG XR 300 mg/day N=112	LTG XR 250 mg/day N=111
Any AE, n (%)1	**59 (53)**	**68 (61)**
Preferred Term, n (%)		
Headache	29 (26)	31 (28)
Dizziness	12 (11)	10 (9)
Rash	4 (4)	12 (11)
Nasopharyngitis	7 (6)	7 (6)
Nausea	6 (5)	6 (5)
Somnolence	5 (4)	6 (5)
Insomnia	0	5 (5)

Headache was the most frequent adverse event in the pediatric group, 44.6% followed by Nasopharyngitis 4.6%, Nausea 4.6%, pharyngitis 4.6%, abdominal pain upper 3.1%, rash 3.1%, rhinitis allergic 3.1% and seasonal allergy 3.1%. The remaining adverse events accounted for less than 2% each, of the total. This profile is similar to the profile

of common adverse events in adults for the top 5 preferred terms. There is a difference in positions five and six, somnolence and insomnia respectively, where these terms are not present in the list of pediatric adverse events.

Request for Partial Waiver for Conducting Pediatric Studies

The sponsor requests a partial waiver from conducting a study evaluating conversion to monotherapy with LAMICTAL in pediatric patients with partial seizures age 1 month to 16 years who are receiving therapy with a single antiepileptic drug. The sponsor believes that conducting such a trial would not be feasible for ethical reasons a well as the absence of a suitable comparator group.

The sponsor (GSK) provides history which reveals this (b) (4) iteration of such a request for partial waiver. The (b) (4) directive to pursue a study of the safety and effectiveness of conversion to monotherapy with Lamictal in pediatric patients age 1 month to 16 years (receiving valproate) for treatment of partial seizures came as a Phase IV commitment, triggered by the approval to lift the restriction for converting adults on valproate to LAMICTAL monotherapy (January 14, 2004). In a subsequent correspondence on April 7, 2005 the sponsor noted the ethical issues relevant to studies such as 30-31 which was the basis for approval of monotherapy in adults. In addition GSK noted possible safety issues surrounding the use of valproate in pediatric patients less than age two. The FDA agreed to a partial waiver in patients 1 month to 2 years (b) (4)

The sponsor (b) (4) presents additional counter argument in this (b) (4) iteration of request for partial waiver from conducting a study to evaluate conversion to monotherapy with LAMICTAL in pediatric patients with partial seizures age 1 month to 16 years old receiving therapy with a single AED. These counter arguments are twofold, first based on current thinking, a pseudoplacebo type study design such as study 30/31 is no longer considered ethical, second, if a design based on the use of a historic control is utilized, such as in study LAM30055, there is no suitable comparator group. The White Paper historic control is based on data obtained from studies in adults. The sponsor also believes that a monotherapy indication in pediatric patient based on extrapolation from adjunctive efficacy and pharmacokinetic data in adults and pediatric patients and monotherapy efficacy and PK data in adults is also not feasible due to the long interval needed to reach steady state monotherapy LAMICTAL level (14 to 15 weeks in patients needing 10mg/kg/day and 8 weeks in patients taking 5mg/kg/day).

Age band for current labeling

> Lamictal IR is approved for monotherapy to ≥16 years of age, while the proposed label for Lamictal XR is for use in conversion to monotherapy in patients ≥13 years of age. This seems to contradict the sponsor request for pediatric wavier from 1 month to 16 years of age, for how can Lamictal XR be labeled down to age 13 when there is a pediatric waiver to age 16?

Study 30/31, studied to age 13 but only 7 patients 17 and less.

Table 33 Number of Pediatric Participants in LAMICTAL IR monotherapy trial (30/31) and LAMICTAL XR Studies (LAM100034, LAM100036, and LAM30055.

Study 30/31	
AGE	Number subjects
13	1
14	1
15	1
16	2
17	2
Study LAM100036	
AGE	Number subjects
13	1
14	5
15	4
16	3
17	6
Study LAM100034	
AGE	Number Subjects
13	3
14	4
15	3
16	1
17	9
Study LAM30055	
AGE	Number Subjects
13	5
14	9
15	4
16	7
17	7

Table 34 Study LAM30055 Pediatric Exposure to LAMICTAL XR (250mg/300mg)

LAM30055 pediatric exposure 250/300mg				
Subject	Age	Exposure	Dose	Comment
134	13	77 days	250mg	

101	13	85	250	
147	13	112	300	
169	13			max 200mg
170	13	84	250	
141	14	83	250	
148	14	113	300	
166	14	84	250	
177	14	84	250	
179	14	84	300	
522	14	64	300	
722	14	55	300	
862	14	133	250	
140	15	84	300	
144	15	83	300	
145	15	76	300	
167 **Total Exposure**	15	112 1413 total days exposure	300	 630 days at 250mg (7 patients) 783 days at 300mg (9 patients)

Safety of Lamictal XR in monotherapy is supported to age ≥13 based on the currently **labeled approval of Lamictal XR "as adjunctive therapy for primary generalized tonic-clinic (PGTC) seizures and partial onset seizures with or without secondary generalization in patients ≥13 years of age.**"

Efficacy is not supported for use of Lamictal IR conversion to monotherapy for age <16 in current labeling. Study 30/31 had only 3 patients in this age range.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

In this submission the sponsor provides the following narrative on overdose:

"**In Study LAM30055, an overdose of LTG XR** was defined as an ingestion of a dose ≥5 times the target daily dose indicated by the protocol. No overdose of LTG XR was reported during the study.

In the LTG XR clinical development program, there was one report of overdose, a summary of which is provided in the initial submission of NDA 22-115. A subject in the LTG-LTG treatment group in the open-label Continuation Phase of Study LAM100034 **was taking 200 mg/day LTG XR and had a fatal SAE of "acute poisoning by LTG". The**

event was judged by the investigator to have a reasonable possibility of being related to study drug. The investigator indicated that the "acute LTG poisoning" represented a possibly intentional LTG overdose, although there was no circumstantial evidence suggesting an intentional overdose with LTG, and the event did not meet the protocol definition of overdose. Concomitant medications included VPA and clonazepam. No incidences of targeted overdose with LTG XR in the LTG XR clinical development program were reported.

There were no reports of overdose with LTG IR during Study US 30/31 or the individual studies in the Completed Monotherapy Studies grouping (US 30/31, UK 49, UK 74, UK 89, UK 105, UK 106, UK 111, UK 112, UK 115).

Acute ingestion of doses in excess of 10 to 20 times the maximum therapeutic dose of LTG IR has been reported. Overdose 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 the Lamictal XR 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)*

7.7 Additional Submissions / Safety Issues

No additional submissions for review

8 Postmarket Experience

Lamictal XR Distribution data for the interval May 29, 2009 to July 24, 2010 (Annual Report) is provided in table 27. Analysis of the sale and distribution of tablets, not including starter kits and samples, reveal distribution of product sufficient to treat (b) (4) patients with 400mg of Lamictal XR daily, over the report interval of 421 days (1.15 years).

Table 35 Lamictal XR Distribution data for the interval May 29, 2009 to July 24, 2010

Description	Domestic Sales	Domestic Free Issues	Domestic Samples	Foreign Sales	Foreign Free Issues	Foreign Samples
LAMICTAL XR TABLETS 25MG 30s	(b) (4)					
LAMICTAL XR TABLETS 50MG 30s						
LAMICTAL XR TABLETS 100MG 30s						
LAMICTAL XR TABLETS 200MG 30s						
LAMICTAL XR TABLETS 25MG/50MG STARTER KT						
LAMICTAL XR TAB BLUE DE KIT 25MG/50MGSPL						
LAMICTAL XR TABLETS 50MG/100MG/200MG KIT						
LAMICTAL XR TAB GREEN DE KIT 50/100/200						
LAMICTAL XR TABLETS 25MG/50MG/100MG KIT						
LAMICTAL XR TAB ORANGE DE KIT 25/50/100						

Lamotrigine, the active pharmaceutical ingredient of Lamictal XR has extensive post marketing exposure since approval in 1994. In the most recent annual report for the period covering July 25, 2009 to July 24, 2010, for Lamictal (immediate release lamotrigine) the distribution data for tablets, not including multi-strength starter kits, indicate a total distribution of (b) (4) mg. This represents adequate product to treat (b) (4) patients for one year with 400mg of Lamictal daily.

8.1 For a post-marketing update to November 11, 2009 the reader is referred to the medical review of NDA22509. The following review will bring the post marketing review of Lamictal IR and Lamictal XR up to date from November 1, 2009.

Lamictal XR

AERS Examination, Generic term lamotrigine

The AERS database is examined for cases by preferred term for the interval from the end of post marketing review for NDA22509 (November 19, 2009) to January 14, 2011. The top ten preferred terms present in AERS reports for all forms of lamotrigine are; rash, convulsion, drug exposure during pregnancy, drug ineffective, pyrexia, dizziness, **headache, Stevens-Johnson's Syndrome, Product substitution issue, and drug** interaction seen in table 28. A parallel evaluation of the AERS database using Empirica Signal reveals the number of cases identified by Empirica Signal and the associated EB05 score, table 36. The AERS search reveals frequencies which are consistently higher, this is because the Empirica search is for one calendar year, compared to the 14 month interval for the AERS search and the Empirical database is processed to remove duplicate entries.

Table 36 Top Ten Preferred terms (11/19/2009 to 1/14/2011) captured from term "lamotrigine"

Top Ten Preferred terms (11/19/2009 to 1/14/2011) PT	AERS # Cases with PT	Empirica # cases 2010 (database query on 1/14/2011	2010 EB05
Rash - *black box	511	448	8.13
Convulsion - *status epilepticus in warnings & precautions / seizure worsening in patient information	349	276	3.8
Drug Exposure during pregnancy	304	233	2.82
Drug Ineffective	211	201	0.79

Pyrexia - *fever is noted in clinical trials more frequently in treatment than placebo	200	167	2.16
Dizziness	167	143	1.07
Headache	156	122	1.01
Stevens-Johnson Syndrome- *black box	143	126	11.49
Product Substitution issue	130	90	7.20
Drug Interaction	129	99	3.05
* Shaded cells represent EB05 greater than 2.0			

Reviewer Comment: In the table of top ten preferred terms for all forms of lamotrigine there are several with EB05 >2 which are events directly related to the API. These include Rash, Stevens Johnson syndrome, convulsion and pyrexia. All of these events are currently in labeling, the specific labeling entry is provided at the asterisk.

The AERS database is also examined for cases of special interest; serious skin rash, hypersensitivity reactions, blood dyscrasias, liver dysfunction, and suicide events for the interval from the end of post marketing review for NDA22509 (November 19, 2009) to January 14, 2011. The number of cases for each of the preferred terms in the category of special interest found in the AERS database, by an Empirica signal search and the associated EB05 are seen in table 37. The EB05 values are notably elevated only for serious skin rashes, toxic epidermal necrolysis and erythema multiforme in the table below and Stevens-Johnsons Syndrome in the table of top ten preferred terms above. There is a modest EB05 elevation of 2.14 noted for "hepatic enzyme increased".

Table 37 Preferred terms for Events of special interest (11/19/2009 to 1/14/2011), captured from term "lamotrigine"

Preferred terms for Events of special interest (11/19/2009 to 1/14/2011)	AERS # Cases with PT	Empirica # cases 2010 (query on 1/14/2011	2010 EB05
Toxic epidermal necrolysis- black box	37	35	7.62
Erythema multiforme –rare erythema multiforme in clinical trials	13	12	3.27
Completed Suicide	86	69	1.45
Suicide attempt	44	31	1.07
Suicidal ideation	62	47	0.99
Hepatic Enzyme abnormal	2	2	0.68
Hepatic enzyme increased-liver function tests abnormal (adverse events in all clinical trials)	22	21	2.14
Hepatic failure	7	7	1.31

Hepatic function abnormal	24	21	1.69
Neutropenia	14	10	0.66
Leukopenia	15		1.59
Thrombocytopenia	22		1.29
Agranulocytosis	2	2	0.97
Anaemia	12	10	0.62
Aplastic anaemia	3		2.15
aplasia pure red cell	1	1	0.64
Granulocytopenia	2	1	0.08
Pancytopenia	15	10	0.97
Drug hypersensitivity	33	24	1.5
Hypersensitivity	49	39	1.16
Multi-organ failure	12	8	1.05
* Shaded cells represent EB05 greater than 2.0			

Reviewer Comment: Those adverse events of special interest for lamotrigine with an EB05 >2 are present in labeling. The location in labeling is noted.

Disproportionality Evaluation (MGPS) 2009 compared to 2010 for lamotrigine

In this section a disproportionality evaluation is performed for topics of special interest to determine if there has been an increase in signal for these topics with progression from year 2009 to 2010. The search terms for each topic of special interest is presented below.

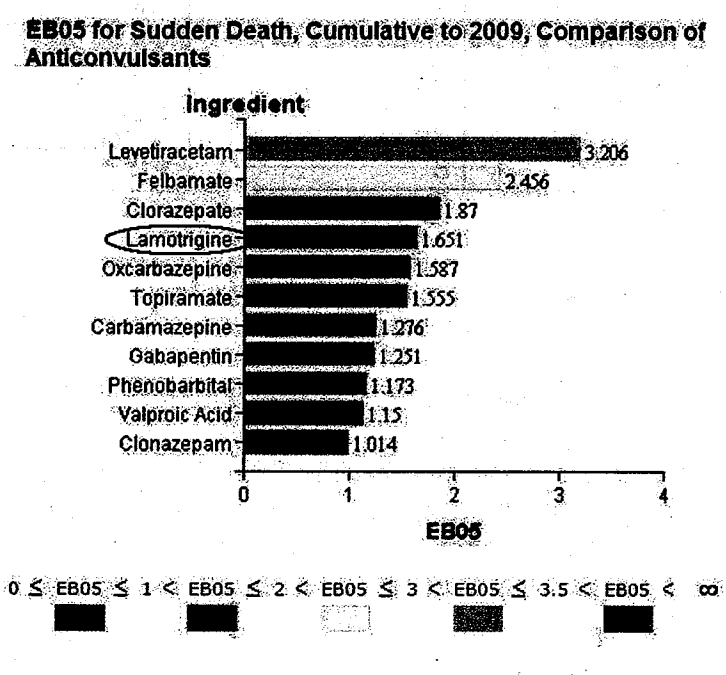
Table 38 lamotrigine safety topics of special interest

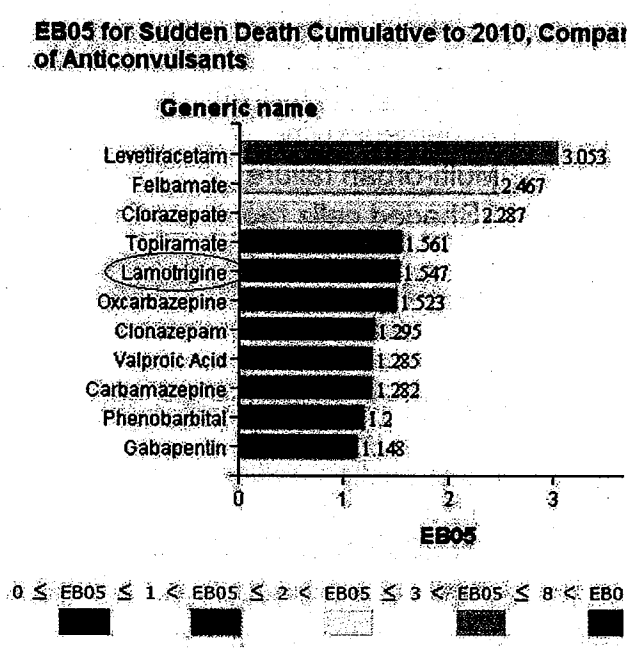
Topic of interest	Search Terms (PTs)
Suicide	Completed suicide, Depression suicidal, Suicidal behaviour, Suicidal ideation, Suicide attempt, intention overdose
Serious Rash	Stevens-Johnson syndrome, Toxic epidermal necrolysis, Erythema multiforme
All Rash	Rash
hypersensitivity	hypersensitivity, drug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

Topic of interest	Search Terms (PTs)
	abnormal, Hyperbilirubinaemia, Liver function test abnormal

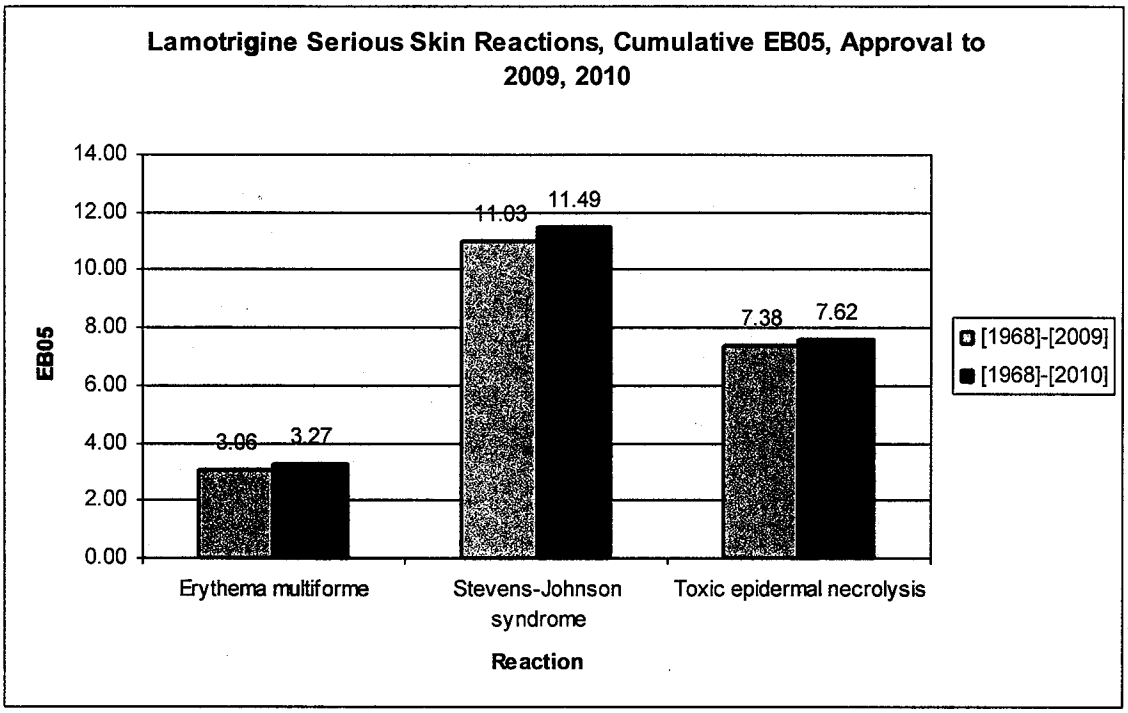
In the graphic below a disproportionality evaluation is performed using the preferred term sudden death for lamotrigine and a panel of commonly prescribed anticonvulsant drugs for the years 2009 and 2010 to assess for any progressive increase in signal with the progression of time. In this analysis the EB05 for lamotrigine remains stable and has a shift in position from 4th to 5th in EB05 value, in addition the EB05 remains below 2.0. This analysis does not indicate a change in the safety signal for sudden death.

Sudden Death

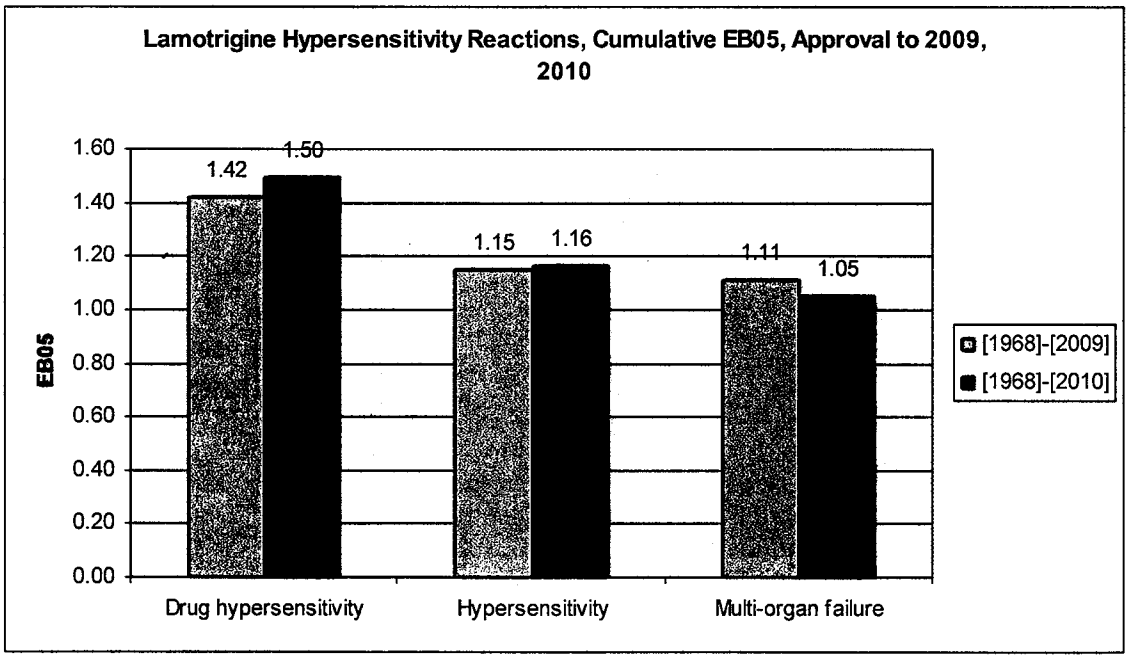




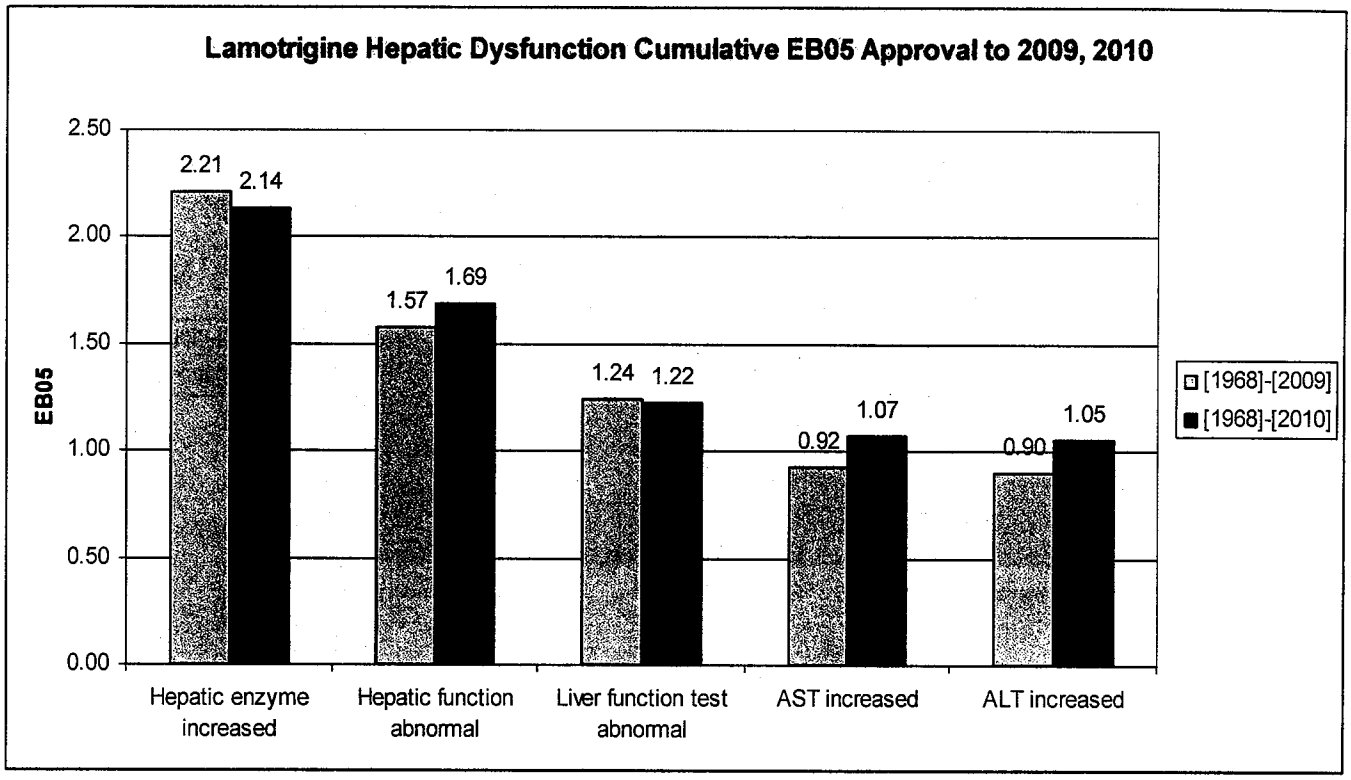
Serious Skin Reaction



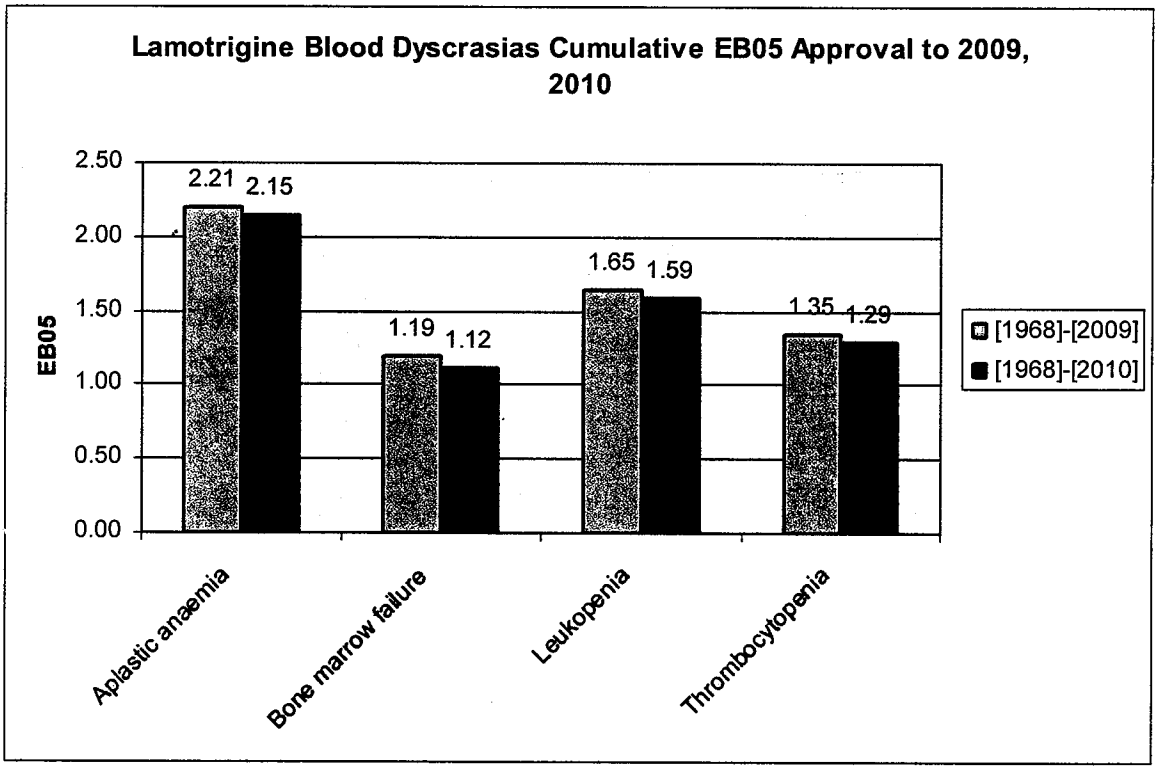
Hypersensitivity Reactions



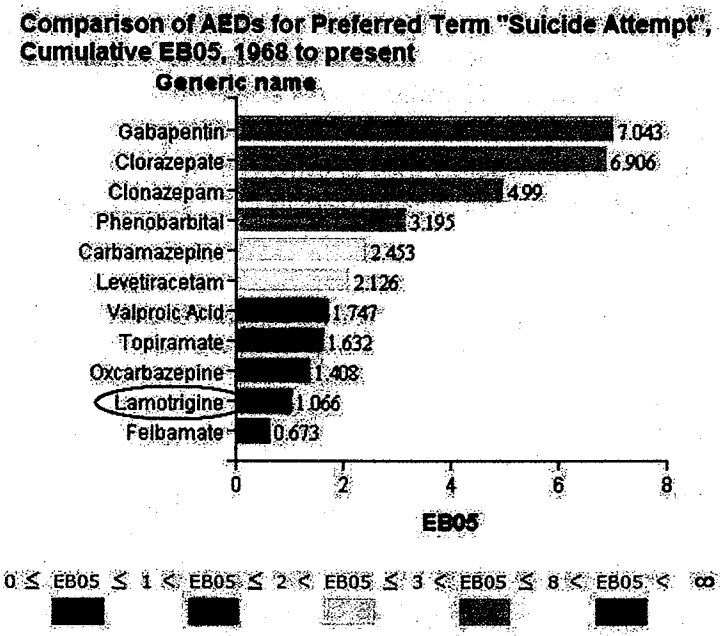
Hepatic Dysfunction

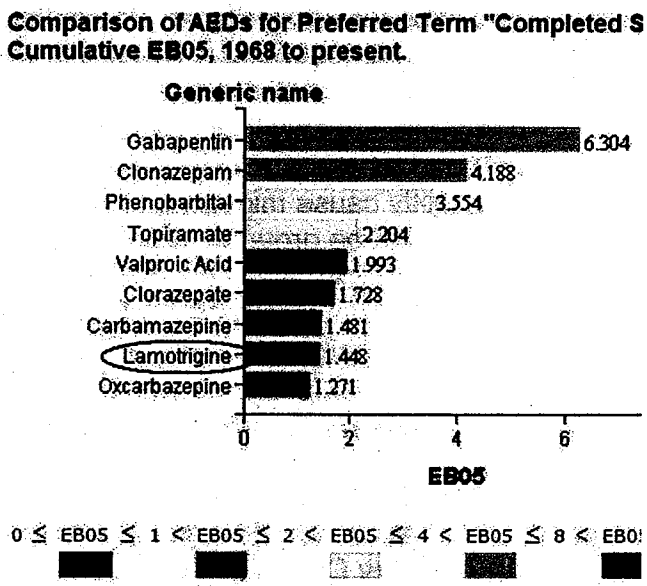


Blood Dyscrasias



Suicide





Reviewer Comment: The EB05 values for topics of special interest are examined for change in the year 2009 to year 2010 interval. There are no notable increases identified. The EB05 for lamotrigine, preferred term sudden death is examined relative to a panel of anticonvulsant drugs frequently used in practice for the years 2009 and 2010. The EB05 does not exceed 2.0 and there is no notable difference between 2009 and 2010. The EB05 for lamotrigine, preferred terms "suicide attempt" and "completed suicide" is examined relative to a panel of frequently used anticonvulsant drugs. The EB05 for "suicide attempt" is close to unity (no difference from background) and the EB05 for completed suicide is well below 2.0. In the cases of both "suicide attempt" and "completed suicide" lamotrigine falls in second from last position of all anticonvulsants in the panel in the magnitude of EB05 signal strength. These post marketing analyses do not indicate a signal for an increase in "suicide attempt", "completed suicide", or "sudden death" in the recent marketing interval. Analyses of the topics of special interest for lamotrigine also do not show an increase signal for increase frequency in the recent marketing interval.

9 Appendices

9.1 Literature Review/References

See footnotes

9.2 Labeling Recommendations

The sponsor has grouped "headache and migraine" as the most common adverse event in study LAM30055. Exploration of the preferred terms headache and migraine in the adverse event dataset reveal that there were a total of 61 patient who suffered heachace but only 2 of these were migraine. The reviewer concludes that the grouping of "headache and migraine" in the label give the impression that LAMICTAL XR may frequently cause migraine. However migraine is a distinct phenomenon from headache and should be grouped separately.

The adverse event section of the label should be edited to reflect headache (alone) is the most common adverse effect (26%).

9.3 Advisory Committee Meeting

A. Advisory Committee Meeting Held and date

An Advisory Committee was convened Because of the novel methodology of the Historic Control study design the Peripheral and Central Nervous System advisory committee meeting was convened on March 10, to address relevant issues.

Questions to the Advisory Committee

1. Does the Committee believe that placebo-controlled monotherapy studies in patients with partial seizures are ethically acceptable? (YES/NO/ABSTAIN)

Committee Discussion: *As the discussion evolved it was agreed that the question could be better served by informative exploration of the topic and no vote was taken at the conclusion. The committee first requested a clarification of this question, asking if "pseudo-placebo" was included in the question. This question generated discussion on trial designs beyond those of the eight trials White Paper trials. One such design is in epilepsy patients who have been withdrawn from their anticonvulsant treatment during pre-surgical evaluation, another in the situation of a degenerative process where no alternative treatment is available. At the conclusion of discussion the committee agreed that long-term outpatient placebo-controlled or pseudo placebo-controlled trials of the sort demonstrated by the historical control studies presented by French et al. would be ethically problematic in general but may be appropriate in a subset of specific patient subsets or in the short-term inpatient setting when there is already demonstrated efficacy as adjunctive therapy.*

2. If the answer to Question 1 is No, does the Committee believe that under the specific circumstances, in which a drug is known to be effective as adjunctive treatment, an historical control approach of the sort proposed by French et al., can be acceptable. YES/NO/ABSTAIN

YES: 14 NO: 0 ABSTAIN: 0

Committee Discussion: *The committee unanimously agreed that a historical control approach, of the sort proposed by French et al., can be acceptable under the specific circumstances in which a drug is known to be effective as adjunctive treatment.*

3. If the answer to Question 2 is Yes, the Committee should discuss the specific methodology performed by French et al. (e.g. the propriety of combining the eight control groups into a single historical control, the specific statistical approach used to combine the groups, the appropriateness of using a prediction interval and the specific prediction interval used to establish effectiveness) and whether it is acceptable.

Committee Discussion: *The committee voiced concerns regarding the heterogeneity of the methodology utilized by French et al., but concurred that it is acceptable as long as the inherent irregularities are addressed. One committed member felt the 8 studies were not adequately similar and the KM curves were also not close. However; the prediction interval was concluded to be overall adequately conservative. Additionally, some of the committee members felt that it may have been problematic for the escape rates to be pooled into one aggregate rate.*

4. If the methodology is considered acceptable, what elements of a study using this approach are critical to consider, for example:

a. Matching demographics (age, race, duration/severity of epilepsy, nationality, etc.)
b. Initial concomitant AED's
c. Differences in conversion methods
d. Temporal trends in response
e. Dropouts
f. Any other elements

Committee Discussion: *The committee agreed that all of the following elements are important: matching demographics, initial concomitant antiepileptic drugs, differences in conversion methods, temporal trends in response, and dropouts. The greatest concern was demographics, two committee members had international clinical experience and their observations lead to a conclusion that diagnosis and medical practice may not be fully parallel to US medical standards. Background AEDs were also a prominent concern as a source of difference between the historic control and current study populations. One committee member had concern abut the temporal difference between the historic control studies and the more recent current study. It was advised that historical control methodology is not a new field. Criteria were set forth by Pocock SJ*[11] *and a committee statistician stated that all of these criteria were violated.*

11 Pocock SJ. The combination of Randomized and Historical Controls in Clinical Trials. J Chron Dis.

5. Does the study under consideration fulfill the necessary criteria to allow for a determination of effectiveness? Specifically, we would like the Committee to discuss:

a. Potential for bias due to the fact that all patients are receiving active treatment.
b. Potential bias due to under-reporting of study endpoints.
c. Number of background AED's
d. The comparability of exit criteria in this study and in the historical control
e. U.S. vs. Foreign data

Committee Discussion: *The potential for bias due to the patient and investigator knowledge that all patients are receiving active treatment was a significant concern to the committee. Some members suggested that an additional arm using an active comparator may reduce this bias. The committee speculated that the low initial escape rate may be due to this bias. Underreporting of study endpoints was corrected by calculated escapes based on seizure diary data. Although post hoc, the retrospective analysis of data should be correct. The difference in background AEDs violates the first Pocock criteria. The difference in country of origin of LAM30055 compared to the historic control was a major concern, two committee members reported discernable differences in diagnostic acumen in their personal interactions with some foreign neurologists. The sponsor commented that the primary investigators were selected because they were at the top of their field.*

In conclusion the committee noted that a drug effect was evident despite the uncertainties that were inherent about the open label bias and heterogeneity in the controls because statistical adjustments were made (prediction interval and lower limit 95% confidence interval). However, it was also noted that it is questionable if there is a drug effect if there is a need for preservation of effect.

6. Has the sponsor submitted substantial evidence of effectiveness for Lamictal XR as monotherapy for the treatment of partial seizures? YES/ NO/ ABSTAIN

YES: 10 NO 2 ABSTAIN; 1

a. If "YES", please discuss whether or not the fact that Lamictal IR is approved for monotherapy was critical to the decision.

Committee Discussion: *Note: one committee member was not present for the vote. The majority of the committee agreed that the sponsor submitted substantial evidence of effectiveness for Lamictal XR as monotherapy for the treatment of partial seizures. All of the committee members who voted "YES" stated that the fact that Lamictal IR is approved for monotherapy was critical to their vote. Please see the transcript for details of the Committee discussion.*

1976;29:175-188.

7. Based on the discussions that transpired, the following question was added during the meeting: Assuming there is a very good match between the active treatment group and the historical controls could you consider approval for a monotherapy indication for a drug that had adjunctive efficacy demonstrated but had not been examined in monotherapy using a different formulation/

Committee Discussion: *The committee agreed that they would recommend approval of a drug that had efficacy demonstrated for adjunctive therapy but had not been evaluated for monotherapy (using a different formulation) if there was a good match between the active treatment group and the historical controls. Please see the transcript for details of the Committee discussion.*

9.4 Study Methodology

9.4.1 Inclusion Criteria- acceptable form of birth control:

a. Complete abstinence from intercourse for 2 weeks before exposure to the study drug, throughout the clinical trial, and for a period after the trial to account for elimination of the drug (a minimum of 2 weeks).
b. Consistent and correct use of one of the following methods of birth control:
• **Male partner who was sterile prior to the female subject's entry into the study** and was the sole sexual partner for that female subject.
• **Any intrauterine device with a documented** failure rate of less than 1% per year.
• **Double barrier method consisting of spermicide** plus a mechanical barrier (e.g., spermicide plus a male condom or a female diaphragm).

NOTE: Women who had had a hysterectomy, tubal ligation, or were post-menopausal were considered to be of non-childbearing potential.

NOTE: A PK interaction has been observed between lamotrigine and estrogen-based oral contraceptives. Therefore, the use of hormonal therapy (e.g., for contraception or hormone replacement therapy) was not allowed.

9.5 Criteria Comparator

Study/ Pub date	Escape Criteria by Study	Matching Properties
1 (1992)	(1) **(3)**an episode of status epilepticus; (2) **(4)**a secondarily generalized tonic-clonic seizure if none had been experienced within 2 years of study entry; (3) **(1)** a 28-day study seizure rate greater than two times the maximum 28-day study seizure rate during baseline (a 28-day period is defined as any four consecutive study weeks);	Does not have # 4 equivalent, removal of 4 leaves Parity **Inherent non-parity before removal of 4**

	(4) **(2)**a 2-day study seizure rate greater than two times the maximum 2-day study seizure rate during baseline; or *(5)* **(3)** an unacceptable increase in the frequency or intensity of seizure activity that did not meet any of the exit criteria but that was, in the opinion of the treating physician, clinically significant	
2 (1998)	1) doubling of average monthly seizure rate; 2) doubling of the highest consecutive 2-day seizure rate; 3) emergence of a new, more severe seizure type; or 4) clinically significant prolongation of generalized tonic-clonic seizures	Parity
3 (1997)	1. a doubling of the average monthly (28-day) baseline seizure frequency, 2. a doubling of the highest 2-day baseline seizure frequency, 3. a single GTCS if none occurred during baseline, 4. Prolongation of generalized seizure duration that was considered serious by the investigator, or serial seizures or status epilepticus of any seizure subtypes.	Criteria #3 could be placed in Criteria 4 in LAM30055 Criteria 4 = criteria 4 in LAM30055 but serial seizures or status epilepticus match **"emergence of a new more severe seizure type" – criteria 3** No representation of criteria # 3, emergence of a new more severe seizure type (except for **special case of " a single GTCS"** The absence of clear 3 would leave contribution from 3 that is not matched here Non-parity with or without criteria 4- **Inherent Non-Parity**
4		
5 (2001)	1) a twofold increase in monthly seizure frequency in any 28-day period relative to the open-label baseline phase; 2) a twofold increase in the highest consecutive 2-day seizure frequency relative to the open-label baseline phase; 3) occurrence of a generalized seizure if none occurred during the open-label baseline phase; or 4) prolongation of generalized seizure duration that, in the opinion of the investigator, required intervention.	Criteria 3 in this study could represent a special case of criteria 3 in LAM30055. **"emergence of a new more severe seizure type" is broader and should capture "occurrence of a generalized seizure if none occurred during open label or baseline". This** could also satisfy LAM30055 category 4. It could be anticipated that criteria #3 of LAM30055 should capture more than this criteria 3
6 (2000)	1) a twofold increase in partial seizure frequency in any 28-day period compared to baseline; 2) a twofold increase in the highest consecutive 2-day seizure frequency that occurred during the baseline phase (patients with a single seizure as the highest 2-day baseline phase seizure frequency exited the trial if three or more seizures occurred during any 2-day period in the double-blind treatment phase); 3) occurrence of a single generalized seizure if none had occurred in the 6 months prior to randomization; or 4) a prolongation or worsening of seizure duration or frequency considered by the investigator to require intervention.	Criteria 4 in this study is roughly equivalent to criteria 3 of LAM30055. Criteria 3 of this study could be captured by criteria 4 of LAM30055 Effect if criteria 4 is censored could be to remove balance to events which would asymmetrically remain in LAM30055 as criteria 3. **Non-parity before and after #4 modification**
7 (1992)	(1) a two-fold increase in average monthly seizure frequency, (2) a two-fold increase in the highest 2-day seizure frequency, (3) a single generalized seizure if none occurred during the baseline period, and (4) a prolongation of generalized seizure duration (serial seizures or status epilepticus) deemed by the investigator to require intervention.	This study criteria #3 could represent a special case of LAM30055 criteria # 3 This criteria # 4 could capture LAM30055 criteria #3 if serial seizures or status epilepticus is considered emergence of new more severe seizure type **Inherent Non parity**

8 (1993)	(1) a doubling in monthly seizure number compared with the average monthly seizure number during the baseline period; (2) a doubling of 2-day seizure number over the worst 2-day period during the baseline (this frequency criterion applied only when two or more seizures had occurred during some 2- day period of the baseline); (3) **(4)** a single generalized tonic clonic tonic clonic seizure, if none had occurred during the baseline; and a significant prolongation of a generalized tonic clonic seizure considered serious by the investigator, **(3)** or serial seizures or status epilepticus of seizure types other than generalized tonic-clonic seizures.	**Parity**
LAM30055	1. Doubling of average monthly seizure frequency calculated as the sum of countable, partial seizures starting the day prior to the study visit and extending back 28 days. 2. doubling of the highest consecutive 2-day seizure frequency. 3. emergence of a new, more severe seizure type. 4. clinically-significant prolongation of generalized tonic-clonic seizures.	

9.6 Comparison of White Paper Active and Pseudoplacebo Study Escapes

Study Escapes with total enrollment denominator (n^1)					
	Pseudoplacebo	**Active**	**Pseudoplacebo Escape / total enrollment (n/n^1) (%)**	**Active therapy Escape / total enrollment (n/n^1) (%)**	**Background AED**
1	Gabapentin 600mg	Gabapentin 2400mg	70/93 (75)	66/91 (73)	1 or 2
2	Valproic Acid 1000mg	Lamictal 500mg	55/80 (69)	32/76 (42)	1 (CBZ or PHT)
3	Topamax 100mg	Topamax 1000mg	21/24 (88)	12 /24 (50)	1
4	Not published				
5	Oxcarbazepine 300mg	Oxcarbazepine 2400mg	40/45 (89)	30/49 (61)	1 (CBZ)
6	Oxcarbazepine 300mg	Oxcarbazepine 2400mg	42/46 (91)	14/41 (34)	1 or 2
7	Valproic Acid 15mg/kg	Felbamate 3600mg	19/22 (86)	3/22 (14)	1 or 2
8	Valproic Acid 15mg/kg	Felbamate 3600mg	39/55 (71)	18/56 (32)	1 or 2

Study escapes as analyzed by study protocol, n^2 varies as directed by study handling of dropouts						
	Pseudoplacebo	**Active**	**Pseudoplacebo Escape / study directed denominator (n/n^2) (%)**	**Active therapy Escape / study directed denominator (n/n^2) (%)**	**Significance**	**1^0 efficacy endpoint**
1	Gabapentin	Gabapentin	70/93 (75)	66/91 (73)	No, dropouts	Primary efficacy

Study escapes as analyzed by study protocol, n^2 varies as directed by study handling of dropouts						
	Pseudoplacebo	**Active**	**Pseudoplacebo Escape / study directed denominator (n/n^2) (%)**	**Active therapy Escape / study directed denominator (n/n^2) (%)**	**Significance**	**1^0 efficacy endpoint**
	600mg	2400mg			included NS	= time to exit, secondary = completion rate
2	Valproic Acid 1000mg	Lamictal 500mg	51/64 (80)	22/50 (44)	P<.001, dropouts excluded	Primary efficacy = Per protocol % escape
3	Topamax 100mg	Topamax 1000mg			Not calculated for % escape Time to exit, p = 0.002	Primary efficacy= time to exit
4	Not published					
5	Oxcarbazepine 300mg	Oxcarbazepine 2400mg	40/40 (100)	30/46 (65)	P=0.0001, dropouts removed	1^0 efficacy = time to exit.
6	Oxcarbazepine 300mg	Oxcarbazepine 2400mg	42/45 (93)	14/34 (41)	P<0.0001 Dropouts excluded	1^0 efficacy = % meeting exit
7	Valproic Acid 15mg/kg	Felbamate 3600mg	19/22 (86)	3/22 (14)	P< 0.0001 Dropouts included	1^0 efficacy = % meeting exit
8	Valproic Acid 15mg/kg	Felbamate 3600mg	39/50 (78)	18/45 (40)	P<0.001 Dropouts excluded	1^0 efficacy = % meeting exit

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/s/

STEVEN T DINSMORE
04/25/2011

NORMAN HERSHKOWITZ
04/25/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-115/S-006

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

COMBINED STATISTICAL& CLINICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	sNDA 22115 / SN 0024
Drug Name:	**Lamictal® XR™ (lamotrigine)** Extended-Release Table
Indication(s):	Monotherapy of partial seizures in patients 13 years of age and older
Applicant:	SmithKline Beecham Corporation d/b/a GlaxoSmithKline
Date(s):	Submission date: March 31, 2010 PDUFA date: Jan. 31, 2011 (Extension date: April 30, 2011)
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Xiang Ling, Ph.D.
Concurring Reviewers:	Kun Jin, Ph.D., Team Leader James Hung, Ph. D.
Medical Division:	Division of Neuropharmacological Drug Products, HFD-120
Clinical Reviewer	Steven Dinsmore, D.O.
Clinical Team:	Steven Dinsmore, D.O. Medical Officer Norman Hershkowitz, M.D., Ph.D., Lead Medical Officer Russell Katz, M.D., Division Director
Project Manager:	Stephanie Keefe

Keywords: historical control, binomial proportion, Kaplan-Meier estimate of proportion, meta analysis, regional comparison, bias

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1. EXECUTIVE SUMMARY

Statistical Reviewer Summary

This supplemental New Drug Application (sNDA) consisted of a single pivotal clinical study (Study LAM30055) evaluating conversion to monotherapy with LTG XR in subjects 13 years of age and older with partial seizures using an historical control from the White Paper (see French et al, Epilepsia 2010[1] for the published version of the White Paper). The use of historical control for monotherapy was mainly due to ethical and clinical consideration. However, due to lack of internal control, Study LAM30055 suffered from the common problems that usually arose in historical controlled trials, such as potential bias, non-comparability of treatment groups to the historical control, and difficulty in interpreting efficacy results.

Specifically, in this study, there was potential bias due to under-reporting of escapes. The investigator-reported escape rate was about 6%, compared to about 30% calculated escapes rate based on seizure data, and 42% reported rate for LTG IR in Study US30/31. In addition, none met escape criterion #4 in this study compared to up to 45% in the historical controls; and post-hoc evaluation of criterion #4 events could not be performed due to the subjective nature of this criterion. Another source of bias came from the handling of dropouts. The sponsor counted dropouts as completers which biased for treatment success.

The study population in Study LAM30055 was not comparable to those in the historical control studies. Study LAM30055 had approximately 75% of subjects enrolled outside US while all of the subjects in the historical control database were enrolled in US. A higher proportion of subjects at US sites met Escape Criteria compared to non-US sites. In addition, Study LAM30055 allowed one background AED while most White Paper studies allowed two background AEDs. The White Paper data suggested that patients with one background AED had fewer escapes than patients with two AEDs.

To make an attempt to adjust for biases, the reviewer conducted analyses which

(1) calculated escapes according to more stringent Escape Criteria used in some of the White Paper studies
(2) included dropouts as treatment failures in the analyses of the White Paper Per Protocol population and the ITT population,
(3) compared to a subgroup of historical control subjects who were on one background AED (consequently the 95% prediction limit changed to 58.6%, from the original 65.3%).

[1] J. French, S. Wang, B. Warnock and N. Temkin: Historical control monotherapy design in the treatment of epilepsy. Epilepsia 1-8, 2010

With above adjustments, LTG XR monotherapy remained superior to the historical controls for both dose groups. For the subgroup of US subjects pooled from the two dose groups, with adjustments (1) and (2), LTG XR monotherapy remained superior to the historical controls except in the ITT worst case analysis. With additional adjustment (3), LTG XR failed to show superiority in the White Paper PP sensitivity analysis or the ITT worst case analysis.

The potential bias due to under-reporting of criterion #4 events was not accounted for in above analyses. It was uncertain how to adequately assess this potential bias.

In summary, the data seemed to suggest some evidence of efficacy of LTG XR as monotherapy treatment of partial seizures. However, interpretability of these analysis results was undermined by the limitations of the historical control design and the problems described above; thus, it was uncertain that the efficacy of LTG XR as monotherapy treatment of partial seizures was conclusive based on this study.

Clinical Reviewer Summary

This submission represents a novel pathway for approval by using an historical control method to demonstrate efficacy of Lamictal XR for use in conversion to monotherapy. Prior approval for monotherapy has been gained through a clinical trial design known as the "pseudo-placebo withdrawal to monotherapy study" which assigns treatment resistant patients to receive study drug or a suboptimal maintenance dose of a safe and effective active drug. Development of the historical control methodology has been motivated by the danger of the "pseudo-placebo" which allows patients to participate in a study arm which is intrinsically sub-therapeutic.

To use an historical control method a study is required to have design features which allow comparability between a current study and the historical control studies. Key criteria are similarity of study design, population, evaluation criteria and analysis plan. Study LAM30055 met this requirement in the elements of conversion to monotherapy, study endpoint and analysis plan; however there was notable divergence in the study population. The first point of divergence was in the composition of the historical control population which was approximately 100% of US patients while LAM30055 was only 25% US. The second divergence was in the allowed number of background AEDs prior to monotherapy conversion. Six of the 8 historical control studies allowed 2 baseline AEDs whereas LAM30055 allowed only one AED for eligibility. In addition to these disparities a difference in study endpoint profile emerged. In the calculation of the White Paper prediction interval and the Lamictal XR monotherapy endpoint confidence interval both were based on percent of patients meeting any of 4 escape criteria; however the Lamictal Study had no criteria # 4 escapes where the historical control studies had escapes due to criteria # 4 ranging from 4% to 45%. In addition the Lamictal XR monotherapy study had lower rates of escape reporting across all criteria.

The statistical reviewer identifies the sources of bias which include different methods of calculating escapes between the Lamictal XR study and the White Paper studies, treatment of dropouts, medical (1 or 2 background AEDs) and regional differences in the study population and under reporting of escapes, especially problematic in Criteria 4. The statistical approach to compensate for the bias was to perform a recalculation of escapes using more stringent criteria

which included dropouts as treatment failures and reanalyzed the historical control (White Paper) dataset using only those patients on a single background AED. There was no clear approach to compensate for the divergence in escape criteria # 4 between the Lamictal XR study and the White Paper studies.

A recalculation of the White Paper prediction interval lower bound based on the population taking only 1 AED yielded a value of 58.6%. Both the 300mg/day and 250mg/day dose groups of the Lamictal XR monotherapy study retain superiority to this threshold in all adjustments to the White Paper escapes (table 8). The US subset of the Lamictal XR monotherapy study retains superiority only in the least conservative White Paper per protocol analysis (table 9).

If the White Paper is accepted as a valid platform for historical control comparison and the population restricted to 1 background AED, the resultant lower bound of the pseudoplacebo group prediction interval is 58.6%. All analysis for overall LAM30055 populations in both dose groups remain superior to this White Paper lower bound. The US subset remains superior only in the White Paper per protocol analysis. The US subset is small and not powered to independently test for significance, therefore this finding in isolation does not supersede the overall study results.

Clinical Reviewer Conclusion

There is adequate support for approval of Lamictal XR for use in conversion to monotherapy for patients ≥13 years of age who are receiving treatment with a single AED. The recommended target dose is 300mg daily, although the 250mg/day dose remained superior to the pseudoplacebo, this dose was not the protocol directed primary efficacy endpoint.

2. INTRODUCTION

Overview

Lamotrigine extended–release (LTG XR) formulation is currently approved as adjunctive treatment of partial seizures and primary generalized tonic clonic seizures in subjects ≥13 years of age. LTG Immediate-release (IR) was initially approved for adjunctive use and was later demonstrated to also be effective as monotherapy following conversion from add-on therapy with a single enzyme-inducing antiepileptic drug (EIAED).

This supplemental New Drug Application (sNDA) consisted of a single pivotal clinical study evaluating conversion to monotherapy with LTG XR in subjects 13 years of age and older with partial seizures using an historical control (referred to as Study LAM30055 subsequently in this document). The study used a conversion to monotherapy design in which eligible subjects with refractory partial seizures had LTG XR added to their current background antiepileptic drug (AED) (valproate or a non-enzyme inducing AED) followed by gradual withdrawal of the background AED and 12 weeks of monotherapy.

Approximately 230 male or female ≥13 years of age with seizures uncontrolled (≥2 per 28 days) by AED monotherapy were enrolled to randomize 164 subjects to the two dosing groups in a 1:1 ratio. The primary treatment comparison evaluated the proportion of subjects who discontinue LTG at 300 mg/d (pre-specified) / meet Escape Criteria (post-hoc) during the last 16 weeks of treatment with LTG compared to an historical pseudo-placebo control rate.

The historical control dataset was the aggregated data from eight monotherapy studies. All of these studies utilized a "pseudoplacebo", either a sub-therapeutic dose of an active drug or a low dose of study drug, and efficacy was based on the proportion of patients who exited the studies as a result of predefined Escape Criteria related to worsening of seizures. In the White Paper, French et al proposed that using the lower bound of the 95% prediction interval (PI) based on the combined percent escape rate (65.3%) for a single study or the lower bound of the 80% PI based on the combined escape rate (72.2%) for 2 studies. Specifically, the upper 95% confidence limit of the test group was compared to the lower prediction limit of the aggregated historical data. Non-overlap indicated a determination that the treatment was efficacious. FDA agreed in principle to accept their use as control during a meeting with GSK on September 08, 2005.

The previous study US 30/31 of LTG IR (immediate-release) was provided as a supportive study. It had a similar design to Study LAM30055 but used a low dose as internal pseudoplacebo. Study US 30/31 supported approval of LTG IR for conversion to monotherapy and was one of the eight studies from which the historical control endpoint was derived.

Clinical Reviewer Comment

History Of Lamictal And Lamictal XR Pertaining To The Current Application

LTG Immediate-release (IR) was initially approved for adjunctive use in December 1994 and was later demonstrated to also be effective as monotherapy following conversion from add-on therapy with a single enzyme-inducing antiepileptic drug (EIAED) and approved for this use in December 1998. Lamictal XR was approved in May of 2009 for adjunctive therapy of partial seizures and in January 2010 as adjunctive therapy for primary generalized tonic-clonic. This background has provided extensive experience in the use and effectiveness of lamotrigine.

A clinical pharmacology review was performed for the submission of Lamictal XR for adjunctive therapy of partial seizures[2]. In the evaluation of proposed conversion dose from lamotrigine IR to Lamictal XR the reviewed examined the lamotrigine steady state relative bioavailability in 3 groups of patients receiving different concomitant AEDs (enzyme inducers, inhibitors and neutrals). The reviewer found the following:

- The steady-state mean trough concentrations for Lamotrigine XR were equivalent to or higher than those of lamotrigine IR depending on concomitant AED.

- A mean reduction in the lamotrigine Cmax by 11-29% was observed for lamotrigine XR compared to lamotrigine IR resulting in a decrease in the peak to trough fluctuation in serum lamotrigine concentrations.

- The fluctuation index was reduced by 17% in patients taking enzyme-inducing AED, 34% in patients taking VPA and 37% in patients taking neutral AEDs.

- Lamotrigine XR and lamotrigine IR regimens were almost similar (6% decrease) with respect to mean AUC(0-24ss), apart from patients receiving EIAEDs, where the relative bioavailability of lamotrigine XR was approximately 21% lower than for lamotrigine IR.

PK parameter	AED Group	Ratio XR:IR	90% CI
AUC(0-24)/Total Daily Dose	Overall	0.90	0.84 – 0.98
	Induced	0.79	0.69 – 0.90
	Neutral	1.00	0.88 – 1.14
	Inhibited	0.94	0.81 – 1.08
Cmax/Total Daily Dose	Overall	0.82	0.76 – 0.90
	Induced	0.71	0.61 – 0.82
	Neutral	0.89	0.78 – 1.03
	Inhibited	0.88	0.75 – 1.03
Cτ/Total Daily Dose	Overall	1.04	0.98 – 1.10
	Induced	0.99	0.89 – 1.09
	Neutral	1.14	1.03 – 1.25
	Inhibited	0.99	0.88 – 1.10

[2] Tandon V. Clinical Pharmacology/Biopharmaceutics Review, NDA22115, Product: Lamictal XR, Indication: Adjunctive therapy for partial onset seizures with or without generalization in patients ≥ 13 years. 9/6/2007

There were however some outlier subjects taking enzyme inducing AEDs with a more marked reduction in AUC and Cmax. In the case of AUC there were two subjects, one with a 57% reduction, the second with a 70% reduction. In the case of Cmax there were three subjects with a range in reduction from 45% to 77%.

These observations offer some support for an expected similarity in performance between Lamictal IR (immediate release), already approved for conversion to monotherapy based on study 30/31, and Lamictal XR. Although those on inducers fell outside of the bioequivalence boundary, this is not relevant to use in monotherapy except in the transition phase where in proposed labeling Lamictal XR is maintained at a higher dose (500mg/day) until two weeks after the completion of background AED withdrawal and is then reduced to a target dose of 250mg to 300mg / day.

There is a robust history of Lamictal XR use, as shown in the table below representing the interval from May 29, 2009 to July 24, 2010. There were (b) (4) mg (the equivalent of (b) (4) 200mg tablets) of Lamictal XR sold in the US in this interval, not including start up kits, freely provided drug or samples[3].

DISTRIBUTION DATA
NDA 022-115; LAMICTAL XR EXTENDED-RELEASE TABLETS
May 29, 2009 to July 24, 2010

Description	NDC Code	Domestic Sales	Domestic Free Issues	Domestic Samples
LAMICTAL XR TABLETS 25MG 30s	0173075400	(b) (4)		
LAMICTAL XR TABLETS 50MG 30s	0173075500			
LAMICTAL XR TABLETS 100MG 30s	0173075600			
LAMICTAL XR TABLETS 200MG 30s	0173075700			
LAMICTAL XR TABLETS 25MG/50MG STARTER KT	0173075800			
LAMICTAL XR TAB BLUE DE KIT 25MG/50MGSPL	0173075860			
LAMICTAL XR TABLETS 50MG/100MG/200MG KIT	0173075900			
LAMICTAL XR TAB GREEN DE KIT 50/100/200	0173075960			
LAMICTAL XR TABLETS 25MG/50MG/100MG KIT	0173076000			
LAMICTAL XR TAB ORANGE DE KIT 25/50/100	0173076060			

Data Sources

The data files are located in the following directory:
\\Cdsesub1\evsprod\NDA022115\0024\m5\datasets\lam30055-double-blind\analysis
\\Cdsesub1\evsprod\NDA022115\0050\m5\datasets\lam30055-double-blind\analysis\datasets
\\Cdsesub1\evsprod\NDA022115\0052\m5\datasets

The study reports are located in the following directory:
\\Cdsesub1\evsprod\NDA022115\0024\m5\53-clin-stud-rep\535-rep-effic-safety-stud\monotherapy\5351-stud-rep-contr\lam30055-double-blind

[3] Lamictal Annual Report covering 7/25/09 through 7/24/10

3. STATISTICAL EVALUATION

Evaluation of Efficacy

Study LAM30055

The study was initiated on 16 May 2006, and completed of double-blind phase on 06 May 2008. The original protocol (dated 19 December 2005) was amended twice (19 January 2006, 30 August 2006) with both amendments applying to all study sites. There were no changes to study conduct implemented with either amendment. SAP was dated 19 December 2007.

Study Design (see 5.3)

This was an international, multicenter, double-blind, randomized study of 2 doses (300 and 250 mg/day) of lamotrigine extended-release (LTG XR) tablets comparing the premature discontinuation rate for each dose to an historical escape rate (65.3%) determined from aggregated pseudo-placebo data. The purpose of the study was to demonstrate the effectiveness of a lower monotherapy dose of LTG XR than the currently approved 500 mg/day of LTG IR.

The study used a conversion to monotherapy design in which eligible subjects with refractory partial seizures had LTG XR added to their current background antiepileptic drug (AED) (valproate or a non-enzyme inducing AED) followed by gradual withdrawal of the background AED and 12 weeks of monotherapy. Subjects who completed the Treatment phase or met Escape Criteria were allowed to enter the Continuation phase. Study phase and duration was shown in Table 1. Approximately 230 male or female ≥13 years of age with partial epilepsy with seizures uncontrolled (>=2 per 28 days) by AED monotherapy were enrolled to randomize 164 subjects to the two dosing groups in a 1:1 ratio.

Table 1. Study Design

Phase	Duration
Screen	<2 weeks
Baseline	8 weeks[1]
LTG XR escalation	6-7 weeks [2]
Background AED withdrew and continuation of LTG XR escalation	4 weeks
Monotherapy	12 weeks
Optional Continuation Phase	24 weeks
Taper-Follow-up or Conversion to immediate release	~2 weeks ~3 days
Total (maximum)	59 weeks

1. With approval from GSK, up to the first 4 weeks of Baseline may be retrospective
2. Differs based on background AED and escalation schedule for LTG-XR

Efficacy Measures

Efficacy measures were variables derived from seizure information that were monitored through subject diary and evaluated at each study visit. Subjects recorded the number of seizures, by seizure type, as well as duration of episodes of innumerable seizure activity in their daily diaries. Site personnel transcribed the daily seizure information from the diary into the electronic Case Report Form (eCRF).

The planned primary endpoint was the proportion of subjects in the 300 mg/day treatment group who prematurely discontinued at any time after starting withdrawal of background AED.

A "completer" was defined as a subject who completed the Baseline, Conversion and Maintenance Phases of the study. In all other cases, the subject was considered to have prematurely discontinued.

Post-hoc primary endpoint was the proportion of subjects meeting pre-defined efficacy Escape Criteria. These criteria were the occurrence of any of the following compared to Baseline:

1. doubling of average monthly seizure frequency calculated as the sum of countable, partial seizures starting the day prior to the study visit and extending back 28 days
2. doubling of the highest consecutive 2-day seizure frequency
3. emergence of a new, more severe seizure type
4. clinically-significant prolongation of generalized tonic-clonic seizures

This post-hoc primary endpoint was one of the original secondary endpoint but transitioned to primary endpoint as discussed in Efficacy Analysis. Other secondary endpoints were:

- Proportion of subjects in the 250 mg/day treatment group who prematurely discontinue
- Time to discontinuation
- Percent change from Baseline in seizure frequency
- Percent seizure-free at last visit

Statistical Analysis Methods

Analysis Population

Per Protocol (PP)
All subjects randomized to treatment who took at least one dose of study medication and began withdrawal of the background AED, excluding those with major protocol violations. The planned primary efficacy analysis was based on the PP population.

Intent-to-Treat (ITT)
All subjects randomized to treatment who took at least one dose of study medication.

White Paper Per Protocol
All subjects randomized to treatment that took at least one dose of study drug and began withdrawal of the background AED. This population was defined post-hoc in order to make a direct comparison with the White Paper. This was the primary population for this review.

Efficacy Analyses

The planned primary treatment comparison in study LAM30055 evaluated the proportion of subjects who discontinued LTG at 300 mg/d during the last 16 weeks of treatment with LTG XR compared to an historical pseudo-placebo control rate. This pre-specified primary endpoint of 'all-cause' discontinuation was based on the way Study US 30/31 data was analyzed as part of the aggregation of 8 studies included in the historical database. After completion of the double-blind phase of LAM30055, it was learned that the analysis of US 30/31 in the 2005 version of the White Paper was incorrect. US 30/31 data were subsequently re-analyzed utilizing only escape data. In response to this, data from LAM30055 were analyzed post-hoc focusing only on subjects who met Escape Criteria. Since this was the endpoint used in the White Paper, the Escape Criteria analyses was referred as post-hoc primary analysis.

As the sponsor found that the Escape Criteria were not correctly applied at study sites (e.g., subjects who met an Escape Criterion were not discontinued), daily seizure data in the database were evaluated against the Escape Criteria (1, 2, and 3) to identify additional escapes following completion of the trial.

The estimated proportion and confidence interval were calculated using binomial distribution. Subjects who dropped out due to reasons other than meeting Escape Criteria were included in Sponsor's analyses as having successfully completed the treatment.

Patient Disposition, Demographic and Baseline Characteristics

A total of 226 subjects (113 per treatment group) were randomized from 7 countries. Three of the 226 randomized subjects did not receive study drug and were not included in ITT Populations (1 subject in each treatment group decided to withdraw, and 1 subject [250 mg/day] had a protocol violation). The PP Population included 93 subjects in the LTG XR 300 mg/day group and 81 subjects in the LTG XR 250 mg/day group. The White Paper PP Population, which did not exclude subjects with major protocol violations, included 108 subjects in the LTG XR 300 mg/day group and 97 subjects in the LTG XR 250 mg/day group. The most common reason for withdrawal from the LTG XR 300 mg/day group was "subject decided to withdraw from the study" (8%). For the LTG XR 250 mg/day group, AE was the most frequent cause for withdrawal (9%) (Table 2).

Table 2. Subject Disposition

	Number (%) of Subjects	
	LTG XR 300 mg/day	**LTG XR 250 mg/day**
Population		
Randomized	113	113
Safety	112 (>99)	111 (98)
Intent-to-Treat (ITT)	112 (>99)	111 (98)
Per Protocol (PP)	93 (82)	81 (72)
White Paper PP	108 (96)	97 (86)
Subject Disposition (Randomized Subjects)		
Completed study	94 (83)	79 (70)
Prematurely withdrawn	19 (17)	34 (30)
Met Escape Criteria[1]	28/112 (25)	25/111 (23)
Reason for premature withdrawal		
Adverse event	4 (4)	10 (9)
Lost to follow-up	0	4 (4)
Protocol violation	0	4 (4)
Subject decided to withdraw from the study	9 (8)	8 (7)
Insufficient therapeutic response[2]	6 (5)	7 (6)
Other, specify[3]	0	1 (<1)

1. Includes post-hoc escape determination.
2. Escapes based on the CRF, does not include the post-hoc escape determination.
3. Other, specify = Subject 130 withdrew due to pregnancy.

Source: Sponsor ISE page 23.

The majority of subjects in both treatment groups were 16 to 65 years and of White – White/Caucasian/European heritage (Table 3).

Table 3. Demographics (ITT Population)

Demographic Characteristic	LTG XR 300 mg/day N=112	LTG XR 250 mg/day N=111
Age (years)		
Mean (SD)	33.8 (14.33)	32.9 (12.60)
Range	13-80	13-59
Age Group (years), n (%)		
<16	10 (9)	7 (6)
16-65	100 (89)	104 (94)
>65	2 (2)	0
Gender, n (%)		
Female	56 (50)	66 (59)
Male	56 (50)	45 (41)
Ethnicity, n (%)		
Hispanic/Latino	33 (29)	30 (27)
Not Hispanic/Latino	79 (71)	81 (73)
Race, n (%)		
African American/African Heritage	5 (4)	4 (4)
Asian - East Asian Heritage	11 (10)	11 (10)
White - Arabic/North African Heritage	0	2 (2)
White - White/Caucasian/European Heritage	96 (86)	94 (85)

Source: Sponsor ISE page 26.

Most subjects in both treatment groups had only partial seizures at Baseline. The median Baseline seizure frequency (number of partial seizures/week) over the entire Baseline was 1.4 for the LTG XR 300 mg/day group and 1.5 for LTG XR 250 mg/day group. Seizure history at Baseline was similar for the two treatment groups with a mean age of 20.5 and 18.7 years, respectively at first seizure, and a mean of 14.3 and 15.2 years, respectively for duration of epilepsy (Table 4.)

Table 4. Baseline Disease Characteristics (ITT Population)

Baseline Characteristic	LTG XR 300 mg/day N=112	LTG XR 250 mg/day N=111
Baseline Seizure Type[1], n (%)		
A (simple partial seizures)	49 (44)	53 (48)
B (complex partial seizures)	71 (63)	67 (60)
C (partial seizures evolving to secondarily generalized seizures)	60 (54)	59 (53)
D5 (primary generalized)[2]	1 (<1)	1 (<1)
Partial seizures only (A, B, or C)	111 (>99)	108 (97)
Both partial and generalized seizures	1 (<1)	1 (<1)
Baseline Seizure Frequency per Week - All Partial Seizures Entire Baseline		
Mean (SD)	3.3 (8.21)	4.3 (10.59)
Median (Range)	1.4 (0.5-69.9)	1.5 (0.5-67.0)
Age at First Seizure (years)		
Mean (SD)	20.5 (13.81)	18.7 (12.72)
Median (Range)	16.5 (1-76)	16.0 (1-49)
Duration of Epilepsy (years)		
Mean (SD)	14.3 (11.61)	15.2 (11.25)
Median (Range)	12.0 (2-67)	13.0 (1-55)

Data Source: CSR LAM30055 DB, Table 6.9, Table 6.10, Table 6.11

1. Subjects may have reported more than one seizure type.
2. One subject in each group (Subject 271 and Subject 1111) reported a history of D5 seizures prior to the Screen Visit. Neither subject experienced a primary generalized seizure in the 8 weeks prior to screen. Subject 271 experienced D5 seizures during the study; Subject 1111 did not.

Source: Sponsor ISE page 27.

Sponsor's Efficacy Results

Planned Analyses Results

Primary efficacy endpoint

The proportion of subjects who discontinued at any time after starting withdrawal (not including calculated escapes) of the background AED in Study LAM30055 was 12% for the LTG XR 300 mg/day group in the PP Population, with a 95% upper limit of 18.4%. However, this analysis was not considered primary analysis for regulatory evaluation as this was not the way the White Paper analyzed the pseudo-placebo data.

Secondary efficacy endpoints

The proportion of subjects who discontinued at any time after starting withdrawal (not including calculated escapes) of the background AED was 16% for the LTG XR 250 mg/day group in the PP Population.

The proportion of subjects in the PP Population who met Escape Criteria (not including calculated escapes) was 4% for the LTG XR 300 mg/day group and 6% for the LTG XR 250 mg/day group.

Response to treatment, as measured by seizure frequency, showed a greater than 50% reduction in both treatment groups for the entire treatment period. Reduction in seizure frequency was evident in the Conversion phase and increased during the Monotherapy phase. During LTG XR monotherapy, the majority of subjects showed a ≥50% reduction in all partial seizure frequency at both 300 mg/day (64.0%; 57/89) and 250 mg/day (56.6%; 43/76) in the PP Population. Additionally, 24.7% (22/89) of subjects in the 300 mg/day group and 10.5% (8/76) of subjects in the 250 mg/day group became seizure-free.

Table 5. Summary of Planned Analyses (PP population)

	LTG XR 300 mg/day N=93	**LTG XR 250 mg/day N=81**
Percent of subjects who discontinued		
n/N (%)	11/93 (12)	13/81 (16)
[95% CI]	[5.3, 18.4]	[8.1, 24.0]
Percent of subjects meeting Escape Criteria		
n/N (%)	4/93 (4)	5/81 (6)
Percent change from Baseline in weekly seizure frequency[1]		
Conversion Phase, n	93	81
Median (range)	45.5 (-124.5-100.0)	50.2 (-168.6-100.0)
p-value[2]	<0.0001	<0.0001
Monotherapy Phase, n	89	76
Median (range)	67.4 (-100.0-100.0)	59.4 (-635.0-100.0)
p-value[2]	<0.0001	0.0150
Entire Treatment Period, n	93	81
Median (range)	54.8 (-124.5-100.0)	52.2 (-221.3-100.0)
p-value[2]	<0.0001	<0.0001
Categorical change in seizure frequency		
Conversion Phase, n	93	81
≥50% reduction, n (%)	43 (46.2)	41 (50.6)
Seizure-free (100% reduction), n (%)	5 (5.4)	6 (7.4)
Monotherapy Phase, n	89	76
≥50% reduction, n (%)	57 (64.0)	43 (56.6)
Seizure-free (100% reduction), n (%)	22 (24.7)	8 (10.5)
Entire Treatment Period, n	93	81
≥50% reduction, n (%)	54 (58.1)	42 (51.9)
Seizure-free (100% reduction), n (%)	3 (3.2)	4 (4.9)

1. Positive number means a decrease in seizure frequency
2. Paired t-test

Source: Sponsor ISE Table 5 & 6.

Post-hoc Analyses Results

The post-hoc primary analysis was the percent of subject meeting Escape Criteria in the White Paper population. While the trial was ongoing, the sponsor evaluated a random sample of subjects for correct application of the Escape Criteria and identified a number of errors (e.g.,

some patients met an Escape Criterion but were not discontinued). As a result, remedial training of study site personnel and monitors was undertaken. Following completion of the study, the analysis of escapes showed that the number of subjects who met pre-defined Escape Criteria was surprisingly small: only 6 to 7 subjects in each group were discontinued due to meeting Escape Criteria (Table 6).

Post-hoc evaluation of the seizure data led to reclassification of many subjects as escapes (i.e., having met Escape Criteria) (Table 6). The proportion of subjects who met calculated Escape Criteria was 24% for the LTG XR 300 mg/day group and 26% for the LTG XR 250 mg/day group. The upper 95% confidence limit did not overlap the lower 95% prediction limit (65.3%) from the historical pseudo-placebo control data for both groups.

Table 6. Proportion of Subjects Meeting Escape Criteria (Sponsor Results for White Paper PP Population)

	LTG XR 300 mg/day	LTG XR 250 mg/day
Investigator Determined Escapes (based on CRF)		
n/N (%)	6/108 (6)	7/97 (7)
[95% CI]	[1.2, 9.9]	[2.1, 12.4]
Calculated Escapes		
n/N (%)	26/108 (24)	25/97 (26)
[95% CI]	[16.0, 32.1]	[17.1, 34.5]

Source: Sponsor ISE Table 2, 8, 11.

Reviewer's Results

Use of an historical control requires that the study design, study population, efficacy evaluation and analyses are consistent with the historical pseudo-placebo studies, which is the focus of the review.

Evaluation of the Escape Criteria

Escape Criterion #1: doubling of average monthly seizure frequency

The White Paper mentioned that "it was unclear if this was done on a rolling basis in all cases. Discussion with the companies involved has determined that the statistical methodology may have varied from trial to trial".

In Study LAM30055, the sponsor calculated the average monthly seizure frequency as the sum of countable, partial seizures starting the day prior to the study visit and extending back 28 days. As calculating the highest seizure frequency for *any* consecutive 28 days was more stringent and was used for some of the White Paper studies, the reviewer used this method for Study LAM30055. Three additional subjects in each group were identified to have met this Escape Criterion, resulting in 3 more escapes for the LTG XR 300 mg/day group and 2 more escapes for

the LTG XR 250 mg/day group (one subject in the 250 mg/day group met multiple Escape Criteria).

Escape Criterion #2: doubling of the highest consecutive 2-day seizure frequency.

In study LAM30055, the highest consecutive 2-day seizure frequency was calculated for the 28 days prior to each visit. The reviewer calculated the highest consecutive 2-day seizure frequency for the *whole treatment phase*. One more subject the LTG XR 300 mg/day group was identified to have met this Escape Criterion but resulting in no additional escapes as this subject met Escape Criterion #1 already.

Escape Criterion #3: emergence of a new, more severe seizure type

In the White Paper, this criterion varies among studies: occurrence of a single generalized seizure if none had occurred in the previous 6 months (Study 6), within two years of study entry (Study 1), during Baseline (Studies 3, 5, 7, 8), and "emergence of a more severe seizure type (which would include generalized seizure).

The criterion in the study LAM30055 Protocol was 'emergence of a new, more severe seizure type compared to the Baseline'. However, the sponsor calculated the escapes by comparing the seizure types during the Double-Blind Phase to the seizure types the subject had in their lifetime history. The reviewer requested that the sponsor re-calculate the escapes using Baseline period for comparison. Two more escapes were identified for LTG XR 300 mg/day group and three more escapes were identified for LTG XR 250 mg/day group.

Escape Criterion #4: clinically-significant prolongation of generalized tonic-clonic seizures

The data suggested that none of the subjects met this criterion (Table 7). The escapes based on this criterion were solely evaluated by the sites/investigators. The sponsor did not perform the re-calculation due to the subjective nature of this criterion. It was recognized the investigators tended to under-report escapes for criteria 1, 2 and 3. Therefore, there was concern that the escapes due to this criterion were also under-reported.

In addition, the criterion #4 in the study LAM30055 may be more restrictive than the White Paper criterion, which was "prolongation or worsening of seizure duration or frequency considered by the investigator to require intervention." Some events may be considered escapes according to the White Paper criteria, but not by the Study LAM30055 criteria. The medical reviewer examined the adverse event database and identified a patient who may have met Escape Criteria according to the White Paper criterion: subject 255 required intervention in the form of hospital admission.

Furthermore, Study US 30/31 was for LTG IR (with an internal control) and the Escape Criteria were defined the same as Study LAM30055. There were 10% subjects in the LTG IR group who met criterion #4 vs 4% for the pseudoplacebo. Other White Paper studies tended to have a large percentages of subjects meeting criterion #4 (19%, 17%, 11%, 7%, 45% and 29% for study 1, 3, 5, 6, 7, 8, respectively).

Therefore, there was serious concern about the bias due to potential under-reporting of escapes for criterion #4.

Table 7. Percentage of Subjects Meeting Each Criterion

Criterion	LTG XR 300 mg/day	LTG XR 250 mg/day
Criterion #1	12/108 (11)	19/97 (20)
Criterion #2	20/108 (19)	18/97 (19)
Criterion #3	8/108 (7)	7/97 (7)
Criterion #4	0	0

* White Paper Per Protocol Population
* Numbers are n/N (%).
* Patients may meet more than one criterion.
Source: FDA reviewer.

Statistical Analysis of the Proportion of Subjects Meeting Escape Criteria

The post-hoc primary analysis by the sponsor estimated the binomial proportion of subjects meeting Escape Criteria. The analyses were conducted for White Paper PP Population in order to make a direct comparison with the White Paper. Subjects who dropped out due to reasons other than meeting Escape Criteria were treated as treatment successes. However, the White Paper used Kaplan-Meier estimate of the proportion, in which subjects who dropped out for other reasons were censored. The estimated binomial proportion will be smaller than the Kaplan-Meier estimate due to the different ways of handling dropouts.

The reviewer conducted a sensitivity analysis in which subjects who dropped out for other reasons were considered treatment failures/escapes. This way the estimated binomial proportion will be larger than the Kaplan-Meier estimate. This was also the planned primary analysis of 'all-cause' discontinuation.

To deal with potential bias due to conducting an essentially open-label study (all patients were on potentially effective test drug), a worst case analysis was conducted by the reviewer in which ITT subjects who dropped out before the background AED withdrawal were also considered escapes.

None of the upper 95% confidence limits generated by all of these analyses are greater than the White Paper 95% prediction limit for escapes (65.3%) from the historical pseudo-placebo control data (Table 8).

Table 8. Proportion of Subjects Meeting Escape Criteria

	LTG XR 300 mg/day	LTG XR 250 mg/day
White Paper PP		
n/N (%)	31/108 (29)	30/97 (31)
[95% CI]	[20.2, 37.2]	[21.7, 40.1]
White Paper PP Sensitivity Analysis		

	LTG XR 300 mg/day	LTG XR 250 mg/day
n/N (%)	37/108 (34)	37/97 (38)
[95% CI]	[25.3, 43.2]	[28.5, 47.8]
ITT Worst Case Analysis		
n/N (%)	41/112 (37)	51/111 (46)
[95% CI]	[27.7, 45.5]	[36.7, 55.2]
The 95% prediction limit is 65.3% for all escapes. The 95% prediction limit is 58.6% for escapes in the subgroup of patients with 1 background AED (the subgroup will be mentioned later in the review).		

*Includes calculated escapes (none met escape criterion #4)
Source: FDA reviewer.

Clinical Reviewer Comment

Study LAM30055 had no escapes due to category #4. This raises a concern of under reporting of escapes. One escape was identified in the adverse event dataset which fits the more general category 4 of the white paper. The observation of no criteria 4 escapes prompts a closer examination of the parity of escape criteria between study LAM30055 and the White Paper composite criteria. The individual criteria are captured for each study and shown in appendix 1. The White Paper creates a composite criteria 3 and 4 which acceptably captures criteria 3 and 4 of the 8 White Paper studies; however as can be seen in the "matching" column of the table (appendix 1), 5 of 7 studies where the data is available do not have strict 1:1 matching with the criteria of LAM30055. Criteria 1 and 2 best approximate a clear 1:1 mapping between the Lamictal XR monotherapy study and the White Paper studies but the distinction is blurred for criteria numbers 3 and 4 which confounds a clear statistical solution to this bias.

Evaluation of the Study Population

Background AED

Most White Paper studies allowed two background AEDs. The percent of subjects receiving two background AEDs ranged between 17% and 34%. Enzyme-inducing antiepileptic drugs (EIAEDs) such as carbamazepine (CBZ) were often the background AED from which subjects were converted. Study LAM30055 allowed one background AED and excluded subjects taking EIAEDs. The White Paper indicated that withdrawal from CBZ did not increase the likelihood of escape, which was confirmed by the reviewer.

The White Paper data suggested that patients on one background AED had fewer escapes than patients on two AEDs. For patients on one background AED, the estimated percent escape is 83.0% with a lower prediction limit of 58.6%. Comparing to this limit, both groups remained superior to the historical pseudo-placebo.

Clinical Reviewer Comment

The LAM30055 design allowed patients only on stable monotherapy to enter the trial. As noted above, this design is divergent from White Paper studies which allowed up to two background

AEDs. There is a potential for the population on stable monotherapy to be less refractory than those requiring polytherapy. Those on two AEDs may be more prone to escape events. The statistical reviewer has reanalyzed the White Paper dataset with modifications which restricted analysis to patients on one background AED. When compared to the revised 58.6% lower bound prediction interval the upper 95% CI of both the 300mg/day and 250mg/day dose groups of study LAM30055 remain superior to the pseudoplacebo group (table 8).

Regional Comparisons

Study LAM30055 was conducted in 7 countries (Argentina, Chile, Costa Rica, Korea, Russian, Ukraine and US) with approximately 75% of subjects enrolled outside the US. In contrast, virtually all of the subjects in the historical control database were enrolled in the US. Table 9 showed the percent escape by region (US vs non-US). Due to the small size in the US, the two dose groups (300 mg/d and 250 mg/d) were pooled. A higher proportion of subjects at US sites met Escape Criteria compared to non-US sites. The proportion of US subjects meeting Escape Criteria remained superior to the historical control except for the ITT worst case analysis. When comparing to the prediction limit for subgroup of patients with one background AED, LTG XR did not show superiority over the historical pseudo-placebo for the US population in the White Paper PP sensitivity analysis or the ITT worst case analysis (Table 9).

Table 9. Proportion of Subjects Meeting Escape Criteria by Region

	US	Non-US
White Paper PP		
n/N (%)	19/50 (38)	42/155 (27)
[95% CI]	[24.5,51.5]	[20.1,34.1]
White Paper PP Sensitivity Analysis		
n/N (%)	25/50 (50)	49/155 (32)
[95% CI]	[36.1,63.9]	[24.3,38.9]
ITT Worst Case Analysis		
n/N (%)	31/56 (55)	61/167 (37)
[95% CI]	[42.3,68.4]	[29.2,43.8]
The 95% prediction limit is 65.3% for all escapes. The 95% prediction limit is 58.6% for escapes in the subgroup of patients with 1 background AED.		

* Includes calculated escapes (none met escape criterion #4)
Source: FDA reviewer.

The sponsor stated that the regionally unbalanced use of VPA was the most likely reason for the regional difference in escape percentage at US compared to non-US sites. Approximately 80% patients were receiving VPA as the background AED at non-US sites compared to about 20% at the US sites. The escape percentage was lower in subjects who transitioned from VPA vs neutral AEDs.

The above argument was not convincing in the reviewer's opinion. As shown in Table 10, the escape rates were similar between VPA and neutral AEDs within each region. The escape rate was higher at US compared to non-US sites for each type of background AEDs.

Table 10. Region and Background AED Comparisons (White Paper PP)

	US		Non-US	
	Neutral AEDs	VPA	Neutral AEDs	VPA
n/N (%)	15/40 (38)	4/10 (40)	9/31 (29)	33/124 (27)
[95% CI]	[22.5,52.5]	[9.6,70.4]	[13.1,45.0]	[18.8,34.4]

* Includes calculated escapes (none met escape criterion #4)
Source: FDA reviewer.

The Agency requested the Sponsor to establish the comparability of placebo escape rate among the regions. The Sponsor provided US vs non-US placebo rates for recent LAMICTAL adjunctive studies, and conducted literature review of analysis of placebo response by region for various indications. While there may be regional differences in placebo response, the data was limited and the regional differences were inconsistent (sometimes higher in the US, sometimes non-US).

Clinical Reviewer Comment

As noted above in study LAM30055 25% of subjects were recruited from US sites while 75% were from non-US or Western European sites. This raises two concerns, first that study LAM30055 may not be generalizable to the US population. Second is the concern that the LAM30055 study population may not be comparable to the White Paper pseudoplacebo population which is 100% North American.

The concern of generalizability to the US population is addressed first. There is uncertainty about the comparability of US to foreign clinical trial sites, especially those that are non-North American, non-Western European sites. There may be differences between the US and foreign sites based on differences in practice of medicine, cultural framework of heath care, the level of investigator and staff training at non-US sites and pharmacogenomic differences in the studied population[4].

There is a suggestion of differences between US and Non-US populations in prior Lamictal XR trials. In study LAM0034 a placebo controlled trial of Lamictal XR for treatment of partial seizures, which was composed of approximately 40% US sites, the efficacy subset analysis of US sites did not reach a threshold of significance. This raised a concern that efficacy within the study as a whole was driven by the foreign data. In study LAM00036, a placebo controlled trial of Lamictal XR in primary generalized tonic-clonic seizures; the placebo response of the US sites was notably larger than in the non-US sites. In another placebo controlled study (LAM40097) of Lamictal XR in primarily generalized tonic-clonic seizures the findings were reversed with a placebo response in the non-US sites which was larger than the US placebo

[4] Glickman SW, McHutchinson JG, et.al. Ethical and Scientific Implications of the Globalization of Clinical Research. NEJM 2009;360(8):816-823.

response rate. The reversal in placebo response rate between studies LAM0036 and LAM40097 suggests non-systematic variation in the placebo response between studies, a favorable observation, which at face value poses less of a challenge to the generalizability of foreign data to the US. The situation may be more complex. In study LAM40097 the non-US placebo treatment patients were all from South America whereas in study LAM0036 only 16% of 62 non-US, placebo treated patients were from South America and the remainder were from Germany, Russia, Ukraine, Malaysia, and India. The majority were from India. Therefore it may be postulated that there is a higher placebo response in the South American cohort which was diluted, in this second case, by the larger numbers of European and Asian patients. In conclusion, regional differences in placebo response cannot be ruled out by the reversal of placebo response observations in studies LAM100036 and LAM40097.

In the current study, LAM0035, there is a divergence in the escape rate between the US and non-US patient groups. The upper 95% CI of the US subset was below the original White Paper lower CI of the prediction interval (65.3%) for the White Paper PP analysis and the White Paper sensitivity analysis (table 9), Subsequently following a reanalysis of the White Paper with only patients on one background AED included, the statistical reviewer has found the US subset breaches the resulting modified White Paper lower bound of 58.6% in both the ITT worst case analysis and the White Paper sensitivity analysis (table 9). This observation is again suggestive of a different population behavior in the US and non-US cohorts.

The sponsor analysis explained this difference as, quite plausibly, due to imbalance in treatment with valproic acid (VPA) as a background anticonvulsant agent. In order to further investigate this possibility the statistical reviewer has performed an analysis of the LAM30055 escape rate by background AED type, either VPA or enzyme induction neutral. The US and non-US escape rates were extracted. This analysis revealed that within region the background AED is not associated with a difference in escape rate (table 10). This observation undermines the proposition that difference in the proportion of patients entering the study with VPA as a background AED is responsible for the difference in US vs non-US escape rate. The cause of this difference remains unexplained but underscores the concern that non-US cohorts may not be generalized to the US population.

Is the LAM0035 treatment population appropriately paired with the historical control (pseudoplacebo group)? The first point of examination again is related to the US, non-US composition of the study population. The aggregate pseudoplacebo group derived in the White Paper is a very close approximation to a 100% US sample while study LAM30055 is 75% non-US. To be a valid placebo for LAM30055 it must be accepted that the non-US treatment component of the study (LAM30055) and the US pseudoplacebo will behave as homogenous groups in response to treatment. Based on the discussion of differences in placebo response and escape rate between US and non-US groups, adequate parity does not appear to be present for the composite pseudoplacebo cohort to act as a placebo comparator for study LAM30055.

Baseline Seizure Frequency

In the White Paper studies, the minimum number of Baseline seizures required for randomization ranged from at least 2 seizures per 4 weeks (3 studies) to at least 4 seizures per 4 weeks (4 studies). The median Baseline seizure frequency ranged between 1.4 and 2.5 seizures per week. Study LAM30055 required at least 2 seizures per 4 weeks of Baseline. The median Baseline seizure frequency was 1.4 seizures per week for LTG 300 mg/d group and 1.5 for LTG 250 mg/d group, which is at the lower end of the range of the White Paper studies.

Table 11 showed that the escape rate was 42% for subjects with Baseline seizure frequency less than 4 per 4 weeks and 25% for subjects with Baseline seizure frequency of at least 4. The escape rate was higher for the subset of patients with 2-4 seizures per 4 weeks at Baseline. Therefore, there was no evidence that the relatively low Baseline seizure frequency in Study LAM30055 led to lower escape rate.

Table 11. Escape Rate by Baseline Seizure Frequency (White Paper PP)

	2- 4 Seizures per 4 weeks	At Least 4 Seizures per 4 weeks
n/N (%)	25/59 (42)	36/146 (25)
[95% CI]	[29.8,55.0]	[17.7,31.6]

* Includes calculated escapes (none met escape criterion #4)
Source: FDA reviewer.

Clinical Reviewer Comment

There is variability in the eligibility requirement for baseline seizure frequency among the White Paper studies. As noted by the statistical reviewer in the above section on baseline seizure frequency. Three White Paper studies had an eligibility of 2 seizures per four weeks and 4 studies had a requirement of 4 seizures per four weeks with a resulting range of 1.4 to 2.5 seizures per week at baseline, in the White Paper pseudoplacebo group. Study LAM30055 required 2 seizures per 4 weeks with a resulting median of 1.4 seizures / week. This places study LAM30055 at the lowest end of the White Paper pseudoplacebo baseline seizure frequency. This observation raises the possibility that the two populations are not matched. The lower baseline seizure frequency rate of the LAM30055 population may be represent a more stable population, physiologically inclined toward more stable epilepsy and lower escape rate. In order to test this hypothesis, the statistical reviewer examined the escape rate by baseline seizure frequency. The escape rate was found to be higher in those with a lower baseline seizure frequency. This finding, although counterintuitive, indicates the difference in baseline seizure rate between the White Paper pseudoplacebo group and the LAM30055 treatment group does not reduce the study validity.

Baseline Seizure Types

Data on the distribution of simple partial (SP), complex partial (CP) and secondarily generalized tonic-clonic (SGTC) seizure subtypes at Baseline were available from 4 of the 8 historical studies. There were 83 to 95 percent of the subjects in these 4 studies having CP seizures during Baseline compared to approximately 62% of subjects in Study LAM30055.

Table 12 showed that the escape rate was higher for the subset of patients without CP in Study LAM30055. Therefore, there was no evidence that the lower percentage of subjects with CP in Study LAM30055 contributed to the lower escape rate.

Table 12. Escape Rate by Baseline seizure Type (White Paper PP)

	Subjects without CP	Subjects with CP
n/N (%)	27/77(35)	34/128(27)
[95% CI]	[24.4,45.7]	[18.9,34.2]

* Includes calculated escapes (none met escape criterion #4)
Source: FDA reviewer.

Clinical Reviewer Comment

There is a notable difference in the baseline seizure type of study LAM30055 and in 4 studies of the White Paper pseudoplacebo group where this information is available. Those patients with complex partial seizures comprised 83 to 95 percent of the White Paper studies whereas 62% of patients in study LAM30055 had complex partial seizures. In order to determine if this difference of seizure type distribution would influence escape rate in a direction that would favor the success of study LAM30055, the statistical reviewer performed an analysis of the escape rate according to baseline seizure type. The sample from LAM30055 was analyzed. This revealed that patients with complex partial seizures had a lower escape rate. Study LAM30055 had a smaller proportion of CP seizures than the White Paper pseudoplacebo group, thus this difference in background seizure type does not bias toward success of study LAM30055.

Supportive Study (LTG IR) – US 30/31

The previous study US 30/31 which used the LTG IR formulation was the basis for the LTG IR monotherapy indication at a dose of 500 mg/day. Study US 30/31 was one of the eight studies from which the historical control endpoint was derived.

US 30/31 was combined from two studies US 30 and US 31 due to slow enrollment. The design of Study US 30/31 was similar to Study LAM30055 consisting of an 8-week Baseline phase followed by randomization to one of two treatment groups (LTG IR, 500 mg/day or pseudo-placebo valproic acid (VPA), 1000 mg/day). There was an 8-week Conversion phase from background AED monotherapy to either LTG IR or VPA comprised of 4 weeks of escalation of LTG IR or VPA followed by 4 weeks of withdrawal of the background AED. Twelve weeks of monotherapy followed and a Continuation phase was provided by roll-over to another study. Unlike Study LAM30055 which excluded subjects taking EIAEDs, Study US 30/31 included only subjects taking an EIAED as their background monotherapy.

Subject disposition was presented in Table 13. A total of 156 subjects were randomized. The ITT Population which consisted subjects randomized to treatment who received at least one dose of the assigned treatment included 76 subjects in the LTG IR group and 80 subjects in the VPA group. The PP Population of subjects who met Escape Criteria or completed 12 weeks of

monotherapy (i.e., completers; differently from Study LAM30055 PP) included 50 subjects in the LTG IR group and 64 subjects in the VPA group. More subjects in the LTG IR group than the VPA group prematurely discontinued the study (34% vs 20%, respectively) for reasons other than having met Escape Criteria, primarily due to a higher occurrence of AEs (20% vs 8%, respectively).

Table 13. Subject Disposition (All Randomized Subjects: Study US 30/31)

	Number (%) of Subjects	
	LTG IR	**VPA**
Population		
Randomized	76	80
Intent-to-Treat (ITT)	76	80
Per Protocol (PP)	50	64
Completion status		
Completed study	28 (37)	13 (16)
Met Escape Criteria	22 (29)	51 (64)
Prematurely withdrawn	26 (34)	16 (20)
Reason for premature withdrawal		
Adverse event (AE)	15 (20)	6 (8)
Protocol violation	2 (3)	4 (5)
Subject decided to withdraw from the study	4 (5)	2 (3)
Insufficient therapeutic response	5 (7)	3 (4)
Death	0	1 (1)

Source: Sponsor ISE Table 16.

The primary measure used to evaluate efficacy was the proportion of subjects meeting Escape Criteria (escapes) after the start of AED taper in the PP Population. A secondary measure used to evaluate efficacy was the proportion of escapes in the ITT Population. In this analysis, subjects who prematurely discontinued from the study and did not meet Escape Criteria were analyzed in two ways. In the first analysis, both LTG IR and VPA dropouts were also counted as escapes. This analysis was post-hoc and was labeled the ITT analysis. In the second ITT analysis, LTG IR dropouts were counted as escapes while VPA dropouts were counted as completers. This analysis was labeled the worst case analysis. An additional analysis was conducted on the ITT Population by the agency during the review of the LTG IR monotherapy sNDA that added subjects withdrawing due to inadequate response to those who met Escape Criteria (FDA Drug Approval Package; NDA 20-241/S003 and NDA 20-764/S001, approved 14 December 1998). The worst case analysis revealed no statistically significant difference between LTG and VPA. Other analyses showed that LTG was superior (Table 14).

Table 14. Proportion of Subjects Meeting Escape Criteria (Study US 30/31)

	Number n/N (%) of Subjects	
	LTG IR	**VPA**
US 30/31 PP Population[1]	22/50 (44)	51/64 (80)
ITT	48/76 (63)	67/80 (84)

	Number n/N (%) of Subjects	
	LTG IR	VPA
ITT worst case analysis	48/76 (63)	51/80 (64)
ITT Agency[2]	32/76 (42)	55/80 (69)

1. Different from the PP population is Study LAM30055.
2. Subjects who escaped were defined as meeting Escape Criteria or withdrawing due to an inadequate response. Subjects withdrawing due to AEs were not counted as escapes.

Source: Sponsor ISE Table 19-21.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Gender, Race and Age

Table 15 showed the subgroup analysis results for age, gender and race subgroups for Study LAM30055. Majority of the patients are 16 years old or older (92%), White (87%), female (53%). The escape rate was consistent across the race subgroups, but appeared higher in young (<16 years) and old (>=55 years) male patients. Logistic regressions indicated that there was no effect of age or gender on the escape rate.

Table 15. Escape Rate by Gender, Race and Age in Pooled Treatment Group (Study LAM30055 White Paper PP)

	Subgroups	n/N (%)	[95% CI]
Gender	Female	27/109 (25)	[16.7,32.9]
	Male	34/96 (35)	[25.8,45.0]
Race	White - White/Caucasian/European Heritage	53/178 (30)	[23.1,36.5]
	Asian - East Asian Heritage	6/19 (32)	[10.7,52.5]
	African American/African Heritage	2/6 (33)	[-4.4,71.1]
Age	Less than 16	8/17 (47)	[23.3,70.8]
	16 - 55	45/171 (26)	[19.7,32.9]
	55 or Greater	8/17 (47)	[23.3,70.8]

Source: FDA reviewer.

5. SUMMARY AND CONCLUSIONS

Statistical Issues and Collective Evidence

The formulation and dosage of LTG were different in the pivotal study LAM30055 and the supportive study US 30/31. The main differences in study design between the two studies were (1) Study US 30/31 was placebo-controlled but Study LAM30055 was not; (2) Study US 30/31 was conducted in the US while Study LAM30055 was conducted in 7 countries with approximately 75% of subjects enrolled outside the US; (3) and Study US 30/31 included only subjects taking an EIAED as their background monotherapy but Study LAM30055 excluded subjects taking EIAEDs. The study results were presented in Table 16. The proportion of subjects meeting Escape Criteria was lower in Study LAM30055 than Study US 30/31. The identified issues were discussed below.

Table 16. Summary of Escape Rate by Study

	LAM30055[1]		US 30/31	
	LTG XR 300 mg/day	LTG XR 250 mg/day	LTG IR	VPA
White Paper PP	31/108 (29, 37.2)	30/97 (31, 40.1)		
White Paper PP Sensitivity Analysis[2]	37/108 (34, 43.2)	37/97 (38, 47.8)		
ITT Worst Case Analysis[2]	41/112 (37, 45.5)	51/111 (46, 55.2)	48/76 (63)	51/80 (64)
Study US 30/31 PP (Completer Analysis)	31/102 (30)	30/90 (33)	22/50 (44)	51/64 (80)
ITT[3]	33/112 (29)	30/111 (27)	32/76 (42)	55/80 (69)
The 95% prediction limit is 65.3% for all escapes. The 95% prediction limit is 58.6% for escapes in the subgroup of patients with 1 background AED.				

*Numbers are: n/N (%, confidence upper bound%) or n/N (%)
1.Includes calculated escapes (none met escape criterion #4)
3.LTG dropouts were counted as escapes while VPA dropouts were counted as completers.
2.Subjects who escaped were defined as meeting Escape Criteria or withdrawing due to an inadequate response. Subjects withdrawing due to other reasons were counted as treatment successes.

Post-hoc Analyses

The analyses of the pivotal trial Study LAM30055 were altered post-hoc in the following aspects.

The primary endpoint and analysis population were changed to reflect the analysis of the White Paper. This post-hoc change did not seem to be a concern since this analysis could be viewed as pre-specified in the White Paper.

While the trial was ongoing, the sponsor evaluated a random sample of subjects for correct application of the Escape Criteria and identified a number of errors (e.g., some patients met an Escape Criterion but were not discontinued). As a result, remedial training of study site personnel and monitors was undertaken. Following completion of the study, planned analysis of

escapes showed that the number of subjects who met pre-defined Escape Criteria was surprisingly small. Only about 6% of the subjects met Escape Criteria compared to 42% in Study US 30/31 (Table 17). Therefore, to correct errors by sites/investigators, seizure data were evaluated post-hoc leading to reclassification of many subjects as 'escapes' (Table 16).

Table 17. Escapes As Determined by Investigator (ITT Population)

LAM30055		US 30/31	
LTG XR 300 mg/day	**LTG XR 250 mg/day**	**LTG IR 500 mg/day**	**VPA**
6/112 (5)	7/111 (6)	32/76 (42)	55/80 (69)

* Numbers are n/N (%).
* Subjects who escaped were defined as meeting Escape Criteria or withdrawing due to an inadequate response, as determined by investigator.

Potential Biases

It is well known that trials with internal control provide greater assurance than afforded by comparison to historical controls. The absence of an internal control arm is of particular concern when the primary endpoint is adverse outcome and involves subjective evaluation. In epilepsy monotherapy trials, dropouts, under-reporting seizures/escapes, etc, could bias toward treatment success and undermine the validity of the trial.

In Study LAM30055 subjects who dropped out for reasons other than meeting Escape Criteria were treated as completers in the sponsor's analysis, which biased toward treatment success (analysis for White Paper PP population). The White Paper used Kaplan-Meier estimate of the proportion, in which subjects dropped out due to other reasons were censored. This gives a higher estimated escape rate. The reviewer conducted a sensitivity analysis which included dropouts as treatment failures. This was also the planned primary endpoint of 'all-cause' discontinuation. To deal with potential bias due to conducting an essentially open-label study (all patients were on potentially effective test drug), a worst case analysis was conducted by the reviewer in which ITT subjects who dropped out before the background AED withdrawal were also considered escapes. The results remained positive for those analyses (Table 16).

The bias from under-reporting escapes was present in Study LAM30055. This bias was corrected to some extend by performing the post-hoc calculation of escapes using seizure data. However, there was no criterion #4 events reported and it was difficult to identify such events post-hoc due to the subjective nature of this criterion. Of the White Paper studies, Study US 30/31 was designed most comparable with Study LAM30055. Study US 30/31 had 10% subjects in the LTG IR group who met criterion #4 and 4% in the pseudo-control group. Other White Paper studies tend to have a large percentage (19%, 17%, 11%, 7%, 45% and 29% for study 1, 3, 5, 6, 7, 8 pseudo-control group, respectively). The criterion #4 in the LTG studies may be more restrictive than the White Paper criterion. Some events may be considered escapes according to the White Paper criteria, but not by the Study LAM30055 criteria. Therefore, comparing the Study LAM30055 escape rate with the combined escape rate due to all 4 criteria from the White Paper studies may bias towards treatment success. However, it was uncertain how to adequately assess the potential bias due to under-reporting criterion #4 events.

Population Comparability

Study LAM30055 had approximately 75% of subjects enrolled outside the US while all of the subjects in the historical control database were enrolled in the US. A higher proportion of subjects at US sites met Escape Criteria compared to non-US sites. The comparability of the US and non-US subjects was not established. The result for the US subgroup was positive except for the ITT worst case analysis (Table 9).

The White Paper data suggested that patients on one background AED had fewer escapes than patients on two AEDs. For patients on one background AED, the estimated percent escape is 83.0% with a lower prediction limit of 58.6%. In comparison to this limit, both LTG dose groups remained superior to the historical pseudo-placebo. However, LTG XR failed to show superiority for the US subgroup in the White Paper PP sensitivity analysis or the ITT worst case analysis (Table 9).

Conclusions and Recommendations

In summary, the data seem to suggest some evidence of efficacy of LTG XR as monotherapy treatment of partial seizures. However, interpretability of these analysis results is undermined by the limitations of the historical control design; thus, it is uncertain that the efficacy of LTG XR as monotherapy treatment of partial seizures is conclusive based on this study.

Clinical Reviewer Comments

The sponsor analysis revealed an unexpectedly low escape rate prompting re-evaluation of seizure data to create "calculated escapes". The proportion of subjects meeting escape criteria based on this analysis was 26/108 (24%) with lower and upper bound of 95% confidence intervals of 16% and 32.1% respectively for the 300mg /day group. The statistical reviewer notes that the sponsor analysis conducted for the White Paper per protocol population is based on the binomial proportion of subjects meeting escape criteria. The reviewer indicates that the White Paper used Kaplan-Meier estimate of the proportion in which subjects who dropped out for other reasons were censored. This results in a larger estimate of escapes. The statistical reviewer also created two additional analysis of the proportion of subjects meeting escape criteria, these three analysis methods are defined for as follows:

- White Paper Per Protocol: White Paper per protocol population where Kaplan-Meier estimate of the proportion in which subjects who dropped out for other reasons were censored.

- White Paper Sensitivity Analysis: Subjects who dropped out for reasons other than meeting escape criteria were considered escapes.

- ITT Worst Case: ITT subjects who dropped out before the background AED withdrawal were also considered escapes.

The results of study LAM30055 based on these analysis may be seen in table 8. Based on the White Paper 95% prediction limit of 65.3% all of the 300mg/day or 250mg/day upper 95% confidence intervals in addition to the US subset where the White Paper per protocol and sensitivity analysis remain superior to this threshold (table 9).

Comparability of the White Paper and LAM 30055 study populations reveals difference in two elements of composition; region and number of background anticonvulsant drugs allowed at study entry. The White Paper is derived from an almost 100% US population while study LAM30055 is 75% non-US.

In 6 the 8 White Paper studies where the data is available the participants were on 2 background AEDs at entry while study LAM30055 required background monotherapy for eligibility. The statistical reviewer has found that the White Paper data indicate that patients with one background AED had fewer escapes than patients with two AEDs. An analysis of the White Paper pseudoplacebo population on only 1 background AED is performed and reveals a Kaplan Meier escape rate of 83% with a lower bound prediction interval of 58.6%. The overall study LAM30055 results were not changed based on the statistical reviewer escape groups of table 8. The US subset results did lose superiority to the White Paper sensitivity analysis (table 9)

From within the White Paper studies there was only one non-US study site which was located in Canada. Study LAM30055 has only a 25% US composition. As discussed in the section on regional comparisons, the non-US results may not be generalizable to the US. The small US subset of LAM30055 was not designed to be a stand alone comparator to the White Paper pseudoplacebo composite.

The most valid modification for comparing study LAM30055 to the White Paper pseudoplacebo composite group appears to be restriction to those participants on 1 AED. It is not clear that those on 1 AED are a distinct population from those on 2 AED; however the statistical reviewer examined the White Paper data and found fewer escapes among those on 1 AED. Therefore those in the White Paper on 1 AED are most suited to compare to the study population of LAM30055.

The use of an historical control comparator is a novel methodology. There are multiple components of the White Paper pseudoplacebo aggregate which present a challenge to confidence in this approach as a valid comparator to study LAM30055. The populations are different across time and region. The span of the pseudoplacebo population ranges from approximately 1992 to 2001. In the oldest White Paper study the pseudoplacebo patients will be almost a generation older than the study population of LAM30055. The regional divergence is discussed above. The variation in mapping of escape criteria between the Lamictal XR monotherapy study and the White Paper studies are features which point to insufficient uniformity between studies to act as a pooled comparator. There are also features which support the validity of this aggregate pseudoplacebo group. First, in every study the pseudoplacebo escape rate was larger than the active therapy escape rate and in 6 of 7 studies where the data is available; the active therapy was statistically superior to the pseudoplacebo arm (see appendix 2).

The common core feature of all 8 White Paper trials was a study endpoint of patient exit (escape) rate.

Additional support for efficacy is provided by the bioequivalence data on Lamictal IR and XR presented in the Clinical Pharmacology review of Lamictal XR (adjunctive therapy in partial seizures)[5]. This data provides an expectation that this extended release form of Lamictal will perform similarly to Lamictal IR which is approved for conversion to monotherapy. Conceptual support for efficacy of Lamictal XR monotherapy is provided by the established effectiveness of Lamictal XR for treatment of partial and primary generalized tonic-clinic seizures.

Summary

If the White Paper is accepted as a valid platform for historical control comparison, modified by restricting the population to those on 1 background AED, then the resultant lower bound of the pseudoplacebo group prediction interval is 58.6%. All analysis subsets for study LAM30055 populations in both the 300mg/day and 250mg/day dose groups remain superior to this (58.6%) White Paper lower bound. The US subset remains superior only in the White Paper per protocol analysis derived by the statistical reviewer. The US subset is small and not powered to independently test for significance, therefore this finding in isolation does not supersede the overall study results.

Conclusion

There is adequate support for approval of Lamictal XR for use in conversion to monotherapy for patients ≥13 years of age who are receiving treatment with a single AED. The recommended target dose is 300mg daily, although the 250mg/day dose remained superior to the pseudoplacebo, this dose was not the protocol directed primary efficacy endpoint.

[5] Tandon V. Clinical Pharmacology/Biopharmaceutics Review, NDA22115, Product: Lamictal XR, Indication: Adjunctive therapy for partial onset seizures with or without generalization in patients ≥ 13 years. 9/6/2007

Appendix 1. Criteria Comparator

Study/ Pub date	Escape Criteria by Study	Matching Properties
1 (1992)	(1) **(3)**an episode of status epilepticus; (2) **(4)**a secondarily generalized tonic-clonic seizure if none had been experienced within 2 years of study entry; (3) **(1)** a 28-day study seizure rate greater than two times the maximum 28-day study seizure rate during baseline (a 28-day period is defined as any four consecutive study weeks); (4) **(2)**a 2-day study seizure rate greater than two times the maximum 2-day study seizure rate during baseline; or *(5)* **(3)** an unacceptable increase in the frequency or intensity of seizure activity that did not meet any of the exit criteria but that was, in the opinion of the treating physician, clinically significant	Does not have # 4 equivalent, removal of 4 leaves Parity **Inherent non-parity before removal of 4**
2 (1998)	1) doubling of average monthly seizure rate; 2) doubling of the highest consecutive 2-day seizure rate; 3) emergence of a new, more severe seizure type; or 4) clinically significant prolongation of generalized tonic-clonic seizures	Parity
3 (1997)	1. a doubling of the average monthly (28-day) baseline seizure frequency, 2. a doubling of the highest 2-day baseline seizure frequency, 3. a single GTCS if none occurred during baseline, 4. Prolongation of generalized seizure duration that was considered serious by the investigator, or serial seizures or status epilepticus of any seizure subtypes.	Criteria #3 could be placed in Criteria 4 in LAM30055 Criteria 4 = criteria 4 in LAM30055 but serial seizures or status epilepticus match **"emergence of a new more severe seizure type" – criteria 3** No representation of criteria # 3, emergence of a new more severe seizure type (except for **special case of " a single GTCS"** The absence of clear 3 would leave contribution from 3 that is not matched here Non-parity with or without criteria 4- **Inherent Non-Parity**
4		
5 (2001)	1) a twofold increase in monthly seizure frequency in any 28-day period relative to the open-label baseline phase; 2) a twofold increase in the highest consecutive 2-day seizure frequency relative to the open-label baseline phase; 3) occurrence of a generalized seizure if none occurred during the open-label baseline phase; or 4) prolongation of generalized seizure duration that, in the opinion of the investigator, required intervention.	Criteria 3 in this study could represent a special case of criteria 3 in LAM30055. **"emergence of a new more severe seizure type" is broader and should capture "occurrence of a generalized seizure if none occurred during open label or baseline". This** could also satisfy LAM30055 category 4. It could be anticipated that criteria #3 of LAM30055 should capture more than this criteria 3
6 (2000)	1) a twofold increase in partial seizure frequency in any 28-day period compared to baseline; 2) a twofold increase in the highest consecutive 2-day seizure frequency that occurred during the baseline phase (patients with a single seizure as the highest 2-day baseline phase seizure frequency exited the trial if three or more seizures occurred during any 2-day period in the double-blind treatment phase); 3) occurrence of a single generalized seizure if none had occurred in the 6 months prior to randomization; or 4) a prolongation or worsening of seizure duration or frequency	Criteria 4 in this study is roughly equivalent to criteria 3 of LAM30055. Criteria 3 of this study could be captured by criteria 4 of LAM30055 Effect if criteria 4 is censored could be to remove balance to events which would asymmetrically remain in LAM30055 as criteria 3.

	considered by the investigator to require intervention.	**Non-parity before and after #4 modification**
7 (1992)	(1) a two-fold increase in average monthly seizure frequency, (2) a two-fold increase in the highest 2-day seizure frequency, (3) a single generalized seizure if none occurred during the baseline period, and (4) a prolongation of generalized seizure duration (serial seizures or status epilepticus) deemed by the investigator to require intervention.	This study criteria #3 could represent a special case of LAM30055 criteria # 3 This criteria # 4 could capture LAM30055 criteria #3 if serial seizures or status epilepticus is considered emergence of new more severe seizure type **Inherent Non parity**
8 (1993)	(1) a doubling in monthly seizure number compared with the average monthly seizure number during the baseline period; (2) a doubling of 2-day seizure number over the worst 2-day period during the baseline (this frequency criterion applied only when two or more seizures had occurred during some 2- day period of the baseline); (3) **(4)** a single generalized tonic clonic tonic clonic seizure, if none had occurred during the baseline; and a significant prolongation of a generalized tonic clonic seizure considered serious by the investigator, **(3)** or serial seizures or status epilepticus of seizure types other than generalized tonic-clonic seizures.	**Parity**
LAM30055	1. Doubling of average monthly seizure frequency calculated as the sum of countable, partial seizures starting the day prior to the study visit and extending back 28 days. 2. doubling of the highest consecutive 2-day seizure frequency. 3. emergence of a new, more severe seizure type. 4. clinically-significant prolongation of generalized tonic-clonic seizures.	

Appendix 2. Comparison of White Paper Active and Pseudoplacebo Study Escapes

Study Escapes with total enrollment denominator (n^1)					
	Pseudoplacebo	**Active**	**Pseudoplacebo Escape / total enrollment (n/n^1) (%)**	**Active therapy Escape / total enrollment (n/n^1) (%)**	**Background AED**
1	Gabapentin 600mg	Gabapentin 2400mg	70/93 (75)	66/91 (73)	1 or 2
2	Valproic Acid 1000mg	Lamictal 500mg	55/80 (69)	32/76 (42)	1 (CBZ or PHT)
3	Topamax 100mg	Topamax 1000mg	21/24 (88)	12 /24 (50)	1
4	Not published				
5	Oxcarbazepine 300mg	Oxcarbazepine 2400mg	40/45 (89)	30/49 (61)	1 (CBZ)
6	Oxcarbazepine 300mg	Oxcarbazepine 2400mg	42/46 (91)	14/41 (34)	1 or 2
7	Valproic Acid 15mg/kg	Felbamate 3600mg	19/22 (86)	3/22 (14)	1 or 2
8	Valproic Acid 15mg/kg	Felbamate 3600mg	39/55 (71)	18/56 (32)	1 or 2

Study escapes as analyzed by study protocol, n^2 varies as directed by study handling of dropouts						
	Pseudoplacebo	**Active**	**Pseudoplacebo Escape / study directed denominator (n/n^2) (%)**	**Active therapy Escape / study directed denominator (n/n^2) (%)**	**Significance**	**1^0 efficacy endpoint**
1	Gabapentin 600mg	Gabapentin 2400mg	70/93 (75)	66/91 (73)	No, dropouts included NS	Primary efficacy = time to exit, secondary = completion rate
2	Valproic Acid 1000mg	Lamictal 500mg	51/64 (80)	22/50 (44)	P<.001, dropouts excluded	Primary efficacy = Per protocol % escape
3	Topamax 100mg	Topamax 1000mg			Not calculated for % escape Time to exit, p = 0.002	Primary efficacy= time to exit
4	Not published					
5	Oxcarbazepine 300mg	Oxcarbazepine 2400mg	40/40 (100)	30/46 (65)	P=0.0001, dropouts removed	1^0 efficacy = time to exit.
6	Oxcarbazepine 300mg	Oxcarbazepine 2400mg	42/45 (93)	14/34 (41)	P<0.0001 Dropouts excluded	1^0 efficacy = % meeting exit
7	Valproic Acid 15mg/kg	Felbamate 3600mg	19/22 (86)	3/22 (14)	P< 0.0001 Dropouts included	1^0 efficacy = % meeting exit
8	Valproic Acid 15mg/kg	Felbamate 3600mg	39/50 (78)	18/45 (40)	P<0.001 Dropouts excluded	1^0 efficacy = % meeting exit

Addendum. Updated Results Including Additional Escapes Due To Meeting Escape Criterion #4

On February 16, 2011, the Sponsor submitted response to the Agency's January 6, 2011 request of identifying patients who qualify for escape based on the need for intervention by examining patient medication records and adverse event records. Additional 3 and 5 escapes were identified for 300mg/d group and 250 mg/d group, respectively, for the ITT population. Table 7-10 were updated to include those additional escapes.

Table 18. Percentage of Subjects Meeting Each Criterion (Updated)

Criterion	LTG XR 300 mg/day	LTG XR 250 mg/day
Criterion #1	12/108 (11)	19/97 (20)
Criterion #2	20/108 (19)	18/97 (19)
Criterion #3	8/108 (7)	7/97 (7)
Criterion #4	7/108 (6)	10/97 (10)

* White Paper Per Protocol Population
* Numbers are n/N (%).
* Patients may meet more than one criterion.

Source: FDA reviewer.

Table 19. Proportion of Subjects Meeting Escape Criteria (Updated)

	LTG XR 300 mg/day	LTG XR 250 mg/day
White Paper PP		
n/N (%)	34/108 (31)	34/97 (35)
[95% CI]	[22.7,40.2]	[25.6,44.5]
White Paper PP Sensitivity Analysis		
n/N (%)	40/108 (37)	40/97 (41)
[95% CI]	[27.9,46.1]	[31.4,51.0]
ITT Worst Case Analysis		
n/N (%)	44/112 (39)	54/111 (49)
[95% CI]	[30.2,48.3]	[39.4,57.9]
The 95% prediction limit is 65.3% for all escapes. The 95% prediction limit is 58.6% for escapes in the subgroup of patients with 1 background AED (the subgroup will be mentioned later in the review).		

*Includes calculated escapes

Source: FDA reviewer.

Table 20. Proportion of Subjects Meeting Escape Criteria by Region (Updated)

	US	Non-US
White Paper PP		
n/N (%)	21/50 (42)	47/155 (30)
[95% CI]	[28.3, 55.7]	[23.1, 37.6]
White Paper PP Sensitivity Analysis		
n/N (%)	27/50 (54)	53/155 (34)
[95% CI]	[40.2, 67.8]	[26.7, 41.7]
ITT Worst Case Analysis		
n/N (%)	33/56 (59)	65/167 (39)
[95% CI]	[46.0, 71.8]	[31.5, 46.3]
The 95% prediction limit is 65.3% for all escapes. The 95% prediction limit is 58.6% for escapes in the subgroup of patients with 1 background AED.		

* Includes calculated escapes
Source: FDA reviewer.

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

/s/

XIANG LING
03/21/2011

KUN JIN
03/21/2011
I concur with this review.

HSIEN MING J J HUNG
03/22/2011
concur with Stat Review

STEVEN T DINSMORE
03/24/2011

NORMAN HERSHKOWITZ
04/05/2011

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

MF Number: 024581

Indication(s): Monotherapy of partial seizures

Biometrics Division: Division of Biometrics I

Statistical Reviewer: Xiang Ling, Ph.D. ; Tristan Massie, Ph.D.

Concurring Reviewers: Kun Jin, Ph.D., Team Leader

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Keywords: historical control, meta analysis

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1. INTRODUCTION

1.1 Overview

French et al submitted a White Paper to the FDA proposing use of an historical control for studying conversion to monotherapy for partial seizures. The authors stated that alternative trial designs were either unethical or not feasible. The historical data were gathered from 8 "conversion to monotherapy" studies, all of which used "pseudoplacebo", either a sub-therapeutic dose of an active drug or a low dose of study drug as the comparator. Efficacy evaluation was based on the proportion of patients who escaped the studies as a result of meeting predefined escape criteria related to worsening of seizures. The authors proposed that the lower limit of a 95% prediction interval of escape rate based on the aggregated pseudoplacebo data be used as the margin for a study drug to rule out; that is, the escape rate of a study drug needs to be statistically superior to this escape rate in order to demonstrate monotherapy efficacy.

1.2 Data Sources

The analysis dataset used for the analyses in the White Paper was submitted to the Agency. However, the patient level data of Study 7 was not available. Additional data were obtained from NDA database for all studies except for Study 4. References of the White Paper also provided useful summary data/information where individual patient data were not available. Table 1 lists the information on the White Paper Studies.

Table 1. Information on White Paper Studies

White Paper Study	Ref. #	NDA #	Drug	Sponsor	Study
1	13	20-235 / (b) (4)	Neurontin (gabapentin)	Pfizer (Parke-Davis)	945-82
2	16	20-241 / S-003	Lamictal (lamotrigine)	GSK	US30/31
3	18	20-505 / S-018	Topamax (topiramate)	J & J	YI
4	NA	20-189	Felbatol (felbamate)	MEDA (Wallace Labs)	NA
5	19	21-014	Trileptal (oxcarbazepine)	Novartis	Study 26
6	14	21-014	Trileptal (oxcarbazepine)	Novartis	Study 28
7	17	20-189	Felbatol (felbamate)	MEDA (Wallace Labs)	Protocol 284
8	15	20-189	Felbatol (felbamate)	MEDA (Wallace Labs)	Protocol 244

The data files are located in the following directory:
\\fdswa150\nonectd\MF024581\N_001\2011-02-01.

2. STATISTICAL EVALUATION

The review primarily checked the numerical results in the White Paper using the submitted data set used for the White Paper as well as the available original NDA data sets. The review also pointed out some possible problems with the implementation of this approach. This review should not be considered as an attempt to statistically validate the use of historical controls in clinical trials in general. It is well known that there are many shortcomings of using historical controls instead of placebo controls in clinical trials.

2.1 Data and Analysis Quality

The White Paper data included the following variables: patient number, age, race, gender, baseline carbamazepine (CBZ) use, time to escape (days from Study Day 1), whether the subject was censored, time to escape in the original analysis (days from the start of background antiepileptic drug [AED] taper), time cut-off at 112 days (from background AED taper), whether the subject was censored at Day 112.

The NDA database had more information, including demographics, baseline disease characteristics, seizure summary by study phase/visit, disposition and subject escapes, etc. However, individual seizure counts for patients were available only for 4 studies (Study 1, 2, 5 & 6).

The reviewers checked if the White Paper analysis dataset could be reproduced from NDA datasets and if the derivation of the analysis dataset was consistent across the studies. In summary, there were a few minor discrepancies/issues but none of them would significantly impact the results. Below are the findings.

For Study 1, the White Paper dataset defined 'time to escape' as (time to escape – 14 days), i.e., the two weeks prior to the planned start of baseline drug taper were excluded. The reviewer recalculated it using the actual start day of baseline drug taper (time to escape – study day of the start of baseline drug taper).

For Study 8, the White Paper dataset calculated 'time to escape' by (Last Date Drug Taken - First Date Drug Taken). The reviewer recalculated it as (Date Subject Qualified for Escape - First Date Drug Taken). This resulted in two more escapes than the White Paper data. In addition, there were a few discrepancies in whether subjects took CBZ at baseline.

For Study 2, the definition of the variables was not clear and it was not certain to the reviewer how the variable 'time to escape' was derived. There was inconsistency regarding one patient's escape status between the two data sources. Request for clarification had been sent to the sponsor and the responses had not been received when this document was written.

The reviewers generated several variables based on NDA datasets including patient escapes due to each escape criterion (information not available for Study 3 & Study 4) and the number of background AEDs (information not available for Study 4).

2.2 Study Design and Endpoints

The study designs were similar; all the trials were randomized, double-blind, parallel group design with a baseline phase followed by a double-blind phase divided into a conversion phase and a monotherapy phase. The conversion phase ranged from 4 to 10 weeks, and the monotherapy phase ranged from 11 to 16 weeks across the trials. The trial continued until either all phases were completed or patients met pre-specified escape criteria related to worsening of seizures. All studies were conducted in the US except that Study 1 also enrolled subjects from Canada.

There were a few differences in the study design. Study 3, 5, 6, 7 & 8 started background drug taper right after randomization, while study 1 and 2 started background drug taper 2 and 4 weeks, respectively, after randomization. Study 5 was the single study that removed background medication prior to randomization. Study 1 and 2 had longer conversion periods (10 and 8 weeks respectively) while the rest of the studies had 4-6 weeks. However, the differences in the conversion phase were not considered critical as all subjects were on pseudoplacebo monotherapy for a sufficient period of time to allow the evaluation of study outcome.

Five studies allowed up to two background AEDs. Of them, four required that one of the AEDs be taken at less than 50% of the minimum recommended dose or that the serum concentration be less than 50% the minimum effective serum level. Study 2 and Study 5 allowed only one background AED, which had to be an enzyme-inducing antiepileptic drug (EIAED) or CBZ, respectively.

The White Paper used the percentage of patients escaping at day 112 after starting withdrawal of background AED(s) as the primary endpoint. The escape criteria were:

1. A two-fold increase in partial seizure frequency in any 28-day period compared to baseline. (As the White Paper pointed out that it is unclear if this was done on a rolling basis in all cases. Discussion with the companies involved has determined that the statistical methodology may have varied from trial to trial).

2. A two-fold increase in the highest consecutive 2-day seizure frequency that occurred during the baseline phase.

3. Occurrence of a single generalized seizure if none had occurred in the previous 6 months (Study 6, Ref 14) , within two years of study entry (Study 1, Ref 13), during baseline (Studies 3, 5, 7, 8, Refs 18, 19, 17, 15), and "emergence of a more severe seizure type (which would include generalized seizure) (Study 2, Ref 16).

4. A prolongation or worsening of seizure duration or frequency considered by the investigator to require intervention for all trials (although Studies 2, 5, and 7 require the worsening seizures to be generalized) or episode of serial seizure/status epilepticus for Studies 3,7,8, and episode of status epilepticus for Study 1.

2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 398 participants were enrolled in the 8 pseudoplacebo cohorts, although seven participants left the trial prior to the start of the baseline drug taper and were excluded from the analyses presented here.

Demographic and baseline characteristics are provided in Table 2. The mean patient age ranged between 34 and 38 year and the majority of the patients were white (73%-100%). Most subjects were on carbamazepine (CBZ) at baseline. For studies that allowed 2 AEDs at baseline, the percentages of patients on 2 AEDs ranged between 17% and 33%.

Table 2. Baseline Characteristics

Study	N	Age Mean years	Female n (%)	Race White n (%)	Race Black n (%)	Race Other n (%)	On 2 AEDs n (%)	CBZ Use n (%)
1	93	34	42 (45.2)	76 (81.7)	13 (14.0)	4 (4.3)	31 (33.3)	67 (72.0)
2	74	35	44 (59.5)	54 (73.0)	8 (10.8)	12 (16.2)	0 (0.0)	43 (58.1)
3	24	35	15 (62.5)	20 (83.3)	1 (4.2)	3 (12.5)	4 (16.7)	16 (66.7)
4	32	NA	NA	NA	NA	NA	NA	NA
5	45	35	21 (46.7)	39 (86.7)	4 (8.9)	2 (4.4)	0 (0.0)	45 (100.0)
6	46	36	27 (58.7)	42 (91.3)	4 (8.7)	0 (0.0)	9 (19.6)	21 (45.7)
7	22	38	16 (72.7)	22 (100.0)	0 (0.0)	0 (0.0)	7 (31.8)	13 (59.1)
8	55	35	35 (63.6)	47 (85.5)	8 (14.5)	0 (0.0)	11 (20.0)	33 (60.0)

Subject disposition is summarized in Table 3. The percent of subjects who dropped out due to reasons other than meeting escape criteria ranged from 0 to 11%.

Table 3. Subject Disposition

Study	N	Complete n (%)	Dropout n (%)	Escape n (%)
1	93	17 (18.3)	9 (9.7)	67 (72.0)
2	74	13 (17.6)	7 (9.5)	54 (73.0)
3	24	4 (16.7)	0 (0.0)	20 (83.3)
4	32	NA	NA	28 (87.5)
5	45	0 (0.0)	5 (11.1)	40 (88.9)
6	46	3 (6.5)	1 (2.2)	42 (91.3)
7	22	2 (9.1)	1 (4.5)	19 (86.4)
8	55	11 (20.0)	5 (9.1)	39 (70.9)
Total	359	50 (13.9)	28 (7.8)	281 (78.3)

*Dropouts did not include withdrawals due to meeting escape criteria.

2.4 Statistical Methodologies

For each of these studies, the White Paper authors calculated Kaplan-Meier (KM) estimates of the percent escape as a function of time and the asymptotic standard error of the estimates. To use a consistent time frame, escape rates were calculated from the start of withdrawal of the background AED (or start of drug taper for Study 5) to 112 days. Additionally, the rate of escape in Study 5 was 100%. In order to provide an estimate of the percent escape and associated standard error, 2 successes (i.e. completed without meeting escape criteria) and 2 failures were added to the total[1].

The authors used a non-iterative random effects approach proposed by DerSimonian and Laird[2] to compute the combined percent escape rate and standard error. A 2-sided 95% prediction interval on the percent escape was calculated, based upon a projected sample size of 50 subjects and a pseudoplacebo escape rate of 80%.

The reviewer also calculated the estimated binomial proportion. Subjects who dropped out without meeting escape criteria were included as having successfully completed the trial. This is the method used in some studies. The estimated binomial proportions will be smaller than the KM estimates which censor the dropouts instead of include them as completer.

The reviewer checked the homogeneity of the study outcomes (binomial proportions of escapes) using a likelihood ratio test. A logistic model was fit for the study outcome 'escape' (yes, no) with study as the main effect. The consistency for each Escape Criterion was also examined using a summary table.

2.5 Results and Conclusions

Using the White Paper data, the reviewer confirmed the White Paper result: the estimate of the combined percent escape based on the non-iterative mixed effects model is 85.1% with a lower bound of the 95% prediction interval of 65.3%.

Analyses using the NDA data had similar results. Table 4 summarizes the estimates of percent escapes for each study using the NDA data. The KM estimate of the combined percent escape was 85.2% with a lower bound of 65.7%. The estimated combined binomial proportion was 81.7% with a lower bound of 62.7%.

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[1] Agresti A, Coull B. (1998) Approximate is better than "exact" for interval estimation of binomial proportions. Am Stat 52:119–126.

[2] DerSimonian R, Laird N. (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188.

Table 4. Outcome for the White Paper Studies

Study	N	# escape by day 112	KM Est. (%)	KM Standard Error (%)	Binomial Est. (%)	Binomial Standard Error (%)
1	93	67	76.6	4.7	72.0	4.7
2	74	54	77.2	5.2	73.0	5.2
3	24	20	83.3	7.6	83.3	7.6
4	32	28	87.5	5.9	87.5	5.8
5	45	40	95.9[1]	2.8	88.9	4.7
6	46	42	93.2	3.8	91.3	4.2
7	22	19	86.4	6.7	86.4	7.3
8	55	39	76.3	6.1	70.9	6.1

1. Two successes and two escapes were added to estimate percent escape and the standard error.

Homogeneity of the studies in the escape rate was examined by fitting a logistic model for escape (yes, no) with study as the main effect. The p-value of the likelihood ratio test is 0.0182, suggesting that there is a difference in the escape rate among the studies. This raises a concern on the validity of pooling 8 studies to calculate the overall escape rate. Whether the random effects model would be an appropriate model in this situation was not discussed in the White Paper.

Furthermore, we calculated the percentages of subjects meeting each criterion for 6 of the studies with available data. For Study 3, data for individual criterion were not available for each subject and the summary information was obtained from White Paper reference #18. The percentages varied a lot for criterion #4 ranging between 4% and 45% (Table 5). A possible explanation is that this criterion was subjective and the specification of this criterion varied among the studies.

Table 5. Percentage of Subjects Meeting Each Criterion

Study	N	Criterion #1 (%)	Criterion #2 (%)	Criterion #3 (%)	Criterion #4 (%)
1	93	26	15	12	19
2	74	27	22	22	4
3	24	25	21	25	17
4	32	NA	NA	NA	NA
5	45	18	38	22	11
6	46	33	39	13	7
7	22	27	14	9	45
8	55	35	22	18	29

*Patients may meet more than one criterion.

3. FINDINGS IN SPECIAL/SUBGROUP POPULATION

3.1 Gender, Race, and Age

The White Paper authors examined the possible effect of explanatory variables (e.g. age, gender, race, withdrawal from CBZ) by fitting a Cox model stratified by study with the possible explanatory variables as covariates. An unstratified Cox model was used to examine effect of randomization before or after baseline medication withdrawal. Only studies with individual data on the variable of interest were included. The reviewer found no effect of gender, race (White, Black, Other), age, or baseline CBZ use.

3.2 Other Special/Subgroup Populations

The Cox model stratified by study with the number of background AEDs (1, 2) as covariate suggested that subjects with two background AEDs were more likely to escape than subjects with one AED (p-value=0.0161, hazard ratio=1.49). The result was confirmed by the logistic model with similar specification (p-value=0.0256, odds ratio=2.59).

Table 6 summarizes the estimates of percent escapes for subjects on one background AED for each study. The Kaplan-Meier estimate of the combined percent escape for subjects with one background AED is 83.0% with a lower bound of 58.6%. The estimate of the binomial proportion of escapes is 78.7% with a lower bound of 56.0%.

Table 6. Outcome for Subjects on One Background AED

Study	N	# escape by day 112	KM Est. (%)	KM Standard Error (%)	Binomial Est. (%)	Binomial Standard Error (%)
1	62	42	72.2	6.1	67.7	5.9
2	74	54	77.2	5.2	73.0	5.2
3	20	16	80.0	8.9	80.0	8.9
4	NA	NA	NA	NA	NA	NA
5	45	40	95.9[1]	2.8	88.9	4.7
6	36	33	94.1	4.1	91.7	4.6
7	15	12	84.8	9.8	80.0	10.3
8	44	29	70.3	7.2	67.3	6.3

1. Two successes and two escapes were added to estimate percent escape and the standard error.

4. SUMMARY AND CONCLUSIONS

The White Paper data were consistent with the NDA datasets except for minor discrepancies. This review confirmed the White Paper result: the estimate of the combined percent escape is 85.1% with a lower bound of the 95% prediction interval of 65.3%.

The results using the available original NDA datasets are summarized in Table 7.

Table 7. Summary of the Results

Population	KM Est. (Lower Bound) (%)	Binomial Est. (Lower Bound) (%)
All subjects	85.2 (65.7)	81.7 (62.7)
Subjects with one AED	83.0 (58.6)	78.7 (56.0)

Potential heterogeneity in the escape rate among the suggested by the heterogeneity test raised a concern on the validity of pooling the 8 studies to calculate the overall escape rate.

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/s/

XIANG LING
03/21/2011

TRISTAN S MASSIE
03/21/2011

KUN JIN
03/21/2011
I concur with this review.

HSIEN MING J J HUNG
03/22/2011
concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-115/S-006

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA:	22-115 (Sn-0024)
Brand Name:	Lamictal® XR
Generic Name:	Lamotrigine
Sponsor:	GlaxoSmithKline
Type of Dosage Form:	Extended-Release Oral Tablets
Strengths:	25 mg, 50 mg, 100 mg, 200 mg, and 300 mg
Indications:	Monotherapy for partial onset seizures (in patients 13 years of age and older)
OCP Reviewer:	Ta-Chen Wu, Ph.D.
OCP Team Leader:	Angela Yuxin Men, M.D., Ph.D.
OCP Division:	DCP-1 HFD-860
OND Division:	Neurology Drug Products HFD-120
Submission Date:	March 31, 2010
Type of Submission:	Prior Approval Efficacy Supplement

BACKGROUND:

The Sponsor is seeking the approval for Lamictal® XR™ (lamotrigine) Extended-Release Tablets for conversion to monotherapy in patients ≥13 years of age with partial seizures who are receiving therapy with a single antiepileptic drug (AED).

A pivotal clinical study (LAM30055) was conducted in subjects 13 years of age and older with partial seizures to support the efficacy of LAMICTAL XR, compared to the historical control, for this indication. Study LAM30055 was a 59-week, double-blind, randomized, historic control study. Eligible patients were randomized (1:1) to receive either 250 or 300 mg/day of Lamicatal XR. The double-blind treatment phase consisted of a 10~11-week Conversion Phase and a 12-week Maintenance (monotherapy) Phase. The LAMICTAL XR dose was escalated to the target dose, followed by the withdrawal of the background AED. The data for the historic control were pulled from 8 "conversion to monotherapy" studies which used a low dose of an approved AED (pseudoplacebo) as the comparator.

A pharmacokinetic study (Study LEP 105972) in the elderly subjects was ongoing at the time of the submission; however, results of the study were not submitted. No additional clinical pharmacology information submitted in this application and, therefore, no review on study report was conducted.

CONCLUSION:

Office of Clinical Pharmacology has reviewed the proposed labeling for the Lamictal® XR™ and provided input on dosage adjustment and revision labeling languages. The agreement on the labeling recommendations was reached at the teleconference with the Sponsor on April 22, 2011. The final label will be available in the Approval Letter.

Ta-Chen Wu, Ph.D.
Reviewer, Neurology Drug Products, DCP-1, OCP

Angela Yuxin Men, M.D., Ph.D.
Team Leader, Neurology Drug Products, DCP-1, OCP

Cc: HFD-120 CSO/D. Demczar
HFD-860 /TL Clin Pharm/A. Men
/DDD DCP-1/R. Uppoor
/DD DCP-1/M. Mehta

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/s/

TA-CHEN WU
04/23/2011

YUXIN MEN
04/24/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-115/S-006

OTHER REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

Division of Neurology Products (HFD-120)
Center for Drug Evaluation and Research

Date: April 25, 2011

From: Lois M. Freed, Ph.D.
Supervisory Pharmacologist

Subject: NDA 22-115 (Lamictal XR [lamotrigine]), S-006 (received March 31, 2010)

NDA 220115/S-006 provides clinical data to support a new indication for Lamictal XR, i.e., "conversion to monotherapy in patients 13 years and older with partial seizures who are receiving therapy with a single antiepileptic drug." This supplemental NDA was originally received on March 31, 2010, but the goal date was extended by 3 months following receipt of a major amendment on November 19, 2010. No nonclinical data were included in this submission; however, the currently approved labeling was reviewed.

Labeling History

NDA 22-115 was originally approved on May 29, 2009, with labeling in PLR format. Since the original approval, other labeling changes have been approved (S-001, April 14, 2010; S-009, October 24, 2010; S-010, October 24, 2010). None of the labeling revisions involved changes to the nonclinical sections, so those sections were not reviewed at the times of approval.

The proposed labeling revisions included in S-006 also do not involve the nonclinical sections; however, upon reviewing currently approved labeling for Lamictal XR, it was clear that much of the nonclinical wording needed to be updated to conform to current standards and formatting.

Labeling Recommendations

The following labeling revisions are recommended, using the sponsor's proposed labeling (based on current approved labeling, October 24, 2010) and taking into consideration recommendations made by Dr. Fisher (Pharmacologist, DNP) and information provided by the sponsor (email, 4/21/11).

Section	Sponsor's proposed	Recommended changes
HIGHLIGHTS	(b) (4)	Remove
		Add: ------**USE IN SPECIFIC POPULATIONS**----- • Pregnancy: based on animal data, may cause fetal harm. Pregnancy Registry available. (8.1)
5 WARNINGS AND PRECAUTIONS		Retain, but is now **5.13**
8 USE IN SPECIFIC POPULATIONS		**8.1 Pregnancy** As with other AEDs, physiological changes during pregnancy may affect plasma lamotrigine concentrations and/or therapeutic effects. There have been reports of

Section	Sponsor's proposed	Recommended changes
	(b) (4)	decreased lamotrigine concentrations during pregnancy and restoration of pre-partum concentrations after delivery. Dosage adjustments may be necessary to maintain clinical response. Pregnancy Category C There are no adequate and well-controlled studies in pregnant women. In animal studies, lamotrigine was developmentally toxic at doses lower than those administered clinically. LAMICTAL XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. When lamotrigine was administered to pregnant mice, rats, or rabbits during the period of organogenesis (oral doses of up to 125, 25, and 30 mg/kg, respectively), reduced fetal body weight and increased incidences of fetal skeletal variations were seen in mice and rats at doses that were also maternally toxic. The no-effect doses for embryo-fetal developmental toxicity in mice, rats, and rabbits (75, 6.25, and 30 mg/kg, respectively) are similar to (mice and rabbits) or less than the human dose of 400 mg/day on a body surface area (mg/m^2) basis. In a study in which pregnant rats were administered lamotrigine (oral doses of 5 or 25 mg/kg) during the period of organogenesis and offspring were evaluated postnatally, behavioral abnormalities were observed in exposed offspring at both doses. The lowest effect dose for developmental neurotoxicity in rats is less than the human dose of 400 mg/day on a mg/m^2 basis. Maternal toxicity was observed at the higher dose tested. When pregnant rats were administered lamotrigine (oral

Section	Sponsor's proposed	Recommended changes
	(b) (4)	doses of 5, 10, or 20 mg/kg) during the latter part of gestation, increased offspring mortality (including stillbirths) was seen at all doses. The lowest effect dose for peri/postnatal developmental toxicity in rats is less than the human dose of 400 mg/day of a mg/m^2 basis. Maternal toxicity was observed at the two highest doses tested. Lamotrigine decreases fetal folate concentrations in rat, an effect known to be associated with adverse pregnancy outcomes in animals and humans. Pregnancy Registry: To provide information regarding the effects of in utero exposure to LAMICTAL XR, physicians are advised to recommend that pregnant patients taking LAMICTAL XR enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll-free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website http://www.aedpregnancyregistry.org.

Section	Sponsor's proposed	Recommended changes
	(b) (4)	
		retain
		8.3 Nursing Mothers Preliminary data indicate that lamotrigine is excreted in human milk. Caution should be exercised when LAMICTAL XR is administered to a nursing woman.
		8.4 Pediatric Use LAMICTAL XR is indicated as adjunctive therapy for PGTC and partial onset seizures with or without secondary generalization in patients ≥13 years of age. Safety and effectiveness of LAMICTAL XR for any use in patients <13 years of age have not been established. Immediate-release lamotrigine is indicated for adjunctive therapy in patients ≥2 years of age for partial seizures, the generalized seizures of Lennox-Gastaut syndrome, and PGTC seizures. Safety and effectiveness of immediate-release lamotrigine, used as adjunctive treatment for partial seizures, were not demonstrated in a small, randomized, double-blind, placebo-controlled withdrawal study in very young pediatric patients (aged 1 to 24 months). Immediate-release lamotrigine was associated with an increased risk for infectious adverse reactions (lamotrigine 37%, placebo 5%) and respiratory

Section	Sponsor's proposed	Recommended changes
	(b) (4)	adverse reactions (lamotrigine 26%, placebo 5%). Infectious adverse reactions included bronchiolitis, bronchitis, ear infection, eye infection, otitis externa, pharyngitis, urinary tract infection, and viral infection. Respiratory adverse reactions included nasal congestion, cough, and apnea. In a juvenile animal study in which lamotrigine (oral doses of 5, 15, or 30 mg/kg) was administered to young rats (postnatal days 7-62), decreased viability and growth were seen at the highest dose tested and long-term behavioral abnormalities (decreased locomotor activity, increased reactivity, and learning deficits in animals tested as adults) were observed at the two highest doses. The no-effect dose for adverse effects on neurobehavioral development is less than the human dose of 400 mg/day on a mg/m^2 basis.
12 CLINICAL PARMACOLOGY		**12.1 Mechanism of Action** The precise mechanism(s) by which lamotrigine exerts its anticonvulsant action is unknown. In animal models designed to detect anticonvulsant activity, lamotrigine was effective in preventing seizure spread in the maximum electroshock and pentylenetetrazol tests, and prevented seizures in the visually and electrically evoked after-discharge tests for antiepileptic activity. Lamotrigine also displayed inhibitory properties in a kindling model in rats both during kindling development and in the fully kindled state. The relevance of these models to human epilepsy, however, is not known. One proposed mechanism of action of lamotrigine, the relevance of which remains to be established in humans, involves an effect on sodium channels. *In vitro* pharmacological studies suggest that lamotrigine inhibits voltage-sensitive sodium channels, thereby stabilizing

Section	Sponsor's proposed	Recommended changes
	(b) (4)	neuronal membranes and consequently modulating presynaptic transmitter release of excitatory amino acids (e.g., glutamate and aspartate). [Removal of this paragraph was not negotiated with the sponsor; therefore, it should be considered for the next labeling revision.]

Section	Sponsor's proposed	Recommended changes
13 NONCLINICAL TOXICOLOGY	(b) (4)	**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility** No evidence of carcinogenicity was seen in mouse or rat following oral administration of lamotrigine for up to 2 years at doses up to 30 mg/kg/day and 10 to 15 mg/kg/day in mouse and rat, respectively. The highest doses tested are less than the human dose of 400 mg/day on a body surface area (mg/m^2) basis. Lamotrigine was negative in *in vitro* gene mutation (Ames and mouse lymphoma *tk*) assays and in clastogenicity (*in vitro* human lymphocyte and *in vivo* rat bone marrow) assays. No evidence of impaired fertility was detected in rats given oral doses of lamotrigine up to 20 mg/kg/day. The highest dose tested is less than the human dose of 400 mg/day on a mg/m^2 basis.

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/s/

LOIS M FREED
04/25/2011

SEALD LABELING: PI SIGN-OFF REVIEW

APPLICATION NUMBER	NDA 022115/S006
APPLICANT	GlaxoSmithKline
PRODUCT NAME	Lamictal XR
SUBMISSION DATE	31 March 2010
PDUFA DATE	30 April 2011
SEALD SIGN-OFF DATE	25 April 2011
OND ASSOCIATE DIRECTOR FOR STUDY ENDPOINTS AND LABELING	Laurie Burke

This memo confirms that all critical prescribing information (PI) deficiencies noted in the SEALD Labeling Review filed 21 April 2011, have been addressed in the final agreed-upon PI. SEALD has no objection to PI approval at this time.

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/s/

LAURIE B BURKE
04/25/2011

SEALD LABELING REVIEW

This SEALD Labeling Review identifies major aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 022115/S006
APPLICANT	GlaxoSmithKline
PRODUCT NAME	Lamictal XR
SUBMISSION DATE	03/31/2010
PDUFA DATE	04/30/2011
SEALD REVIEW DATE	04/21/2011
SEALD LABELING REVIEWER	Jun Yan, Pharm.D.

The following checked Selected Requirements for Prescribing Information items are outstanding labeling issues that must be corrected before the final draft labeling is approved.

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**
  - ☐ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
  - ☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
  - ☐ There is no redundancy of information.
  - ☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
  - ☐ A horizontal line must separate the HL and Table of Contents (TOC).
  - ☐ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
  - ☐ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
  - ☐ Section headings are presented in the following order:

• **Highlights Limitation Statement** (required statement)
• **Drug names, dosage form, route of administration, and controlled substance symbol, if applicable** (required information)
• **Initial U.S. Approval** (required information)
• **Boxed Warning** (if applicable)
• **Recent Major Changes** (for a supplement)
• **Indications and Usage** (required information)
• **Dosage and Administration** (required information)
• **Dosage Forms and Strengths** (required information)
• **Contraindications** (required heading – if no contraindications are known, it must state "None")
• **Warnings and Precautions** (required information)
• **Adverse Reactions** (required AR contact reporting statement)
• **Drug Interactions** (optional heading)
• **Use in Specific Populations** (optional heading)
• **Patient Counseling Information Statement** (required statement)
• **Revision Date** (required information)

- **Highlights Limitation Statement**
  - ☐ Must be placed at the beginning of HL, **bolded,** and read as follows: **"These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)."**

- **Product Title**
  - ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**
  - ☐ The verbatim statement "Initial U.S. Approval" followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**
  - ☐ All text in the boxed warning is **bolded**.
  - ☐ Summary of the warning must not exceed a length of 20 lines.
  - ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word **"WARNING"** and other words to identify the subject of the warning (e.g.,**"WARNING: LIFE-THREATENING ADVERSE REACTIONS"**).
  - ☐ Must have the verbatim statement ***"See full prescribing information for complete boxed warning."*** If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**
  - ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
  - ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, "Dosage and Administration, Coronary Stenting (2.2) --- 2/2010."
  - ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line ("margin mark") on the left edge.
  - ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
  - ☐ Removal of a section or subsection should be noted. For example, "Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010."

- **Indications and Usage**

  ☐ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)]." Identify the established pharmacologic class for the drug at:

  http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm.

- **Contraindications**

  ☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state "None."

  ☐ All contraindications listed in the FPI must also be listed in HL.

  ☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.

  ☐ For drugs with a pregnancy Category X, state "Pregnancy" and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

  ☒ Only "adverse reactions" as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).

  ☐ For drug products other than vaccines, the verbatim **bolded** statement, "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**" must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

  ☐ Must include the verbatim statement: "**See 17 for Patient Counseling Information**" or if the product has FDA-approved patient labeling: "**See 17 for Patient Counseling Information and (insert either "FDA-approved patient labeling" or "Medication Guide").**

- **Revision Date**

  ☐ A placeholder for the revision date, presented as "Revised: MM/YYYY or Month Year," must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- ☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- ☐ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- ☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- ☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:

  8.1 Pregnancy

  8.3 Nursing Mothers (not 8.2)

  8.4 Pediatric Use (not 8.3)

  8.5 Geriatric Use (not 8.4)
- ☐ If a section or subsection is omitted from the FPI and TOC, the heading "**Full Prescribing Information: Contents**" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI)

- **General Format**
  - ☐ A horizontal line must separate the TOC and FPI.
  - ☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
  - ☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**
  - ☐ Must have a heading, in UPPER CASE, **bold** type, containing the word "**WARNING**" and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
  - ☐ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**
  - ☐ For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**
  - ☐ Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided.
  - ☐ For the "Clinical Trials Experience" subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

    "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice."
  - ☐ For the "Postmarketing Experience" subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

    "The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure."

- **Use in Specific Populations**
  - ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**
  - ☐ This section is required and cannot be omitted.
  - ☐ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement "See FDA-approved patient labeling (insert type of patient labeling)." should appear at the beginning of Section 17 for prominence. For example:
    - "See FDA-approved patient labeling (Medication Guide)"
    - "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
    - "See FDA-approved patient labeling (Patient Information)"
    - "See FDA-approved patient labeling (Instructions for Use)"
    - "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

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/s/

JUN YAN
04/21/2011

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: March 30, 2011

TO: Stephanie N. Keefe, PharmD, Regulatory Health Project Manager
Steven Dinsmore, D.O., Medical Officer
Division of Neurology Products

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-115

APPLICANT: GlaxoSmithKline

DRUG: Oral Lamictal XR (lamotrigine XR) tablets

NME: No.

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Conversion to monotherapy in patients age 13 years or older with partial seizures.

CONSULTATION REQUEST DATE: October 18, 2010

DIVISION ACTION GOAL DATE: January 31, 2011, extended to April 30, 2011

PDUFA DATE: January 31, 2011, extended to April 30, 2011

I. BACKGROUND:

The sponsor, GlaxoSmithkline, submitted a New Drug Application for the use of oral Lamictal extended-release (LTG XR) a new enteric-coated, extended-release Lamictal XR formulation that may allow subjects with seizures to be on a once daily dosing regimen. The currently approved monotherapy for lamotrigine in the US is 500mg/day, given in 2 divided doses.

According to the Applicant, the 500mg/day monotherapy dose of lamotrigine may be unnecessarily high for some patients. The approval for a conversion to monotherapy indication was based on a US study, Study 30/31, which demonstrated superiority of LTG IR at 500 mg/day to valproic acid (VPA) at 1000 mg/day in the proportion of subjects completing therapy. In Study 30/31, separation of LTG IR from the control drug began during the Conversion Phase when the effective dose of lamotrigine was 250 mg/day. The Applicant proposes that in an inadequately-controlled partial epilepsy population, a monotherapy dose of 250 mg or 300 mg/day would be expected to provide at least as effective therapy and reduce potentially unnecessary exposure to lamotrigine.

The sponsor has submitted data from a single study of oral LTG XR formulation to support approval of LAM 30055 for the following indication:

> "Lamotrigine XR (300and 250 mg/day) to historic escape rate and to demonstrate the effectiveness of a lower monotherapy lamotrigine dose than the currently-approved 500 mg/day in subjects with partial epilepsy who were receiving AED monotherapy with VPA or non-enzyme inducing AED but were still experiencing partial seizures".

This was an international, multicenter, double-blind, randomized study of 2 doses (300 mg and 250 mg/day) of lamotrigine extended-release (LTG XR) tablets comparing the premature discontinuation rate for each dose to an historic escape rate determined from aggregated pseudoplacebo data. The study used a conversion to monotherapy design in which eligible subjects with refractory partial seizures had LTG XR added to their current background antiepileptic drug (AED),valproate (VPA) or a non-enzyme inducing AED, followed by gradual withdrawal of the background AED.

The primary objective of Study LAM30055 was to demonstrate the safety and effectiveness of LTG at 300 mg and 250 mg/day compared to pooled historic pseudoplacebo data and to evaluate the safety and tolerability of LTG extended release as monotherapy at 59 weeks including the study phases.

The primary efficacy endpoint was the proportion of subjects in the 300 mg treatment group who prematurely discontinued.

The secondary endpoints were: 1) the proportion of subjects in the 250 mg/day group who prematurely discontinued, 2) time to discontinuation after LTG escalation, 3) proportion of subjects meeting the predefined escape criteria, 4) percent change from baseline in the seizure frequency, and 5) percent seizure-free at last visit.

The review division requested inspection of three clinical investigators to cover the above listed protocol as data from Study LAM30055 are considered essential to the approval decision. Two foreign clinical investigators were selected from Protocol Study LAM30055 and one domestic investigator was selected from the same Protocol. These sites were targeted for inspection due to enrollment of a relatively large number of subjects and significant primary efficacy results pertinent to decision-making.

II. RESULTS (by protocol/site):

Name of CI, site # and location	**Protocol and # of subjects**	**Inspection Dates**	**Final Classification**
Sofiya Rymsha, M.D Psychiatry Dept. Vinnytsia National Medical University 109, Pirogova Str. Vinnytsia, Ukraine 21005 Site# 40378	Protocol LAM30055 Number of subjects listed 10	2/18-24/2011	Pending Preliminary: NAI
Stella M. Ferraro, M.D. Hospital Italiano de Buenos Aires Gascon 450 (C1181 ACH) Buenous Aires, Argentina Site # 27193	Protocol LAM30055 Number of subjects listed 9	1/10-14/2011	VAI
Bassel F. Shneker, M.D. The Ohio State University Medical Center 1654 Upham Drive 411 Means Hall Columbus, OH 43210 Site # 26166	Protocol LAM30055 Number of subjects listed 8	11/15-22/2010	VAI

Key to Classifications
NAI = No deviations
VAI = Deviation(s) from regulations
OAI = Significant deviations for regulations. Data unreliable.
Pending = Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending.

Note: Observations noted below for one site are based on an e-mail communication from the field; EIR has not been received from the field and complete review of the EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

Protocol Study LAM 30055

1. **Sofiya Rymsha, M.D.**
   Vinnysia, Ukraine

   a. What Was Inspected: At this site, a total of 10 subjects were screened, 10 subjects were randomized and 10 subjects completed the study. There were no deaths reported at this site. Review of Informed Consent Documents, for all records reviewed, verified that subjects signed prior to enrollment.

   A review of the medical records/source documents was conducted. The medical records for 10 subjects were reviewed, including drug accountability records, vital signs, laboratory test results, sponsor correspondence, and inclusion/exclusion criteria; source documents were compared to case report forms and to data listings, including primary efficacy endpoints and adverse events.

   b. General observations/commentary: At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Rymsha. The medical records reviewed were found to be in order and the data verifiable. There were no known limitations to the inspection. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the pending application.

   c. **Assessment of Data Integrity:** The data in support of the clinical efficacy and safety at Dr. Rymsha's site are considered reliable and appear acceptable in support of the application.

2. **Stella M. Ferraro, M.D.**
   Buenos Aires, Argentina

   a. What Was Inspected: At this site, a total of 10 subjects were screened; one subject was reported as screen failure. Nine (9) subjects were randomized into the study. Seven subjects completed the study and two subjects were discontinued and the reasons were documented. There were no deaths reported at this site. One subject became pregnant and was discontinued from the study and another subject needed rescue medication and was terminated. Review of Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

   The medical records/source data for all subjects were reviewed, including drug accountability records, vital signs, laboratory results, IRB records, inclusion/exclusion criteria, adverse events, and laboratory results; source documents for all subjects were compared to case report forms and to data listings, to include primary efficacy endpoints.

   b. General Observations/Commentary: At the conclusion of the inspection, a two item Form FDA 483 was issued to Dr. Ferraro. Our investigation found protocol violations and inadequate record keeping.

Protocol violations:

a. Subject 121 experienced an increased frequency and intensity of seizures, with one seizure on 12/3/2007 (type B) and a second seizure, much more intense (type C)) on 12/6/2007. The clinical investigator discontinued the subject from the study and prescribed another seizure drug Clobazam. The clinical investigator did not consider the seizures as an adverse event, contrary to protocol requirements.

b. Subject 126 was diagnosed with pharyngitis at Visit 6, for which penicillin was prescribed. This event meets the criteria for being considered an adverse event in accordance with protocol section 10.1; however, this non-serious adverse event was not reported on the e-CRF.
c. Subject 124 received incorrect total daily doses of the study drug for a five-week period from 7/25/2007 through 9/4/2007. The subject received only 150 mg instead of a total daily dose of 300 mg.
d. Subject 126 received incorrect total daily doses of study drug for a five-week period from 9/19/2007 through 10/16/2007. The subject received only a total daily dose of 150 instead of a total daily dose of 300 mg.

Record keeping violations:

a. The clinical investigator did not follow written procedures for preparing and dispensing of study drugs. Study drugs were dispensed by the unblinded pharmacist prior to confirming the randomization number and treatment arm assignment from the "randomization confirmation form" (IVRS). There were no records of any periodic checks of the website, reportedly made by the unblinded pharmacist, to periodically confirm dispensing information.
b. Medication Order Dispensing Records, prepared by the unblinded pharmacist, were inaccurate regarding the number of "tablet per well" for each dosette dispensed. For each dispensing, the total number of tablets dispensed was incorrectly recorded in the blocks designated for "tablets per well". The actual number of tablets per well were not recorded for any study drug dispensed.
c. Source data for dosing instructions provided for each subject, and for the sequence number assigned for each dosette were not retained as part of study records, however, the only place dosing instructions, including the number of tablets and the sequence number were recorded by the unblinded pharmacist were directly on the labels of the dosettes and were subsequently destroyed.

Reviewer's Comments: Despite the noted findings above, there don't appear to have been any issues with adequate drug dispensing to subjects. These findings are unlikely to impact data reliability since there are other records to support adequate drug dispensation and accountability. DSI reviewer discussed this with the review division medical officer who stated that although two subjects received the incorrect dose this would have no significant impact. The review division may choose to exclude the two subjects from final analyses.

The sponsor on behalf of the clinical investigator provided a written response (not dated received by DSI on (2/8/2011), in which the sponsor acknowledged the findings and added that the two subjects who received the wrong dose of the study medications were not included in the final analyses. The review division was informed about the two subjects and agreed to exclude the two subjects from the final analyses.

c. Assessment of Data Integrity: Although regulatory violations were noted, the findings are unlikely to affect data integrity due to a small number of subjects involved. However, the review division may choose to consider excluding the two subjects based on the findings noted above with respect to protocol violations in their assessment of efficacy or safety.

3. **Bassel F. Shneker, M.D.**
Columbus, Ohio

a. What Was Inspected: At this site, a total of 11 subjects were screened, 3 subjects were reported as screen failures, 8 subjects were randomized into the study, two subjects withdrew from the study due to adverse events, one subject withdrew consent, and one subject withdrew due to lack of seizure control. Four subjects completed the study. There were no deaths and not all adverse events were reported to the sponsor (Subject 000809 experienced nausea, vomiting and diarrhea and Subject 000810 experienced acute renal failure during hospitalization (between Period Visit 8 and 9) for motor vehicle collision). Review of Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source documents for 11 subjects were reviewed, including drug accountability records, vital signs, IRB files, laboratory test results, inclusion/exclusion criteria, use of concomitant medications, and protocol deviations; source documents were compared to case report forms and data listings, to include primary efficacy endpoints and adverse events.

b. General Observations/Commentary: At the conclusion of the inspection, a two item Form FDA 483 was issued to Dr. Shneker. Our investigation found protocol deviations, not all adverse events were reported to the sponsor and inadequate record keeping violations.

Protocol Violations:

According to the protocol, prospective subjects that had any clinically significant cardiac, renal, hepatic condition, or a condition that affects the absorption, distribution, metabolism or excretion of drugs should be excluded from the study. Subject 000809's abnormal reported clinical chemistry results were: BUN-116 mg/dl; Creatinine-22.88mg/dL; Uric Acid-14.3mg/dL and Potassium- 14.4 mmol/L. DSI Branch Chief concurs with the CI's response that these are likely laboratory errors as the values are not compatible with life. These significant clinical chemistries should have been repeated; however, were not repeated to confirm that the results were valid and that the subject met inclusion criteria for enrollment in the study. In addition, the protocol

required a pharmacokinetic (PK) trough (pre-dose) blood samples be obtained at treatment Period Visits 5 and 7 before taking the study medications that day for measurement of Lamotrigine (LTG) blood levels. For at least 5 subjects the blood samples were obtained after the subjects took their study medication/LTG dose at either Visit 5 or Visit 7.

Additionally, not all adverse events experienced by subjects were reported to the sponsor:

- Subject 000809 reported in his/her diary experiencing nausea, vomiting and diarrhea.
- Subject 000810 experienced acute renal failure of questionable etiology, during hospitalization (between Visit 8 and 9) for motor vehicle collision. In addition, subject 000810 was administered Vicodin, Dilantin and Phenergan during hospitalization. These concomitant medications were not reported to the sponsor.

Record Keeping Violations:

Subject 000821 experienced and reported in the subject diary between Visit 5 and 6 two complex partial seizures. These seizures were not reported to the sponsor.

The clinical investigator acknowledged the observations noted above in a written response date December10, 2010, in which he stated that all possible corrective and preventive measures will be taken to remedy the situation from occurring in future studies. I find his response to be acceptable.

With the exception of the items noted above, the records reviewed were found to be in order and the data verifiable and the data generated by this site appear acceptable in support of the respective indication. There were no known limitations to this inspection.

c. Assessment of Data Integrity: Although regulatory violations were noted, these are unlikely to impact data reliability, as they are considered isolated in nature. However, the review division may choose to consider excluding Subject 000809 with respect to protocol violation in their assessment of efficacy and safety. The remaining data from Dr. Shneker's site are considered reliable and appear acceptable in support of the pending application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Three clinical investigators were inspected in support of this application. Two foreign clinical investigators and one domestic investigator were selected to cover the audit of Protocol LAM30055.The inspections of Drs. Rymsha, Ferraro and Shneker revealed no significant problems that would adversely impact data acceptability. Overall, the data submitted from these sites are acceptable in support of the pending application.

Note: Observations noted for one site are based on an e-mail communication from the field; EIR has not been received from the field and complete review of the EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

{See appended electronic signature page}

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

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

ANTOINE N EL HAGE
04/04/2011

TEJASHRI S PUROHIT-SHETH
04/04/2011

DSI CONSULT: Request for Clinical Inspections

Date: October 12, 2010

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Antoine El Hage
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: *Steven Dinsmore, D.O.,Medical Officer, DNP*
Norman Hershkowitz, M.D., Neurology Team Leader, DNP
Russell Katz, M.D., Director, DNP

From: *Stephanie N. Keefe, Regulatory Health Project Manager/DNP*

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-022115
Applicant/ Applicant contact information (to include phone/email): GlaxoSmithKline
Contact: Elizabeth McConnell, Pharm.D. 919-483-6466
Drug Proprietary Name: Lamictal XR
NME or Original BLA (Yes/No): No
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): Yes
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Conversion to monotherapy in patients age 13 years or older with partial seizures.

PDUFA:
Action Goal Date: January 31, 2011
Inspection Summary Goal Date: November 30, 2010

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site ID- 40378 Sofiya Rymsha Psychiatry Dept. Vinnytsia National Medical University, 109, Pirogova Str., Vinnytsia, Ukraine 21005	LAM30055	10	Large influence on outcome measure
Site ID- 26166 Bassel F. Shneker, MD The Ohio State University Medical Center 1654 Upham Drive 411 Means Hall Columbus, OH 43210 Phone: 614-293-4974 Fax: 614-293-4688 Email: Shneker.1@osu.edu	LAM30055	8	Largest US enrolment, 2 protocol violations

III. Site Selection/Rationale

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Rationale for DSI Audits

- *Ukraine Site, Dr.* Rymsha is requested because statistical analysis reveals this site has a large effect in driving outcome measure. In addition the discontinuation rate was higher for US sites vs non- US sites.

- *US Site , Dr.* Shneker is requested as the largest domestic site. This site has only 25% US patient composition. Although the site does not drive the overall study results the relative large size among the US sites will have significant influence on the US sub analysis. In addition the discontinuation rate was higher for US sites vs non- US sites.

Domestic Inspections:

Reasons for inspections (please check all that apply):

__X__ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
__X__ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
____ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact *Stephanie N. Keefe, RPM,* at *301-796-4098 or Steven Dinsmore, D.O.,* at 301-796-4155.

Concurrence: (as needed)

_____*X*_____ Medical Team Leader
_____*X*_____ Medical Reviewer

_____X_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

******Things to consider in decision to submit request for DSI Audit***

- *Evaluate site specific efficacy. Note the sites with the greatest efficacy compared to active or placebo comparator. Are these sites driving the results?*
- *Determine the sites with the largest number of subjects. Is the efficacy being driven by these sites?*
- *Evaluate the financial disclosures. Do sites with investigators holding financial interest in the sponsor's company show superior efficacy compared to other sites?*
- *Are there concerns that the data may be fraudulent or inconsistent?*
    - *Efficacy looks too good to be true, based on knowledge of drug based on previous clinical studies and/or mechanism of action*
    - *Expected commonly reported AEs are not reported in the NDA*
- *Evaluate the protocol violations. Are there a significant number of protocol violations reported at one or more particular sites? Are the types of protocol violations suspicious for clinical trial misconduct?*
- *Is this a new molecular entity or original biological product?*
- *Is the data gathered solely from foreign sites?*
- *Were the NDA studies conducted under an IND?*

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/s/

STEPHANIE N KEEFE
10/14/2010

NORMAN HERSHKOWITZ
10/15/2010

RUSSELL G KATZ
10/24/2010

DSI CONSULT: Request for Clinical Inspections

Date: October 18, 2010

To: Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Antoine El Hage, Ph.D.
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: *Steven Dinsmore, D.O.,Medical Officer, DNP*
Norman Hershkowitz, M.D., Neurology Team Leader, DNP
Russell Katz, M.D., Director, DNP

From: *Stephanie N. Keefe, Regulatory Health Project Manager/DNP*

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-022115
Applicant/ Applicant contact information (to include phone/email): GlaxoSmithKline
Contact: Elizabeth McConnell, Pharm.D. 919-483-6466
Address: 5 Moore Drive, P.O. Box 13398, Research Triangle Park, NC 27709
Fax: 919-315-0033
Email: betty.a.mcconnell@gsk.com
Drug Proprietary Name: Lamictal XR
NME or Original BLA (Yes/No): No
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): Yes
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Conversion to monotherapy in patients age 13 years or older with partial seizures.

PDUFA:
Action Goal Date: January 31, 2011
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Site ID- 26166 Bassel F. Shneker, MD The Ohio State University Medical Center 1654 Upham Drive 411 Means Hall Columbus, OH 43210 Phone: 614-293-4974 Fax: 614-293-4688 Email: Shneker.1@osu.edu	LAM30055	8	Largest US enrolment, 2 protocol violations
Site ID- 27193 Dr. Stella Maris Ferraro Hospital Italiano de Buenos Aires Gascón 450 (C1181ACH) Buenos Aires, Argentina Phone: 54 11 4805 4434 Fax: 54 11 4959 0200 int 8459 Email: stella.ferraro@hospitalitaliano.org.ar	LAM30055	9	Large influence on outcome measure

III. Site Selection/Rationale

Rationale for DSI Audits

- *Argentina and Ukraine Sites:* requested because statistical analysis reveals these sites have a large effect in driving the outcome measure. In addition the discontinuation rate was higher for US sites vs. non- US sites.

- *US Site:* Dr. Shneker is requested as the largest domestic site. Although the site does not drive the overall study results, it does represent 14% of the total US enrollment, and 3.5% of the total study enrollment. This large component of US total enrollment occurs in study LAM30055, which has only a 25% US composition; therefore, it is compelling to examine the largest contribution to this relatively small US study component. This study also had two protocol violations: one violation for poor compliance, and one violation of the requirement for stable AED monotherapy on inclusion, both of which could influence seizure occurrence.

Domestic Inspections:

Reasons for inspections (please check all that apply):

__X__ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
____ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
__X__ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
____ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

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If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact *Stephanie N. Keefe, RPM,* at *301-796-4098 or Steven Dinsmore, D.O.,* at 301-796-4155.

Concurrence: (as needed)

_____*X*_____ Medical Team Leader
_____*X*_____ Medical Reviewer
_____X_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

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/s/

HAMET M TOURE
10/19/2010

ERIC P BASTINGS on behalf of RUSSELL G KATZ
10/20/2010

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-115/S-006

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEBARMENT CERTIFICATION

GlaxoSmithKline certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application (sNDA 022115: supplemental NDA for Lamictal XR Conversion to Monotherapy in Adults with Partial Seizures).

Craig Wozniak

January 2010

EXCLUSIVITY SUMMARY

NDA # 022115 SUPPL # 006 HFD # 120

Trade Name Lamictal XR

Generic Name lamotrigine

Applicant Name GlaxoSmithKline

Approval Date, If Known April 25, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE1 – new indication for an approved drug.

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.") **Yes, required efficacy study**

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

(3) three years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.
YES, API previously approved in LAMICTAL XR for adjunctive treatment of partial & PGTC seizures

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# **22115** **LAMICTAL XR**

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation. **YES, report of LAM30055**

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

N/A

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

N/A

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

N/A

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.") **NO, LAM30055 has not been used for prior efficacy determination- only safety, this study was part of the safety package for approval of Lamictal XR for PGTC seizures.**

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

N/A

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"): **LAM30055: A Multicenter, Double Blind, Randomized Conversion to Monotherapy comparison of two doses of lamotrigine for the treatment of partial seizures.**

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 69,254	YES ☒	! NO ☐
		! Explain:
Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? **N/A**

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

N/A

==========

Name of person completing form: Stephanie N. Keefe
Title: Regulatory Health Project Manager
Date: April 26, 2011

Name of Office/Division Director signing form: Russell Katz, M.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

STEPHANIE N KEEFE
05/02/2011

RUSSELL G KATZ
05/02/2011

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 022115 BLA #	NDA Supplement # 006 BLA STN #	If NDA, Efficacy Supplement Type: 6
Proprietary Name: Lamictal XR Established/Proper Name: lamotrigine Dosage Form: Extended release tablets		Applicant: GlaxoSmithKline Agent for Applicant (if applicable): Elizabeth McConnell, Pharm.D.
RPM: Stephanie N. Keefe		Division: Neurology Products

NDAs:
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is January 30, 2011 (Extension Date: April 30, 2011)	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☒ N/A

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics [2]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☒ N/A
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☒ N/A
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ N/A
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ N/A
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ N/A
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	☒ N/A
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☒ N/A
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☒ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☒ N/A

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☒ N/A

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☒ N/A

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☒ **N/A**

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☒ N/A
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	☒ Included
[Tab L] Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
[Tab M] Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval April 25, 2011
[Tab N] Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	March 31, 2010 and March 18, 2011
• Original applicant-proposed labeling	March 31, 2010 and March 18, 2011
• Example of class labeling, if applicable	N/A

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	See March 31, 2010 and March 18, 2011 labels
• Original applicant-proposed labeling	See March 31, 2010 and March 18, 2011 labels
• Example of class labeling, if applicable	N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	N/A
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	N/A
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ NON-CLINICAL April 25, 2011 ☐ DMEPA ☐ DRISK ☐ DDMAC ☒ SEALD April 21, 2011; April 25, 2011
[Tab O] Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	RPM – 7/8/2010
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☒ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
○ If yes, Center Director's Exception for Review memo *(indicate date)*	N/A
○ If yes, OC clearance for approval *(indicate date of clearance communication)*	N/A
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ N/A
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	Filing Communication 6/11/2010 General Advice 7/16/2010

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

	Information Request 10/18/2010 Information Request 11/8/2010 Review Extension 12/3/2010 Information Request 1/10/2011 Information Request 1/10/2011 Information Request 2/24/2011
❖ Internal memoranda, telecons, etc.	OSE Consult 9/23/2010 PMHS 9/23/2010 DSI Consult 10/20/2010 DSI Consult 10/24/2010 DDMAC Consult 2/14/2010
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ No mtg. -- Preliminary Comments 6/17/10
• Pre-NDA/BLA meeting *(indicate date of mtg)*	N/A
• EOP2 meeting *(indicate date of mtg)*	N/A
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	Type B Meeting – 8/14/2009
❖ Advisory Committee Meeting(s)	☒ AC meeting
• Date(s) of Meeting(s)	March 10, 2011
• 48-hour alert or minutes, if available *(do not include transcript)*	Included
[Tab P] Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ N/A
Division Director Summary Review *(indicate date for each review)*	☒ April 25, 2011
Cross-Discipline Team Leader Review *(indicate date for each review)*	☒ April 25, 2011
PMR/PMC Development Templates *(indicate total number)*	☒ None
[Tab Q] Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	See CDTL Review
• Clinical review(s) *(indicate date for each review)*	Combined Clinical/Statistics Review **April 4, 2011**; Clinical Review **April 25, 2011**
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable

[5] Filing reviews should be filed with the discipline reviews.

❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	March 31, 2010; November 18, 2010 ☐ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ March 25, 2011, April 4, 2011, April 8, 2011
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
[Tab R] Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ See Tab Q – Combined Clinical/Statistics Review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ See Tab Q – Combined Clinical/Statistics Review
Statistical Review(s) *(indicate date for each review)*	☒ White Paper/Historical Control March 22, 2011
[Tab S] Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ See April 24, 2011 review
Clinical Pharmacology review(s) *(indicate date for each review)*	☒ April 24, 2011
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☒ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☐ None requested

Product Quality ☒ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

From: Betty McConnell
To: Keefe, Stephanie;
Subject: RE: FDA Request for Information - NDA 022115/Lamictal XR (lamotrigine) tablets
Date: Wednesday, February 23, 2011 1:01:08 PM

Yes, we did receive the request. We're working on it....

Regards,
Betty

Betty McConnell
Global Regulatory Affairs, Neurosciences
919-483-6466
betty.a.mcconnell@gsk.com

From: Keefe, Stephanie [mailto:Stephanie.Keefe@fda.hhs.gov]
Sent: Wednesday, February 23, 2011 12:19 PM
To: Betty McConnell
Subject: RE: FDA Request for Information - NDA 022115/Lamictal XR(lamotrigine) tablets

Betty,

Can you please confirm receipt of the IR below, from 2/16/11? Thank you,

Stephanie

From: Keefe, Stephanie
Sent: Wednesday, February 16, 2011 3:19 PM
To: 'Betty McConnell'
Subject: RE: FDA Request for Information - NDA 022115/Lamictal XR(lamotrigine) tablets

Dear Betty,

Below is a follow-up request for information, in response to your February 14, 2011

"Response to FDA Request/Comment" submission:

```
In the response to FDA request 2, the program for the
sensitivity analysis used a dataset named 'escape2_vis'. The
reviewer could not locate this dataset in the submission.
Please provide us this dataset and related documents such as
definition file, raw datasets and programs that generated
this dataset.
```

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

From: Keefe, Stephanie
Sent: Thursday, January 06, 2011 1:50 PM
To: 'Betty McConnell'
Subject: FDA Request for Information - NDA 022115/Lamictal XR(lamotrigine) tablets
Importance: High

Dear Betty,

Below is a request from the Clinical team related to their ongoing review of the Lamictal XR application (N 22-115). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

* Please see the comment below from the Clinical reviewer:

In Study LAM30055 there is a divergence from the historic control group of the white paper in the number of patients who meet escape criteria # 4. None are noted in study LAM30055 compared to a generally large number of patients in the historic control group (for example, 19%, 17%, 11%, 41%, and 11% of subjects escaped due to this sole criterion in studies 1, 3, 5, 7, and 8 respectively). Examination of escape criteria # 4 reveals the criteria in the white paper may differ from that used in study LAM30055, with the latter criteria consisting of "clinically-significant prolongation of generalized tonic-clonic seizures" and the former criteria consisting of "prolongation or worsening of seizure duration or frequency

considered by the investigator to **require intervention** ." Because of this we examined the adverse event database and identified a patient who may have met exit criteria according to the white paper, but was not included as having met exit criteria in your database. Thus, patient 255 required intervention in the form of hospital admission. This begs the question as to why he was hospitalized and whether this case may fulfill exit criteria 4. This also raises the possibility that additional patients may have missed detection based upon escape criteria. For example, the adverse event database contains eight patients with AEs related to seizure, either in the preferred term or in the narrative. Among these eight patients 3 fulfilled escape criteria, 2 had head injury from seizure, included is case 255 noted above, and the final two cases, 155 and 812 have no narrative to examine but may contain features that fulfill criteria #4. Based on this possibility, we request that you search the database for patients who qualify for escape based on the need for intervention. Thus, you should determine if any other patients requiring intervention also exhibited "prolongation or worsening of seizure duration or frequency." You should clarify the reasons for hospitalization of patient 255 and if any others are identified we ask you to justify their exclusion if you believe these do not meet escape criteria. In addition, you should also examine patient medication records to determine if any patients required supplemental anticonvulsant treatment.

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~~~~~~~~~~~~~~~~~~~~~~

Stephanie N. Keefe
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4355
Silver Spring, MD 20993-0002

phone: 301-796-4098
email: stephanie.keefe@fda.hhs.gov
~~~~~~~~~~~~~~~~~~~~~~~~~~

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/s/

STEPHANIE N KEEFE
02/24/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:
CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)
Russell Katz, MD, Division of Neurology Products

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
February 14, 2011		22-115	NDA Efficacy Supplement (S-006)

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Lamictal (lamotrigine) XR tablets	Standard	6	Wrap Up mtg: December 27, 2010 AC mtg: March 10, 2011

NAME OF FIRM:
GlaxoSmithKline

PDUFA Date: PDUFA goal date: April 30, 2011

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☐ PACKAGE INSERT (PI)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☐ CARTON/CONTAINER LABELING
- MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- × EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☐ LABELING REVISION

EDR link to submission:
The entire submission may be accessed at : \\CDSESUB1\EVSPROD\NDA022115\022115.enx

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS: NDA 22-115 was received on March 31, 2010 and provides for monotherapy in patients 13 years of age and older with partial seizures who are receiving therapy with a single antiepileptic drug (AED). This is an Efficacy Supplement.

Mid-Cycle Meeting: August 30, 2010 2-3 pm

Labeling Meetings: March 16, 28; April 12, 19, 21, 26;

Wrap-Up Meeting: December 27, 2010

SIGNATURE OF REQUESTER
Stephanie Keefe, Regulatory Project Manager, DNP
Food and Drug Administration
Phone: 301-796-4098
Email: stephanie.keefe@fda.hhs.gov

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)
× eMAIL ☐ HAND

~~Reference ID: 2905188~~
~~Reference ID: 2943033~~

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/s/

STEPHANIE N KEEFE
02/14/2011

Keefe, Stephanie

From: Betty McConnell [betty.a.mcconnell@gsk.com]
Sent: Thursday, September 23, 2010 10:55 AM
To: Keefe, Stephanie
Subject: RE: FDA Request for Information - NDA 022115/Lamictal XR(lamotrigine) tablets

Stephanie-

Is this request coming as part of the monotherapy sNDA that was submitted to NDA 22-115 on March 31, 2010, or is it part of an overall review of lamotrigine? My sense is that this would be the latter, even if the report was part of the monotherapy sNDA. Thus, if labeling were to be submitted, shouldn't it be a labeling supplement to all the Lamictal NDAs rather than an amendment to the pending Lamictal XR monotherapy supplement?

Also, we will need more than 10 days to respond to this request. Would we be able to negotiate new timings?

Finally, you mentioned a reference that was attached to the request, but it didn't seem to be attached. Would you be able to send that?

Thanks.

Regards,
Betty

Betty McConnell
Global Regulatory Affairs, Neurosciences
919-483-6466
betty.a.mcconnell@gsk.com

From: Keefe, Stephanie [mailto:Stephanie.Keefe@fda.hhs.gov]
Sent: Thursday, September 23, 2010 10:30 AM
To: Betty McConnell
Subject: FDA Request for Information - NDA 022115/Lamictal XR(lamotrigine) tablets

Dear Betty,

Below is a request from the Clinical team related to their ongoing review of the Lamictal XR application (N 22-115). Please submit your response to this request in electronic archival format as an amendment to the above NDA. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email &

archive) contain identical information.

* Please see the comment below from the Clinical reviewer:

A review of unlabeled serious adverse events for Lamictal CD and Lamictal XR revealed a case under the preferred term "cyanosis neonatal'. The associated case identifies a breastfeeding mother receiving Lamictal CD 850mg/day. The subject was breastfeeding and her 16 year old infant who experienced two episodes of apnea, one requiring basic cardiac life support. The child was found to have a serum lamotrigine concentration of 4.87 ug/ml, see attached reference.

The present label notes that: "Preliminary data indicate that lamotrigine passes into human milk. Because the effects on the infant exposed to lamotrigine by this route are unknown, breastfeeding while taking LAMICTAL is not recommended " This case suggests that the label may require revision.

The division is concerned that neonatal exposure and associated adverse effects may occur in breastfed infants of mothers on lamotrigine therapy. In order to evaluate if there have been similar events the division requests an evaluation of the sponsor database for preferred terms to capture emergencies in breastfeeding neonates, including but not limited to the following preferred terms: "cyanosis neonatal", "apparent life threatening event", "sudden infant death syndrome", "hypoventilation neonatal", "infantile apnoeic attack", "neonatal anoxia", "neonatal asphyxia", "neonatal hypoxia".

To broaden the scope of this risk evaluation the division also requests an assessment of the available scientific literature on this topic with a report on the current knowledge of lamotrigine transfer via breast milk and the associated safety profile for the breastfed infants.

If supported by the results of this evaluation the division welcomes any recommended changes in labeling as appropriate

Please respond to this request within 7-10 days; if you are unable to meet this timeframe, please contact me to discuss.

Thank you,

~~~~~~~~~~~~~~~~~~~~~~~~~~

Stephanie N. Keefe
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4355
Silver Spring, MD 20993-0002

phone: 301-796-4098
email: stephanie.keefe@fda.hhs.gov
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/s/

STEPHANIE N KEEFE
01/10/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022115/S-006

REVIEW EXTENSION – EFFICACY SUPPLEMENT

GlaxoSmithKline
Attention: Elizabeth McConnell, PharmD
Associate Director, Neurology, US Regulatory Affairs
PO Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Dr. McConnell:

Please refer to your March 31, 2010 Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamictal XR (lamotrigine) Extended-Release tablets.

On November 19, 2010, we received your November 19, 2010, solicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is April 30, 2010.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2008 THROUGH 2012." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by March 31, 2010.

If you have any questions, contact Stephanie N. Keefe, Regulatory Project Manager, at (301) 796-4098.

Sincerely,

{See appended electronic signature page}

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

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/s/

RUSSELL G KATZ
12/03/2010

From: Betty McConnell
To: Keefe, Stephanie; Eric Benson;
Subject: RE: NDA 022115/ S-0006; Sequence 0050
Date: Monday, November 08, 2010 11:09:52 AM
Attachments: image002.png

Stephanie-

Yes, we have, and we're currently working on the response.

Regards,
Betty

Betty McConnell
Global Regulatory Affairs, Neurosciences
919-483-6466
betty.a.mcconnell@gsk.com

From: Keefe, Stephanie [mailto:Stephanie.Keefe@fda.hhs.gov]
Sent: Monday, November 08, 2010 11:08 AM
To: Eric Benson
Cc: Betty McConnell
Subject: RE: NDA 022115/ S-0006; Sequence 0050

Betty/Eric,

Please confirm receipt of the email and attachment, from the email sent to you on November 5, 2010. Thank you,

Stephanie

From: Keefe, Stephanie
Sent: Friday, November 05, 2010 2:21 PM
To: 'Eric Benson'
Cc: 'Betty McConnell'
Subject: RE: NDA 022115/ S-0006; Sequence 0050

Mr. Benson,

Please find our attached comments in response to your email below. Please confirm receipt of this email and it's attachment. Thank you.

Stephanie N. Keefe

From: Eric Benson [mailto:eric.b.benson@gsk.com]
Sent: Thursday, October 28, 2010 11:08 AM
To: Toure, Hamet (LT,USPHS); Keefe, Stephanie
Cc: (b) (4) Betty McConnell
Subject: NDA 022115/ S-0006; Sequence 0050

Dear Drs. Toure and Keefe,

Attached please find our response to the requests/comments in your e-mail of October 18, 2010 regarding this pending supplemental NDA. As noted below, this amendment successfully transmitted via the gateway today and we are also providing the information via e-mail as requested.

Sincerely,

Eric Benson

Director, Global Regulatory Affairs

Phone: (919) 483-3627

Cell: (919) 906-2263

Fax: (919) 483-5756

EMail: eric.b.benson@gsk.com

From: (b) (4)
Sent: Thursday, October 28, 2010 9:29 AM
To: Eric Benson
Cc: Betty McConnell
Subject: NDA 022115 Sequence 0050

Hello Eric,

This e-mail is to inform you that the submission referenced above has been transmitted via the Electronic Submissions Gateway and both acknowledgments have been received. Please contact your Project Manager to ensure that the submission was received correctly. If there were any problems, with the transmission please let me know as soon as possible so I may contact Technical Support for assistance.

As requested, I have attached PDF copies of the cover letter, 356h and the 1.11.3

response document to this e-mail.

You may now distribute your cover letter in CARDs.

Kind regards,
Randy

(b) (4)
Lead Submission Publisher
Global Regulatory Operations, RTP
(b) (4)

Thank you for your preliminary response dated **October 28, 2010**, which responded to our request for additional information dated **October 18, 2010**. We have a request for additional information to complete the submission, which consists of answers to your questions dated **October 21, 2010**.

Question 1: The division is in agreement with your plan for analysis of US vs. Non-US placebo response in studies LAM100034, LAM100036 and LAM40097. If there are additional double-blind, placebo-controlled trials of Lamictal which contains both US and Non-US adult subjects with epilepsy, no matter what type, we ask that these also be included in the analysis. A literature search and review should also be performed to determine if there are any discussions/studies on the issue of national/regional differences in the placebo effect in studies in general, including non-epilepsy studies.

The division is in disagreement with your decision to decline sending the datasets from studies LAM100034, LAM100036 and LAM40097. You need to provide key analysis datasets that are used to support your conclusion, as we need to verify or may need to analyze further.

Question 2: No, the key is what standard should be used for comparison to the white-paper standard, rather than what is considered "clinically meaningful." Four studies in the White Paper used a more conservative approach in determining Exit Criterion #3, using Baseline events for comparison (page 15 of the White Paper). Therefore, for the primary analysis, you need to recalculate the escapes relative to the Baseline events. The analysis using subject's lifetime history of seizure types is considered a secondary analysis.

Question 3: See our response to Q1.

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/s/

STEPHANIE N KEEFE
11/08/2010

Toure, Hamet (LT,USPHS)

From: Toure, Hamet (LT,USPHS)
Sent: Monday, October 18, 2010 10:41 AM
To: 'betty.a.mcconnell@gsk.com'
Cc: Keefe, Stephanie; Toure, Hamet (LT,USPHS)
Subject: 022115_18 October 2010_First request

Dear Dr. McConnell,

We refer you to NDA 022115.

1. The majority (75%) of the subjects in Study LAM30055 was from foreign sites while the historical pseudoplacebo group in the White Paper was from US studies. The comparability of the placebo escape rate among the regions should be established. One possible way to establish the comparability is to compare placebo responses between US sites and non-US sites in relevant studies for which you have data, including add-on therapy and mono-therapy studies. The differences in placebo effect as it varies country-to-country in comparison to that of the US should be included in this analysis as is pertinent to the population of the present monotherapy study. For example, certain countries in Eastern Europe may have a different placebo effect from those in particular countries in Western Europe and from the US.

2. You stated that the number of subjects deemed by the investigator to have met pre-defined Escape Criteria was surprisingly small and a number of errors were detected (ISE page 17, 20). Therefore, daily seizure data in the database were evaluated against the Escape Criteria to identify additional escapes. This evaluation was conducted for Escape Criteria 1, 2, and 3, but not for Escape Criterion #4 'clinically-significant prolongation of generalized tonic-clonic seizures'. The data suggested that none of the patients was deemed by the investigator to have met the Escape Criterion #4. Please address the potential bias caused by under-reporting for Escape Criterion #4.

3. The exit criterion #3 in the Protocol is 'emergence of a new, more severe seizure type compared to the Baseline'. However, the 8-week prior to Screening was used for the Calculated Escapes. Please recalculate the Escapes using Baseline for comparison.

Please provide us the analysis results, derived datasets for these analyses (including a variable for the White Paper PP population and a variable for Study US 30/31 PP Population for Study LAM30055), listing of involved raw datasets, the involved raw datasets if they are not already submitted, and programs for generating the analysis datasets and tables.

Please provide your email response to Ms. Keefe, and follow with an archival submission to NDA 022115.

Best regards,

Hamet Touré, PharmD MPH
LT, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation – Division of Neurology Products
Bldg. 22, Room 4395
10903 New Hampshire Ave
Silver Spring, MD 20993
Office: 301-796-7534
Fax: 301-796-9842
Email: hamet.toure@fda.hhs.gov

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/s/

HAMET M TOURE
10/18/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*:	FROM *(Name, Office/Division, and Phone Number of Requestor)*:
MAIL: PMHS ttn: Tammie Howard	Russell Katz, MD, Division of Neurology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
September 23, 2010		22-115	PAC preparation	9/23/10; rcv'd 9/23/10

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Lamictal XR Tablets	Standard	Epilepsy	

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☒ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: A review of unlabeled serious adverse events for Lamictal CD and Lamictal XR revealed a case under the preferred term "cyanosis neonatal'. The associated case identifies a breastfeeding mother receiving Lamictal CD 850mg/day. The subject was breastfeeding her 16 year old infant who experienced two episodes of apnea, one requiring basic cardiac life support. The child was found to have a serum lamotrigine concentration of 4.87 ug/ml, see attached reference, see attached reference.

The present label notes that: "Preliminary data indicate that lamotrigine passes into human milk. Because the effects on the infant exposed to lamotrigine by this route are unknown, breastfeeding while taking LAMICTAL is not recommended " This case suggests that the label may require revision.

In reference to the PAC preparation meeting of September 20, 2010 there was a consensus decision to request the participation of both OSE and PMH in an assessment of the risk of lamotrigine maternal – child transfer during breastfeeding.

Recharacterize the risk of lamotrigine exposure in breastfeeding infants DNP requests MH input on the current state

of knowledge from the literature, or any other sources, concerning maternal –child transfer of lamotrigine and consequent adverse events. OSE has been requested to examine reporting rates from the AERS database. [Attachment included in email]

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Stephanie Keefe, Regulatory Project Manager, DNP Food and Drug Administration Phone: 301-796-4098 Email: stephanie.keefe@fda.hhs.gov	☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

STEPHANIE N KEEFE
09/23/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: MAIL: OSE
ttn: Laurie Kellie

FROM *(Name, Office/Division, and Phone Number of Requestor)*: Russell Katz, MD, Division of Neurology Products

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
September 23, 2010		22-115	PAC preparation	9/23/10; rcv'd 9/23/10

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Lamictal XR Tablets	Standard	Epilepsy	

NAME OF FIRM: GlaxoSmithKline

REASON FOR REQUEST

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- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
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- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

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- ☐ OTHER (SPECIFY BELOW):
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- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
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- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS: A review of unlabeled serious adverse events for Lamictal CD and Lamictal XR revealed a case under the preferred term "cyanosis neonatal'. The associated case identifies a breastfeeding mother receiving Lamictal CD 850mg/day. The subject was breastfeeding her 16 year old infant who experienced two episodes of apnea, one requiring basic cardiac life support. The child was found to have a serum lamotrigine concentration of 4.87 ug/ml.

The present label notes that: "Preliminary data indicate that lamotrigine passes into human milk. Because the effects on the infant exposed to lamotrigine by this route are unknown, breastfeeding while taking LAMICTAL is not recommended " This case suggests that the label may require revision.

In reference to the PAC preparation meeting of September 20, 2010 there was a consensus decision to request the participation of both OSE and PMH in an assessment of the risk of lamotrigine maternal – child transfer during breastfeeding.

To evaluate if there have been similar events DNP requests an evaluation of the AERS database for preferred terms to capture emergencies in breastfeeding neonates, including but not limited to the following preferred terms: "cyanosis neonatal", "apparent life threatening event", "sudden infant death syndrome", "hypoventilation neonatal", "infantile apnoeic attack", "neonatal anoxia", "neonatal asphyxia", "neonatal hypoxia". Suggestion of these terms does not indicate that DNP wishes to constrain the OSE evaluation and enhancement of the search strategy as desire by OSE is appreciated. Pediatric and Maternal Health has been asked to examine any information in the literature that may elucidate this issue.
[Attachment included in email]

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check one)
Stephanie Keefe, Regulatory Project Manager, DNP Food and Drug Administration Phone: 301-796-4098 Email: stephanie.keefe@fda.hhs.gov	☐ DFS ☒ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

STEPHANIE N KEEFE
09/23/2010

NDA/BLA REGULATORY FILING REVIEW

(Including Memo of Filing Meeting)

Application Information		
NDA # 22115 BLA#	NDA Supplement #:S- 006 BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Lamictal XR Established/Proper Name: Lamotrigine Dosage Form: tablet Strengths:		
Applicant: Glaxo Smith Kline Agent for Applicant (if applicable):		
Date of Application: 3/31/10 Date of Receipt: 3/31/10 Date clock started after UN:		
PDUFA Goal Date: 1/31/11	Action Goal Date (if different):	
Filing Date: 5/30/10 Date of Filing Meeting: 5/19/10		
Chemical Classification: (1,2,3 etc.) (original NDAs only)		
Proposed Indication(s): Conversion to monotherapy in patients 13 years of age and older with partial seizures who are receiving therapy with a single antiepileptic drug (AED).		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***Refer to Appendix A for further information.***	☐ 505(b)(1) ☐ 505(b)(2) ☒ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.***	☒ Standard ☐ Priority ☐ Tropical disease Priority review voucher submitted
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐	
Part 3 Combination Product? ☐	☐ Drug/Biologic ☐ Drug/Device ☐ Biologic/Device
☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR

601.42)	
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): 69254	
PDUFA and Action Goal dates correct in tracking system? ***If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒ YES ☐ NO
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.***	☒ YES ☐ NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system? ***If not, ask the document room staff to make the appropriate entries.***	☒ YES ☐ NO
Application Integrity Policy	
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ora/compliance_ref/aiplist.html*** **If yes**, explain: **If yes**, has OC/DMPQ been notified of the submission? **Comments**:	☐ YES ☒ NO ☐ YES ☐ NO
User Fees	
Form 3397 (User Fee Cover Sheet) submitted	☒ YES ☐ NO
User Fee Status **Comments:**	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
Note: *505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).*	
Exclusivity	

Does another product have orphan exclusivity for the same indication? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm***	☐ YES ☒ NO
If yes, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)*** **Comments:**	☐ YES ☐ NO
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.* **Comments:**	☒ YES # years requested: 3 ☐ NO
If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***): Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***	☒ Not applicable ☐ YES ☐ NO
505(b)(2) (NDAs/NDA Efficacy Supplements only)	
	☐ **Not applicable**
1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐ YES ☐ NO
2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).	☐ YES ☐ NO
3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?	☐ YES ☐ NO

Note: *If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).*	

4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? ***Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm*** **If yes**, please list below:	☒ YES ☐ NO

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration
22115	Lamictal XR	I-622	Jan 29, 2013
22115	Lamictal XR	NDF	May 29, 2012
22115	Lamictal XR	Ped	Nov. 29, 2012

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Format and Content	
Do not check mixed submission if the only electronic component is the content of labeling (COL). **Comments**:	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?	
If electronic submission: paper forms and certifications signed (non-CTD) or electronic forms and certifications signed (scanned or digital signature)(CTD)? ***Forms** include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); **Certifications** include: debarment certification, patent certification(s), field copy certification, and pediatric certification.* **Comments**:	☒ YES ☐ NO
If electronic submission, does it follow the eCTD guidance? (*http://www.fda.gov/cder/guidance/7087rev.pdf*) **If not,** explain (e.g., waiver granted):	☒ YES ☐ NO

Form 356h: Is a signed form 356h included? ***If foreign applicant, both the applicant and the U.S. agent must sign the form.*** Are all establishments and their registration numbers listed on the form? **Comments**:	☒ YES ☐ NO ☐ YES ☒ NO
Index: Does the submission contain an accurate comprehensive index? **Comments**:	☒ YES ☐ NO
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain:	☒ YES ☐ NO
Controlled substance/Product with abuse potential: Abuse Liability Assessment, including a proposal for scheduling, submitted? Consult sent to the Controlled Substance Staff? **Comments**:	☐ Not Applicable ☐ YES ☒ NO ☐ YES ☐ NO
BLAs/BLA efficacy supplements only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	 ☐ YES ☐ NO
Patent Information (NDAs/NDA efficacy supplements only)	
Patent information submitted on form FDA 3542a? **Comments**:	☒ YES ☐ NO
Debarment Certification	
Correctly worded Debarment Certification with authorized signature? ***If foreign applicant, both the applicant and the U.S. Agent must***	☒ YES ☐ NO

sign the certification. ***Note:*** *Debarment Certification should use wording in FD&C Act section 306(k)(l) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."* **Comments**:	
Field Copy Certification (NDAs/NDA efficacy supplements only)	
Field Copy Certification: that it is a true copy of the CMC technical section (***applies to paper submissions only***) ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐ Not Applicable (*electronic submission or no CMC technical section*) ☒ YES ☐ NO
Financial Disclosure	
Financial Disclosure forms included with authorized signature? ***Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.* **Comments**:	☒ YES ☐ NO
Pediatrics	
PREA ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.* Are the required pediatric assessment studies or a full waiver of pediatric studies included? **If no,** is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included? • ***If no, request in 74-day letter.*** • **If yes**, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO

BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).*** **Comments:**	☐ YES ☒ NO
Prescription Labeling	
Check all types of labeling submitted. **Comments:**	☐ **Not applicable** ☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use ☒ MedGuide ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)
Is electronic Content of Labeling submitted in SPL format? ***If no, request in 74-day letter.*** **Comments:**	☒ YES ☐ NO
Package insert (PI) submitted in PLR format? **If no**, was a waiver or deferral requested before the application was received or in the submission? **If before**, what is the status of the request? ***If no, request in 74-day letter.*** **Comments:**	☒ YES ☐ NO ☐ YES ☐ NO
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **Comments:**	☐ YES ☒ NO
MedGuide or PPI (plus PI) consulted to OSE/DRISK? (*send WORD version if available*) **Comments**: to be done	☐ Not Applicable ☐ YES ☒ NO
REMS consulted to OSE/DRISK? **Comments**: to be done	☐ Not Applicable ☒ YES ☐ NO
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP? **Comments:**	☒ Not Applicable ☐ YES ☐ NO

OTC Labeling	
Check all types of labeling submitted. **Comments:**	☒ **Not Applicable** ☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)
Is electronic content of labeling submitted? ***If no, request in 74-day letter.*** **Comments:**	☐ YES ☐ NO
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.*** **Comments:**	☐ YES ☐ NO
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.*** **Comments:**	☐ YES ☐ NO
Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP? **Comments:**	☐ YES ☐ NO
Meeting Minutes/SPA Agreements	
End-of Phase 2 meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments:**	☐ YES Date(s): ☒ NO
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? ***If yes, distribute minutes before filing meeting.*** **Comments:**	☒ YES Date(s): August 14, 2009 ☐ NO
Any Special Protocol Assessment (SPA) agreements? ***If yes, distribute letter and/or relevant minutes before filing meeting.*** **Comments:**	☐ YES Date(s): ☒ NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 19, 2010

NDA/BLA #: 022115

PROPRIETARY/ESTABLISHED NAMES: Lamictal (lamotrigine) Extended Release

APPLICANT: GlaxoSmithKline

BACKGROUND: This is the second NDA submitted for Lamictal XR (the original, NDA 22-115, is still under review). The overall clinical development for Lamictal XR is found under IND 69,254.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Stacy Metz	y
	CPMS/TL:		y
Cross-Discipline Team Leader (CDTL)	Norman Hershkowitz		y
Clinical	Reviewer:	Steve Dinsmore	y
	TL:	Norman Hershkowitz	y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Veneeta Tandon	y
	TL:		
Biostatistics	Reviewer:	Xian Ling	y
	TL:	Kun Jin	y
Nonclinical (Pharmacology/Toxicology)	Reviewer:		
	TL:		
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:		
	TL:	Martha Heimann	y
Facility (*for BLAs/BLA supplements*)	Reviewer:		
	TL:		
Microbiology, sterility (*for NDAs/NDA efficacy supplements*)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		
Other reviewers			

OTHER ATTENDEES: Russell Katz, Robert Temple, Diem-Kieu Ngo

505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
Per reviewers, are all parts in English or English translation? **If no**, explain:	☐ YES ☐ NO

Electronic Submission comments **List comments:**	☒ Not Applicable
CLINICAL **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☐ YES ☐ NO
• Advisory Committee Meeting needed? **Comments:** ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	☐ YES Date if known: ☐ NO ☒ To be determined Reason:
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments:**	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments:**	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments:** Is the dataset issue a filing issue?	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments:**	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments:**	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments:**	☐ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
• Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments:**	☐ Not Applicable ☐ YES ☐ NO ☐ Not Applicable ☐ YES ☐ NO
• Sterile product? **If yes**, was Microbiology Team consulted for	☐ YES ☒ NO ☐ YES ☐ NO

validation of sterilization? **(NDAs/NDA supplements only)**	
FACILITY (BLAs only) **Comments:**	☐ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Russell Katz, MD -division director

GRMP Timeline Milestones:

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. ☒ No review issues have been identified for the 74-day letter. ☐ Review issues have been identified for the 74-day letter. List (optional): ☒ Standard Review ☐ Priority Review

ACTIONS ITEMS

☒	Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.
☐	If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.
☐	If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	If BLA or priority review NDA, send 60-day letter.
☒	Send review issues/no review issues by day 74
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22115	SUPPL-6	SMITHKLINE BEECHAM CORP	LAMICTAL XR TABLETS

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

/s/

DOROTHY J DEMCZAR
07/08/2010

Summers, Kelly

From: Demczar, Dorothy
Sent: Friday, July 09, 2010 2:03 PM
To: 'Betty McConnell'
Cc: Keefe, Stephanie; Summers, Kelly
Subject: sNDA 22115/S-006 (Lamictal XR- monotherapy efficacy supplement)

Follow Up Flag: Follow up
Flag Status: Green

Dear Betty,

We request that you submit a REMS modification with assessment for NDA 22115. Please submit this REMS modification as a Prior Approval / Labeling supplement. Your REMS modification submission should include a revised comprehensive Medication Guide that includes the new indication for which you are seeking approval in your submitted supplement. Your revised Medication Guide should also reflect changes to the Medication Guide approved on April 14, 2010 as part of your last REMS modification. The REMS modification submission should also include a revised REMS document and a revised REMS supporting document (see attached REMS Appendices A and B).

The timeline for submission of assessments of your REMS will remain the same as was approved in your original REMS on May 29, 2009. Therefore, in your revised REMS document, please specifically state the following in the section entitled **Timetable for Submission of Assessments**:

"GlaxoSmithKline will submit REMS assessments to FDA 18 months, 3 years and 7 years from the date of initial approval of the REMS (May 29, 2009) according to the schedule below:

1st FDAAA assessment: November 29, 2010 (18 months from approval)

2nd FDAAA assessment: May 29, 2012 (3 years from approval)

3rd FDAAA assessment: May 29, 2016 (7 years from approval)

GlaxoSmithKline will submit each assessment so it will be received by the FDA on or before the due date."

Your proposed REMS modification should include an assessment of your approved REMS, to determine if the REMS is meeting its goals. If it is too early to assess your REMS, please declare this in the cover letter for your REMS modification submission. Because your REMS consists solely of a Medication Guide, if it is too early to assess your REMS, please include the following statement in your cover letter: "It is too early to assess the REMS. The Medication Guide would be adequate with the proposed modifications to achieve its purpose."

We request that you submit your proposed REMS modification with assessment as described above by the close of business on July 30, 2010. Please let me know if you have any questions regarding this request.

Thanks,
Dorothy

****

Dorothy Demczar, BS, PharmD
Regulatory Project Manager
Food and Drug Administration
Division of Neurology Products
Bldg. 22, Rm. 4211
10903 New Hampshire Ave

Silver Spring, MD 20993
Phone: (301) 796-2263
Fax: (301) 796-9842
Email: Dorothy.Demczar@fda.hhs.gov

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22115	SUPPL-6	SMITHKLINE BEECHAM CORP	LAMICTAL XR TABLETS

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

/s/

KELLY M SUMMERS
07/16/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022115/S-006

FILING COMMUNICATION

GlaxoSmithKline
Attention: Elizabeth McConnell, PharmD
Associate Director, Neurology, US Regulatory Affairs
PO Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Dr. McConnell:

Please refer to your supplemental new drug application (NDA) dated March 31, 2010, received March 31, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Lamictal XR (lamotrigine) Extended Release tablets.

We also refer to your additional submission dated May 27, 2010.

This "Prior Approval" supplemental new drug application provides clinical data to support a new indication for Lamictal XR - conversion to monotherapy in patients 13 years of age and older with partial seizures who are receiving therapy with a single antiepileptic drug (AED).

We have completed our filing review and have determined that your supplemental application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this supplemental application is considered filed 60 days after the date we received your application. The review classification for this supplemental application is **Standard**. Therefore, the user fee goal date is January 31, 2011.

We are reviewing your supplemental application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by December 31, 2010.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the supplemental application and is not indicative of deficiencies that may be identified during our review.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a partial waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

If you have any questions, call Dorothy Demczar, Pharm.D., Regulatory Project Manager, at (301) 796-2263.

Sincerely,

{See appended electronic signature page}

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22115	SUPPL-6	SMITHKLINE BEECHAM CORP	LAMICTAL XR TABLETS

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/s/

RUSSELL G KATZ
06/11/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 022115

GlaxoSmithKline
Attention: Elizabeth McConnell, PharmD
Associate Director, Neurology, US Regulatory Affairs
PO Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Dr. McConnell:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamictal XR extended release tablets.

We also refer to the telecon between representatives of your firm and the FDA on July 24, 2009. The purpose of the meeting was to discuss your plans for a Supplemental New Drug Application (sNDA) intended to support approval of Lamictal XR tablets as conversion to monotherapy in adults with partial seizures receiving a single antiepileptic drug.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Dorothy Demczar, PharmD at (301) 796-2263.

Sincerely,

{See appended electronic signature page}

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

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	July 24, 2009
TIME:	2:00 – 3:00 PM
APPLICATION:	NDA 22115
PRODUCT:	Lamictal XR extended release tablets
INDICATIONS:	Conversion to monotherapy in adults with partial seizures
SPONSOR:	GlaxoSmithKline
TYPE OF MEETING:	Type B
MEETING CHAIR:	Russell Katz, MD, Director, Division of Neurology Products (DNP)
MEETING RECORDER:	Dorothy Demczar, PharmD, Regulatory Project Manager

FDA ATTENDEES:

Russell Katz, MD, DNP, Division Director
Norman Hershkowitz, MD, PhD, DNP, Clinical Team Leader
Ellis Unger, MD, Deputy Office Director
Kun Jin, PhD, Biostatistics Team Leader
Dorothy Demczar, PharmD, DNP, Regulatory Project Manager

GlaxoSmithKline ATTENDEES:

Elizabeth McConnell, Associate Director, Regulatory Affairs, Neurology
Randal Batenhorst, Vice President, Regulatory Affairs, Psychiatry and Neurology
John Messenheimer, M.D., Group Director, Neurology Clinical Development
Alain Vuong, Director, Neurology Clinical Development
Paul Caldwell, Manager, Neurology Clinical Development
Anne Hammer, Principal Statistician, Neurology Clinical Development
(b) (4)
(consultant)
(b) (4)
(D) (4) (consultant)

BACKGROUND:

A teleconference took place between the Agency and GSK on March 29, 2005 to discuss the design of a conversion to monotherapy study (LAM300055). GSK proposed use of a historic control based on an evaluation by Dr. Jacqueline French and colleagues of previously conducted conversion studies. In a White Paper, French et al proposed that the lower limit of a 95% prediction interval of exit rates for aggregated pseudoplacebo data be used as the comparator and that a study drug needed to be statistically superior to this exit rate in order to demonstrate efficacy [French, 2005]. The Agency agreed in principle that conversion to monotherapy studies in epilepsy could be an appropriate setting for use of historic controls. However, the Agency also noted that it is critical to choose the most appropriate control and define how success will be measured against this control. There was considerable discussion about issues regarding the analysis provided by Dr. French, et al. The requirements for 1 study versus 2 studies using

historic controls was also briefly discussed. A requested analysis using the mixed effects model was ultimately done and a revised White Paper was submitted to the agency in December 2005. Results of LAM30055 are now available and GSK believes that they support the efficacy of Lamictal XR for conversion to montherapy in adult patients with partial seizures.

QUESTIONS AND TOPICS FOR DISCUSSION:

1. Does the Agency agree that a single clinical study using a historic control is sufficient to support approval of LTG XR tablets for conversion to monotherapy in adults with partial seizures?

FDA Preliminary Response:
The Agency has determined that a single clinical study using a historic control could potentially be sufficient to support approval for monotherapy of partial onset seizures after having previously been determined to be effective by adequate and well controlled clinical trials for adjunctive treatment. Lamictal XR has been approved as adjunctive therapy in adults with partial seizures. Therefore, a single clinical study using a historic control might be sufficient to support approval of LTG XR tablets for conversion to monotherapy in adults with partial seizures.

Whether the recently completed study LAM30055 will be adequate to support approval will be a review issue at the time of NDA submission.

Meeting discussion:

See below.

2. Does the Agency agree that the design and analysis of LAM30055 meet the definition of an adequate and well-controlled trial needed to support approval of LTG XR tablets for conversion to monotherapy in adults with partial seizures?

FDA Preliminary Response:
The proposed design and analysis of LAM30055 can potentially support approval (see answer to question 1). Issues to be discussed are presented in answers to questions 3-5.

Meeting discussion:

See below.

3. Does the Agency agree that safety information from clinical trials evaluating monotherapy with LTG IR tablets can be used to support the safety of LTG XR tablets for conversion to monotherapy in adults with partial seizures?

FDA Preliminary Response:
The lack of a concurrent placebo control and the lack of clinical laboratory measures during the trial limit the safety information from LAM30055. Therefore it is appropriate

to also use safety information from clinical trials evaluating monotherapy with LTG IR tablets (e.g. study 30/31) to support the safety of LTG XR tablets for conversion to monotherapy in adults with partial seizures.

Meeting discussion:

Additionally, the Sponsor asked about the need to integrate the ISS data into this new document. The Agency responded that GSK can provide the old ISS (perhaps as an Appendix), but there should be new discussion of the newly acquired safety data from the historical controlled study and how it compares to the older pseudo-placebo controlled monotherapy study. GSK stated that study 30/31 and the ISS were done before the new guidance was published so they do not conform, but they are navigable. They will be providing scanned documents, which are not "word" searchable. The Agency asked whether they can be converted into an alpha/numeric format that is searchable, noting that such programs exist, although the conversion may introduce some inaccuracies. GSK will check with their publishing group to see if they can make the documents searchable.

4. Does the Agency agree with the content and format of the proposed sNDA seeking approval of LTG XR tablets as conversion to monotherapy in adults with partial seizures?

FDA Preliminary Response:
Demographic data should be included and compared to those used from the historical control studies, although it is understood that all data in the historical control studies may not be available. This should include, but not necessarily be limited to, age, gender, race, country, seizures baseline frequency, seizure types (1A, 1B and 1C) number and type of anticonvulsants before conversion.

As you have indicated, all data from the Costa Rica site should be included in the ITT analysis.

From the Biometrics perspective, we agree with the proposed content and format as outlined. However, please also submit with the application SAS programs used in deriving from the raw source data for each patient i) whether or not each escape criterion was met and ii) the associated endpoint for the composite of the various escape criteria. Please also include SAS programs for carrying out the analyses.

Meeting discussion:

The Agency clarified that it would like available datasets: 1) Baseline demographic variables and 2) Reasons for meeting exit criteria or exiting for other reasons. The Sponsor's consultant ((b) (4)) clarified that not all baseline data would be there since data for the White Paper was derived from tables in articles and it was not individual patient data. Discussion took place surrounding this request and whether (b) (4) could actually provide this information due to confidentiality issues and whether she should contact all sponsors to request permission to release this data to the Agency. She also noted that some sponsors no longer exist. The Agency suggested that since the data were

already presumably in our possession (so that we are only requesting that data in another format) and since the data constitute source documents to a publication, or public presentation, we may therefore have the legal right to use it in our review. (b) (4) will see what she can do, but also suggested that the Agency may want to request permission from the sponsors directly. She will provide a list of companies and drugs that comprised the data utilized in the White Paper. The Agency would prefer not to request this information directly but will inquire as to our legal right in obtaining and using such data in our review.

5. Does the Agency agree with GSK's proposal for use of the Clinical Overview as the primary summary of efficacy and safety data for this application?

FDA Preliminary Response:
The Agency does not agree with omitting the integrated summary of safety (ISS) and the integrated summary of efficacy (ISE).

The ISE must include a data from Study 30/31 and a discussion of why Study 30/31 failed to demonstrate efficacy for LTG IR tablets. The study report and data sets for Study 30/31 must be included in an appendix to the NDA submission.

The ISS must include both safety data from LAM30055 and safety data from the clinical trial(s) evaluating monotherapy with LTG IR tablets.

Meeting discussion:

The Sponsor corrected the Agency by noting that, while study 30/31 may have initially been read as negative, the Agency finally considered it a positive study and granted the indication. The Agency noted that this does not preclude the necessity of having an ISE and that this information, with any other pertinent information, should be included in the ISE and used to justify final approval. The ISE should be placed in module 5 but a Summary of Clinical Efficacy (section 2.7.3) does not also need to be included; cross referencing the ISE to section 2.7.3 would be adequate. The Agency also clarified that a comprehensive study report for the new study would be expected but a full comprehensive report for the old study would not be necessary.

ADDITIONAL DISCUSSION:

GSK asked if the company would be held to the new bar or the old bar? The Agency responded that it would be the "new bar" as discussed in the revised White Paper. The bar should be the best calculated number that we have. If there is a discrepancy that does not favor approval, the sponsor may argue otherwise.

The topic of US vs. non-US was discussed. In the White Paper all studies involved were US studies – in LAM30055, 25% were US studies. The Agency stated that the sponsor should make the case that the patients in their study are similar to the historic control patients.

ACTION ITEMS:

- [redacted] (b) (4) will perform an initial inquiry into obtaining approval from the sponsors in providing the datasets used in the White Paper.
- The Agency will obtain advice regarding its legal right to acquire the datasets used in the White Paper.
- The Sponsor will check with their publishing group regarding the creation of searchable copies of legacy documents.
- The Sponsor will provide a summary of what they plan to include in their sNDA submission.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22115	GI 1		LAMICTAL XR TABLETS
NDA 22115	GI 1		LAMICTAL XR TABLETS

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/s/

RUSSELL G KATZ
08/14/2009