

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-115

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 22-115

SUPPL #

HFD # 120

Trade Name Lamictal XR Extended Release Tablets

Generic Name lamotrigine

Applicant Name Glaxo Smith Kline

Approval Date, If Known May 29, 2009

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

505(b)(1)

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 ☒ 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.

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:

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 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?

No

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 ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-421

Lamictal Tablets

NDA# 20-764

Lamictal Chewable Dispersible Tablets

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 ☒ 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:

(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:

(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:

- (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:

LAM100034

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.")

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:

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"):

LAM100034

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 # 069254	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?

Investigation #1

YES ☐

Explain:

!

!

! NO ☐

! Explain:

Investigation #2

YES ☐

Explain:

!

!

! NO ☐

! 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:

Name of person completing form: Vandna Kishore

Title: RPM

Date: October 28, 2009

Name of Office/Division Director signing form: Russell Katz, MD

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/

JACQUELINE H H WARE on behalf of VANDNA N KISHORE
10/28/2009

RUSSELL G KATZ
10/28/2009



INFORMATION REQUEST LETTER

NDA 22-115

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 (lamotrigine) extended-release tablets.

We also refer to your November 13, 2008 submission, containing a briefing package in which GSK is seeking agency agreement to confirm your (b) (4) proposals involving integrating safety information and the format of the Integrated Summary of Safety Information.

We have reviewed the referenced material and have the following comments and requests for information.

1. Does the Agency agree that the results of LAM103579 and LEP111102 could support the bioequivalence of the (b) (4) extended-release formulations to that which is currently under review in NDA 22-115?

Agency response:

The results of Study LAM105379 (b) (4).

However, the results of study LEP111102 did not show BE with respect to AUC_{0-inf} for the (b) (4) LAMICTAL XR tablet compared to (b) (4) LAMICTAL XR tablets. Although BE was established based on C_{max} and AUC₀₋₂₄, the 90% CI for AUC_{0-inf} was 74-96% when all subjects were included in the analysis and 78-100% after excluding the 6 subjects in which a large fraction of AUC_{0-inf} was extrapolated.

Please include in the submission a justification and rationale for the adequacy of the existing data in the NDA submission to support the (b) (4) strength along with a discussion of the clinical significance of the lower AUC_{0-inf}. You should also submit the *in vitro* release data for comparisons to support the (b) (4) tablets. The acceptance of this data will be a review issue as this will entail evaluating the data from individual subjects as well.

2. *Does the Agency agree with GSK's proposal to cross-reference NDA 22-115 for the Chemistry, Manufacturing and Controls information for the 25, 50, 100 and 200 mg tablet strengths of LAMICTAL XR?*

Agency response:

The proposal to cross-reference NDA 22-115 for CMC information if a new NDA is submitted is acceptable.

3. *Does the Agency agree with GSK's proposal to submit 9 months of stability data for the (b) (4) tablet strength with the initial application and update with additional stability data during the review period?*

Agency response:

This will be acceptable to support filing of an s-NDA or new NDA. The expiration dating period assigned will be commensurate with the extent and quality of the available stability data for all tablet strengths. Additional stability data may be submitted during the review cycle. Additional data received prior to mid cycle will be reviewed as part of the original application; however, data received later may not be reviewed during the same review cycle.

4.

(b) (4)

Agency response:

Yes, the Agency accepts your proposed content and format for the NDA.

The proposed NDA will consist of a single pivotal clinical study evaluating LAMICTAL XR in patients 13 years of age and older with PGTC seizures (LAM100036). Two bioequivalence/food effect studies supporting the (b) (4) and 300mg (LAM105379) tablet strengths as well as corresponding Chemistry, Manufacturing, and Controls information will also be included.

You propose that this application be submitted as an NDA because the file will likely be ready for submission while NDA 22-115 is still under review. If NDA 22-115 is approved before you are ready to submit this additional information, separate Supplemental New Drug Applications (sNDA) will be submitted.

5. *Does the Agency agree with GSK's proposals for the analysis of safety information for this NDA?*

Agency response:

Yes, the Agency agrees with your proposed groupings of studies, proposed safety analyses, and the proposed format of the Integrated Summary of Safety.

6. *Does the Agency agree with GSK's proposal to format the Integrated Summary of Safety consistent with the recommendations for the format of the CTD Summary of Safety?*

Agency response:

Yes, the Integrated Summary of Efficacy and Integrated Summary of Safety should be formatted and submitted according to the CTD format. In addition, the Clinical Reviewer's Template should be provided with hyperlinks to all relevant information at the time of NDA submission. (note: This response was provided in advance on January 16, 2009 during a phone conversation that took place between Betty McConnell, Phil Sheridan and Dorothy Demczar)

7. *Does the Agency reconfirm the agreements reached at the August 23, 2007 pre-NDA meeting regarding GSK's proposals for the eCTD?*

Agency response:

Yes, the Agency reconfirms the agreements reached at the August 23, 2007 pre-NDA meeting with the further clarifications given in the answers above.

If you have any questions, call Dorothy Demczar, PharmD, Regulatory Project Manager, at (301) 796-2263.

Sincerely,

{See appended electronic signature page}

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

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

/s/

Russell Katz

2/10/2009 01:39:45 PM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 022115 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Lamictal XR Established/Proper Name: Lamotrigine extended release Dosage Form: tablet		Applicant: GlaxoSmithKline Agent for Applicant (if applicable):
RPM: Dorothy Demczar		Division: DNP
<p>NDAs: NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)</p> <p>(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 NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>☐ If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p>☐ No changes ☐ Updated Date of check:</p> <p>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.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)		05/ 29/09
❖ Actions		
• Proposed action		☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions (specify type and date for each action taken)		☐ None CR 09/21/07
❖ Promotional Materials (accelerated approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____		☐ Received

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 ² Characteristics	
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): <div style="display: flex; justify-content: space-between;"> <div> ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation </div> <div> ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC </div> </div> <div style="display: flex; justify-content: space-between; margin-top: 10px;"> <div> NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC Comments: _____ </div> <div> BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies </div> </div>	
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: _____	04/22/09
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	☐ Yes ☐ No
❖ Public communications (<i>approvals only</i>)	
• 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 All questions in all sections pertain 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	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	☒ No ☐ Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>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.</i> 	☐ No ☐ Yes If yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	☐ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	☐ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	☐ No ☐ Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(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.)</i> 	☐ No ☐ Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> 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.
<ul style="list-style-type: none"> 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. 	21 CFR 314.50(i)(1)(i)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
<ul style="list-style-type: none"> [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). 	☐ No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [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). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	☐ 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?

☐ Yes ☐ No

(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)?

☐ Yes ☐ No

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?

☐ Yes ☐ No

(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)?

☐ Yes ☐ No

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?

☐ Yes ☐ No

(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.

CONTENTS OF ACTION PACKAGE

- ❖ Copy of this Action Package Checklist³

Officer/Employee List - section A

- ❖ 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

Action Letters - section B

- ❖ Copies of all action letters (*including approval letter with final labeling*)

Action(s) and date(s) : Approval
05/29/09; CR 09/21/09

Labeling – section C

- ❖ Package Insert (*write submission/communication date at upper right of first page of PI*)

Attached to Approval Letter
05/29/09

- Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)
- Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)
- Original applicant-proposed labeling
- Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable

- ❖ Medication Guide/Patient Package Insert/Instructions for Use (*write submission/communication date at upper right of first page of each piece*)

☒ Medication Guide
Attached to approval letter
05/29/09
☐ Patient Package Insert
☐ Instructions for Use
☐ None

³ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> Original applicant-proposed labeling 	
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date at upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent division proposal for (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	☐ RPM ☒ DMEDP 08/02/07 ☒ DRISK 04/02/09 ☐ DDMAC ☐ CSS ☒ Other reviews SEALD 04/08/09
❖ Proprietary Name	
<ul style="list-style-type: none"> Review(s) (<i>indicate date(s)</i>) Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) 	05/03/07; 09/20/07; 04/30/09 05/04/07 email to sponsor

Administrative / Regulatory Documents – sections **D thru J**

❖ <u>D</u> Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	12/11/06 – RPM filing review/ Memo of filing meeting
❖ <u>E</u> NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	
<ul style="list-style-type: none"> Applicant in on the AIP 	☐ Yes ☒ No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	☐ Yes ☒ No ☐ Not an AP action
❖ <u>F</u> Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)	☒ Included
❖ <u>G</u> 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 (<i>include certification</i>)	☒ Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	☒ None
<ul style="list-style-type: none"> Outgoing communications (<i>if located elsewhere in package, state where located</i>) Incoming submissions/communications 	
❖ Postmarketing Commitment (PMC) Studies	☒ None
<ul style="list-style-type: none"> Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>) 	

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.

• Incoming submission documenting commitment	
❖ H Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)	NDA ack letter 12/07/06; Filing communication 02/01/07; Info request-CMC 08/17/09; Info Request –CMC 07/03/07; DMETS /DDMAC comments email 05/04/07; Information request 02/10/09; PDUFA goal date extension 02/27/09
❖ I Internal memoranda, telecons, etc.	Meeting request granted 04/21/09; Meeting cancelled 10/24/08
❖ J Minutes of Meetings	
• PeRC (<i>indicate date; approvals only</i>)	☐ Not applicable 04/22/09
• Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)	☒ Not applicable
• Regulatory Briefing (<i>indicate date</i>)	☒ No mtg
• Pre-NDA/BLA meeting (<i>indicate date</i>)	☐ No mtg 05/25/06
• EOP2 meeting (<i>indicate date</i>)	☒ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	PreNDA CMC meeting minutes 08/09/06
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos – section K	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	☒ None
Division Director Summary Review (<i>indicate date for each review</i>)	☐ None 05/08/09
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	☐ None 05/29/09
Clinical Information⁵	
❖ L Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	10/26/07; 05/29/09
• Clinical review(s) (<i>indicate date for each review</i>)	10/14/07; 05/03/09
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	☒ None
❖ M Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	04/23/09
❖ N Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	
❖ O Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☐ None IRT- QT review 09/12/07
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ Not needed

⁵ Filing reviews should be filed with the discipline reviews.

❖ P Risk Management	☒ None
<ul style="list-style-type: none"> Review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review) REMS Memo (indicate date) REMS Document and Supporting Statement (indicate date(s) of submission(s)) 	05/29/09 03/16/09
❖ Q DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	☐ None requested Inspection Summary 02/04/09, 09/21/07 Investigator letters 04/6/09, 01/23/08
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
Biostatistics - section R ☐ None	
❖ Statistical Division Director Review(s) (indicate date for each review)	☐ None 08/23/07
Statistical Team Leader Review(s) (indicate date for each review)	☐ None 08/23/07
Statistical Review(s) (indicate date for each review)	☐ None 08/22/07, 04/10/09
Clinical Pharmacology - section S ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	☐ None 09/06/07
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	☐ None 09/06/07
Clinical Pharmacology review(s) (indicate date for each review)	☐ None Filing Memo 1/11/07; Review 09/06/07
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	☒ None
Nonclinical ☒ None	
❖ Pharmacology/Toxicology Discipline Reviews	
<ul style="list-style-type: none"> ADP/T Review(s) (indicate date for each review) Supervisory Review(s) (indicate date for each review) Pharm/tox review(s), including referenced IND reviews (indicate date for each review) 	☐ None ☐ None ☐ 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
CMC/Quality ☐ None	
❖ T CMC/Quality Discipline Reviews	
<ul style="list-style-type: none"> ONDQA/OBP Division Director Review(s) (indicate date for each review) Branch Chief/Team Leader Review(s) (indicate date for each review) CMC/product quality review(s) (indicate date for each review) BLAs only: Facility information review(s) (indicate dates) 	☒ None ☐ None 09/12/07 ☐ None Filing Review 12/11/06; Review 09/12/07 ☐ None

❖ Microbiology Reviews <ul style="list-style-type: none"> • NDAs: Microbiology reviews (sterility & pyrogenicity) <i>(indicate date of each review)</i> • BLAs: Sterility assurance, product quality microbiology <i>(indicate date of each review)</i> 	☒ Not needed
❖ <u>U</u> Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	
☒ Review & FONSI <i>(indicate date of review)</i>	04/29/07
☒ Review & Environmental Impact Statement <i>(indicate date of each review)</i>	04/27/07
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i> 	Date completed: 08/16/07 ☒ Acceptable ☐ Withhold recommendation
<ul style="list-style-type: none"> • BLAs: <ul style="list-style-type: none"> ○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i> 	Date completed: ☐ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ Hold

Appendix A 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.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-115

INFORMATION REQUEST LETTER

GlaxoSmithKline
Attention: Elizabeth A. McConnell, Pharm.D.
Project Director, Regulatory Affairs
P.O. Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Dr. McConnell:

Please refer to your November 22, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LAMICTAL (lamotrigine) Extended-Release 25mg, 50mg, 100mg, 200mg Tablets.

Further, please refer to our July 3, 2007 Information Request letter and your July 23, 2007 amendment to your application.

We are reviewing the Chemistry, Manufacturing and Controls (CMC) section of your submission and have the following comments and information requests. We request a written response by August 31, 2007, in order to continue our evaluation of your NDA.

Excipients

1. Clarify if the batches illustrated in Figure 1 of your response to FDA Comment 2 contained hypromellose batches with viscosities at the extremes of the USP monograph limits. If not, provide the confirmatory results of the impact of USP monograph hypromellose viscosity extremes on drug product release profiles. Provide the (b) (4), (b) (4) content, and (b) (4) content of the (b) (4) used to generate the batches in Figure 1 as well as any confirmatory results.
2. Due to the identification of residual (b) (4) in (b) (4) as the main contributor to lamotrigine (b) (4) impurity formation, establish a residual (b) (4) limit for the (b) (4) in addition to the USP monograph specification.

Manufacturing

3. Define the frequency of the "periodic challenges" used to verify the accurateness of the tablet inspection and aperture depth control methods mentioned in your response to FDA Comment 8.

Drug Product

4. We do not agree with your intent to eliminate drug-related impurities and water content testing at release. [REDACTED] (b) (4)

[REDACTED] we feel that water content testing at release is necessary based on the limited number of commercial drug product batches produced, to date. For this same reason, we feel that drug-related impurities testing is necessary at release as well. Again, pointing to the limited number of commercial drug product batches produced to date, we feel that not enough drug-related impurities data have been generated incorporating raw material and manufacturing variations. Monitoring drug-related impurities provides assurance of drug product purity and quality. Collecting this data will provide assurance to you, as well as the Agency, that the drug product does not pose any potential risks to humans.

Stability

5. As stated in the original communication, we recommend that additional fill counts be pursued as a post-approval supplement. We recognize your intent to implement a packaging presentation that could potentially reduce safety concerns and the potential for medication errors. However, at this late stage in the review cycle, we cannot guarantee a review of the proposed stability update for the 30-count HDPE bottles in the first review cycle. If we are able to review the information provided, any expiries granted would be based on the amount and quality of data presented. We recommend including the following four items in your stability update submission:

- i. Proposed expiration dating for the 30-count HDPE bottles
- ii. Headspace calculation comparisons for the 30-count, [REDACTED] (b) (4) HDPE bottles
- iii. Revised post-approval stability protocol reflecting the addition of the 30-count HDPE bottles
- iv. Confirmation of the intended fill counts to be marketed for each tablet strength

We recommend updating the stability protocol for the on-going commercial stability program to reflect testing of HDPE bottles across tablet strengths on an annual basis. We recommend testing the 25 mg tablets in the blister presentation, which represents the worst case scenario, on an annual basis as well. We are amenable to a reduced testing schedule for higher strength blister presentations. Please provide an updated stability protocol, reflecting the recommended annual testing of HDPE bottles and 25 mg blisters as well as your proposal for reduced blister presentation testing for the remaining tablet strengths.

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-115

INFORMATION REQUEST LETTER

GlaxoSmithKline
Attention: Elizabeth A. McConnell, Pharm.D.
Project Director, Regulatory Affairs
P.O. Box 13398
Five Moore Drive
Research Triangle Park, NC 27709

Dear Dr. McConnell:

Please refer to your November 22, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LAMICTAL (lamotrigine) Extended-Release 25mg, 50mg, 100mg, 200mg Tablets.

We are reviewing the Chemistry, Manufacturing and Controls (CMC) section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance

1. Provide Certificates of Analysis (CoAs) for drug substance batches used in the NDA stability batches.

Excipients

2. Comment on the effects of variations in (b) (4) content, degree of substitution or viscosity on release rate. Describe any additional control limits for the (b) (4), such as (b) (4) content, (b) (4) content and (b) (4) that are in addition to the USP specifications.
3. Clarify if the excipient analytical procedures described for non-compendial excipients are performed in-house or by the supplier. Provide validation information for any internal non-compendial analytical procedures.

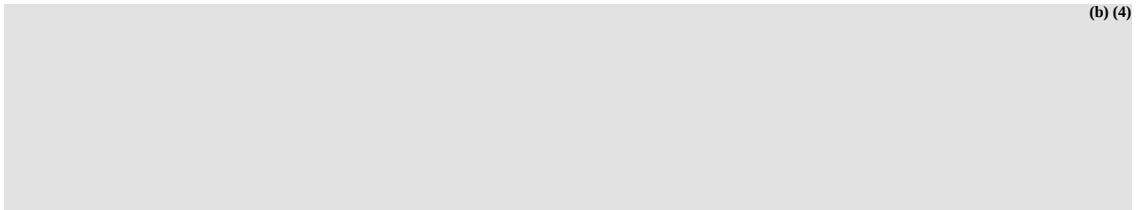
Drug Product

4. Due to the formation of the (b) (4) impurity on stability, include impurity content and water content as drug product release specifications. Update the proposed drug product specifications to reflect only one printing option.
5. Provide an update on the (b) (4) impurity source investigation.

6. Provide confirmatory data for the correlation between aperture depth and tablet weight loss for the 50 and 200 mg strength tablets. Clarify the units for the data provided in Table 65, Section m3.2.P.2. The table title conveys tablet weight loss data will be included but the data provided uses length units.

Manufacturing

7. Explain the exclusion of the proposed target ranges for the critical process parameters and in-process controls for the apertures in the batch records.
8. Provide a summary of the qualification process used for the aperture drilling machine. Describe the incorporation of the tablet inspection and aperture depth control method in the quality system.

9.  (b) (4)

10. Comment on the impact of the aperture drilling process on the enteric coating integrity.

11.  (b) (4)

12.  (b) (4)

13.  (b) (4)

Container Closure System

14. Identify the specific type of blister pack  (b) (4), including the manufacturer's identifying information.

Stability

15. Clarify what is meant by alternating packaging during the commercial stability program.
16. We feel the proposed post-approval stability protocol contains deficiencies. Consider the following three points when revising your protocol:
 - i. Based on your proposed expiration of (b) months, revise the proposed post-approval stability commitment to include testing at Month (b)

- ii. Test two batches at Month 3 and Month 9 for the 25 mg strength tablets in both packaging configurations, due to the sensitivity of this formulation to (b) (4) formation. Mirror this test schedule for the 50 mg strength tablets because of their potential for (b) (4) formation.
 - iii. We feel the proposed design does not provide adequate batch representation for the 100 and 200 mg HDPE bottles. Revise the 100 and 200 mg test schedule, adding testing of two batches at each time point for the HDPE bottles. We also recommend testing two batches at each time point for the 200 mg blisters.
17. Your request to (b) (4) is not supported by appropriate stability data. We recommend that you pursue (b) (4) as part of your post-approval product management, as you generate appropriate stability data.

Label

18. Revise the proposed container label, displaying the tablet strength under the drug product name.

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood

7/3/2007 02:19:56 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-115

SmithKlineBeecham
d/b/a GlaxoSmithKline
Attn: Elizabeth McConnell, Pharm.D.
Associate Director, Regulatory Affairs, Neurology
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Dr. McConnell:

Please refer to your November 22, 2006, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamictal XR (lamotrigine) extended release tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on January 21, 2007, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Labeling:

Highlights:

- The Highlights and Table of Contents should be in a two-column format, 8 point font. Refer to fictitious examples of labeling in the new format at <http://www.fda.gov/cder/regulatory/physLabel/default.htm>.
- Under Use in Specific Populations, consider including the pregnancy registry information.
- Regarding the Boxed Warning for the Contents and FPI, it must read **WARNING** – and insert the words that are appropriate to identify the subject of the warning (i.e., **SERIOUS SKIN RASHES**). [See 21 CFR 201.57(c)(1)]
- Please bold the entire contents of the Boxed Warning.
- Also in the boxed warning, add the reference (5.1) before the colon.
- Under the Dosage Forms and Strengths heading in Highlights, the information for "Potential Medication Errors" appears out of place. Consider including this information under Warnings and Precautions in Highlights.
- Delete the Recent Major Changes heading since it is not applicable for a new NDA.

- Under Indications and Usage, consider making the information one paragraph and removing the first cross reference to 1.1.

Full Prescribing Information (FPI):

- Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), (d)(10)], please use bold print sparingly throughout the labeling. Use another method for emphasis such as italics or underline. See <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for fictitious examples of labeling in the new format.
- The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, *[see Dosage and Administration (2.1)]*, not *[for dosing guidelines, see Dosage and Administration (2.1)]*. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use bold print. Do not use all capital letters. Please fix all cross-references throughout the labeling. [See Implementation Guidance]
- The boxed warning should include a cross-reference to the more detailed information in the FPI.
- Under DOSAGE FORMS AND STRENGTHS, please add the words “Extended-Release” in front of the subsection heading 3.1 so that it reads Extended Release Tablets.
- Regarding subsection 6.3, to help practitioners interpret the significance of data obtained from postmarketing spontaneous reports, the following statement, or an appropriate modification, should precede these data:

The following adverse reactions have been identified during postapproval use of drug X. 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.

Refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format,” available at <http://www.fda.gov/cder/guidance>.

- Remove the date of issue at the end of the section. The revision date at the end of highlights replaces the “issued” date at the end of labeling.
- Delete the statement (b) (4) at the end of the labeling as it appears out of place.

Safety:

- There is potential for confusion with Lamictal XR and the existing Lamictal product line due to the overlap in three strengths (25 mg, 100 mg, and 200 mg), numerical similarity of one strength (150 mg and 50 mg), and potential overlap in dosing frequency. This type

of confusion is common for product-line extensions when most prescribing characteristics overlap. We acknowledge the proposal to make the tablets distinct in appearance and color. However, this strength overlap with the immediate-release Lamictal products is a source of error. Consideration should be given to revising the strengths so that they do not overlap with the currently marketed Lamictal drug products.

- Similarly, post-marketing reports have found Lamictal confused with multiple other drug products including Lamisil, lamivudine, Lomotil, and labetalol. These names would remain a potential source for error as there is generally a knowledge deficit among health care providers to the existence of new product line extensions and a strong familiarity with these currently marketed products. In addition, Lamictal XR overlaps with these recognized error-prone drug products in dosing frequency and possesses numerically similar strengths. Thus, pharmacy staff would have no means to differentiate the products if the modifier is omitted. They would generally revert to the product they know.
- You should assure the container labeling and blister packaging for Lamictal XR is distinct in appearance from Lamisil, lamivudine, and the currently marketed Lamictal. Post-marketing reporting determined that proximity on the shelf in addition to similar labeling resulted in selection errors between these products.

Clinical Pharmacology:

- The NONMEM control streams and output files should be submitted as text files (*.txt) for the population PK-PD and IVIVC reports.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We do not expect a response to this letter, and we may not review any such response during the current review cycle.

If you have any questions, call Courtney Calder, PharmD, Regulatory Project Manager, at (301) 796-1050.

Sincerely,

{See appended electronic signature page}

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

APPEARS THIS WAY ON ORIGINAL



**This is a representation of an electronic record that was signed electronically and
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/s/

Russell Katz
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