CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-251

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 04/30/10
See OMB Statement on Page 3.

NDA NUMBER
022251

NAME OF APPLICANT / NDA HOLDER
SmithKline Beecham Corp.
d.b.a. GlaxoSmithKline

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
LAMICTAL ODT

ACTIVE INGREDIENT(S)	STRENGTH(S)
lamotrigine	25mg, 50mg, 100mg, and 200mg

DOSAGE FORM
tablet (orally disintegrating)

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
4,602,017	07/22/1986	07/22/2008

d. Name of Patent Owner	Address *(of Patent Owner)*	
SmithKline Beecham Corp.	Attn: Vice President, Corporate Intellectual Property 709 Swedeland Road, UW2220, P.O. Box 1539	
	City/State King of Prussia, PA	
	ZIP Code 19406-0939	FAX Number *(if available)* (919) 483-7988
	Telephone Number (919) 483-6983	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) ☞	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

PSC Graphics: (301) 443-1090 EF

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

4.1	Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2	Patent Claim Number(s) *(as listed in the patent)* Claims 7, 8, 9, 10, 11, 12	Does (Do) the patent claim(s) referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes ☐ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)*

Treatment of generalized tonic-clonic seizures as a type of convulsion and/or epilepsy and maintenance treatment of bipolar disorder.

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. ☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Robert H. Brink	25 October 2007

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Robert H. Brink, Esq.	
Address GlaxoSmithKline Attn: Vice President, Corporate Intellectual Property Five Moore Drive, P.O. Box 13398	City/State Research Triangle Park, NC
ZIP Code 27709-3398	Telephone Number (919) 483-3323
FAX Number *(if available)* (919) 483-7988	E-Mail Address *(if available)* rob.h.brink@gsk.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.

Additional copies of these forms may be downloaded from the Internet at: http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.

4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY

NDA # 22-251 SUPPL # HFD # 120

Trade Name Lamictal ODT Tablets

Generic Name lamotrigine

Applicant Name Glaxo Smith Kline

Approval Date, If Known May 8, 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.

Approval based upon bioequivalency study LBI108617 data submitted by sponsor.

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?

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# 20-241 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:

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:

NDA 20-241 referenced via right of reference.

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"):

N/A

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 # 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 ☐	! 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:

==========

Name of person completing form: Vandna Kishore
Title: RPM
Date: November 12, 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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22251	ORIG-1	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE	LAMICTAL ODT

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

/s/

VANDNA N KISHORE
11/12/2009

RUSSELL G KATZ
11/16/2009

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 (NDA 022251).

Craig Wozniak

October 30, 2007

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: April 30, 2009.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	NDA 022251; LAMICTAL® (lamotrigine) Orally Disintegrating Tablets	
	See attached List A of Investigators with no disclosable financial interests/arrangements.	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Craig A. Metz, PhD	Vice President, Global CEDD Regulatory Affairs
FIRM / ORGANIZATION: SmithKline Beecham d/b/a GlaxoSmithKline	
SIGNATURE: Craig A. Metz	DATE: 11/1/07

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

PSC Graphics: (301) 443-1090 EF

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

PDUFA GOAL DATE EXTENSION

NDA 22-251

SmithKline Beecham Corporation
d/b/a GlaxoSmithKline
Attention: Eric Benson, Senior Director, US Regulatory Affairs
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

Dear Mr. Benson:

Please refer to your new drug application (NDA) dated November 28, 2007, received November 28, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamictal ODT (lamotrigine) Orally Disintegrating Tablets, 25mg, 50mg, 100mg, and 200mg.

On September 25, 2008, we received your September 25, 2008, 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 December 28, 2008.

If you have questions, call Jacqueline H. Ware, Pharm.D., Senior Regulatory Project Manager, at (301) 796-1160.

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

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

/s/

Jackie Ware
9/26/2008 03:47:26 PM
Signed for Russell Katz

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:	
Division of Psychiatry Products			**Division of Neurology Products**	
DATE September 5, 2008	IND NO.	NDA NO. 22-251	TYPE OF DOCUMENT New NDA – PI	DATE OF DOCUMENT November 28, 2007
NAME OF DRUG Lamictal (lamotrigine) Orally Disintegrating Tablet	PRIORITY CONSIDERATION Standard		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE September 19, 2008 (PDUFA goal date: 9/28/08)

NAME OF FIRM: Glaxo Smith Kline

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 II 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)*: Package Insert

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV 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
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review the proposed package insert (PI) for NDA 22-251/Lamictal (lamotrigine) Orally Disintegrating Tablets. Specifically, we ask for DPP comments on sections of the PI relevant to the bipolar indication. We also ask that DPP comment on the acceptability of using bioequivalence data for Lamictal ODT and Lamictal IR to support the bipolar claime.

Link to NDA 22-251/Lamictal ODT Tablets \\CDSESUB1\EVSPROD\NDA022251\022251.enx; Labeling is located in module 1, section 1.1.4.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Jackie Ware, Regulatory Project Manager (301-796-1160) for ONDQA (Wendy Wilson & Martha Heimann)	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Jackie Ware
9/17/2008 01:41:25 PM
Sent at request of Dr. Katz; review originally discussed with DPP at team meeting on 9/5/08

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-251 **INFORMATION REQUEST LETTER**

SmithKline Beecham Corporation
d/b/a GlaxoSmithKline
Attention: Eric Benson, Senior Director
US Regulatory Affairs
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Mr. Benson:

Please refer to your new drug application (NDA) dated November 28, 2007, received November 28, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamictal ODT (lamotrigine) Orally Disintegrating Tablets, 25mg, 50mg, 100mg, and 200mg.

We are reviewing the Chemistry, Manufacturing and Controls 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:

1. Based on our review of the residual magnesium stearate and polyethylene data in lamotrigine ODTs, we do not agree that these materials qualify as trace ingredients. Therefore, we recommend that you list magnesium stearate and polyethylene as inactive ingredients in the drug product labeling.
2. As the party responsible for final release of the commercial drug product, explain how you verify that the material received from your drug product supplier meets your final drug product release criteria. Provide the criteria used to release the final drug product.
3. Provide fill counts for each of the blister pack presentations of the commercial drug product. Clarify the total tablet count intended for the institutional blister packs. The draft labels indicate 28 tablets while the package insert indicates that this configuration contains (b) (4) tablets.
4. Revise the descriptions of the patient titration kits in Section 16 of the package insert to include the total tablet fill count for each kit.
5. Revise Section 16 of the package insert and Section 7 of the patient information leaflet to include a statement warning against use of the blister packs if the blisters are torn, broken, or missing.
6. Confirm the intended commercial packaging for the placebo ODT demonstrator tablets. Provide draft carton and container labels for the placebo ODT demonstrator tablets.

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

8/27/2008 10:31:26 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:	
ODS/DMEDP			**Division of Neurology Products**	
DATE June 18, 2008	IND NO.	NDA NO. 22-251	TYPE OF DOCUMENT New NDA – carton& container labels	DATE OF DOCUMENT November 28, 2007
NAME OF DRUG Lamictal (lamotrigine) Orally Disintegrating Tablet	PRIORITY CONSIDERATION Standard		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE August 1, 2008 (PDUFA goal date: 9/28/08)

NAME OF FIRM: Glaxo Smith Kline

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 II 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)*: Carton & Container Labels

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV 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
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review the proposed carton & container labels for NDA 22-251/Lamictal (lamotrigine) Orally Disintegrating Tablets. We ask for your comments on medication error potential of these labels, particularly given the name confusion issues between Lamictal & Lamisil. In addition, please review for safety issues or conflicts with the current packages for the other Lamictal drug products.

Link to NDA 22-251/Lamictal ODT Tablets \\CDSESUB1\EVSPROD\NDA022251\022251.enx; see 11/28/07 & 4/29/08 submissions

Link to NDA 20-241/Lamictal Tablets \\FDSWA150\NONECTD\N20241\Y_013\2007-12-20

Link to NDA 20-764/Lamictal Chewable Dispersible Tablets \\FDSWA150\NONECTD\N20764\Y_009\2007-10-10

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Jackie Ware, Regulatory Project Manager (301-796-1160) for ONDQA (Wendy Wilson & Martha Heimann)	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Jackie Ware
6/18/2008 03:42:24 PM
Sent at request of ONDQA review team

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-251

SmithKline Beecham Corporation
d/b/a GlaxoSmithKline
Attention: Eric Benson, Senior Director, US Regulatory Affairs
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

Dear Mr. Benson:

Please refer to your new drug application (NDA) dated November 28, 2007, received November 28, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lamictal ODT (lamotrigine) Orally Disintegrating Tablets, 25mg, 50mg, 100mg, and 200mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is September 28, 2008.

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 application and is not indicative of deficiencies that may be identified during our review.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. However, we acknowledge receipt of your request for a full waiver of pediatric studies for this application.

If you have questions, call Jacqueline H. Ware, Pharm.D., Senior Regulatory Project Manager, at (301) 796-1160.

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 Katz

2/8/2008 11:35:26 AM

DSI CONSULT
Request for Biopharmaceutical Inspections

DATE: February 4, 2008

TO: CT Viswanathan, Branch Chief
Good Laboratory Practice and Bioequivalence Branch
Division of Scientific Investigations, HFD-48

THROUGH: Russell Katz, Director, Division of Neurology Products

FROM: Jackie Ware, Regulatory Project Manager, Division of Neurology Products

SUBJECT: **Request for Biopharmaceutical Inspections**
NDA 22-251
Lamictal ODT(lamotrigine) Orally Disintegrating Tablets
GlaxoSmithKine

Background:

Lamictal Tablets (approved under NDA 20-241) is indicated for adjunctive therapy for partial seizures, the generalized seizures of Lennox-Gastaut Syndrome, and primary generalized tonic-clonic seizures in adults and pediatric patients. It is also approved for conversion to monotherapy in adults with partial seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single antiepileptic drug. LAMICTAL is also approved for use in the maintenance treatment of bipolar I disorder to delay time to occurrence of mood episodes (depression, mania, hypomania, mixed episodes) in adults treated for acute mood episodes with standard therapy. Lamictal ODT is a new dosage form for the same indications.

This New Drug Application 22-251 seeks approval of LAMICTAL ODT Orally Disintegrating Tablets (25mg, 50mg, 100mg and 200mg dose strengths), a new immediate-release formulation of lamotrigine .

The Pharmacokinetic portion of this new NDA consists of one pilot study (LBI108614) conducted using two prototype ODT formulations to compare two taste-masking methods and a four-arm parallel study (LBI108617) to demonstrate the BE of the ODT formulation to the approved conventional LAMICTAL tablet. This study also investigated the effect of food and water on the bioavailability of the ODT formulation. The orally disintegrating tablet information was integrated into the labeling of the LAMICTAL immediate-release tablet and chewable tablet.

An electronic link to NDA is: \\CDSESUB1\EVSPROD\NDA022251\022251.enx

Study/Site Identification:

DNP is requesting inspection of the following studies/sites pivotal to approval:

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
Study LBI-108617	**Clinical:** Convance Clinical Research Unit 1341 West Mockingbird Lane Suite 400 Dallas, Texas 75247	**Analytical:** **WorldWide Bioanalysis** Drug Metabolism and Pharmacokinetics GlaxoSmithKline R&D; 3030 Cornwallis Road, RTP, NC 27709 USA

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by **August 1, 2008**. We intend to issue an action letter on this application by September 28, 2008.

Should you require any additional information, please contact Jackie Ware, Regulatory Project Manager, at 301-796-1160 or jacqueline.ware@fda.hhs.gov

Concurrence:
Carol Noory, Ph.D., Clinical Pharmacology Reviewer; carol.noory@fda.hhs.gov
Ramana Uppoor, Ph.D., Clinical Pharmacology Team Leader; ramana.uppoor@fda.hhs.gov

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/s/

Jackie Ware
2/4/2008 11:10:09 AM
Sent at request of Dr. Katz

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Office/Division)*: Raanan (Ron) Bloom, OPS/PARS, 301-796-2185

FROM (*Name, Office/Division, and Phone Number of Requestor)*: Martha Heimann, OPS/ONDQA/DPA I, through Linda Athey 301-796-2096.

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
December 14, 2007		22-251		November 28, 2007

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
LAMICTAL ODT			February 15, 2007

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: Request for Environmental Assessment.

SIGNATURE OF REQUESTOR
{see attached signature page}

METHOD OF DELIVERY (Check one)
☒ DFS ☐ EMAIL ☐ MAIL ☐ HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

Linda D Mullins-Athey
12/14/2007 10:55:38 AM

October 15, 2007

GlaxoSmithKline
PO Box 13398
Five Moore Drive
Research Triangle Park
North Carolina 27709-3398

www.gsk.com

Russell G. Katz, M.D., Director
Division of Neurology Products
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: Pre-IND 077440; Lamictal ODT
Minutes of Meeting; Pre-NDA Meeting

Dear Dr. Katz:

Reference is made to our Pre-IND 77,440 for Lamictal® (lamotrigine) Orally Disintegrating Tablets (ODT) and to the October 1, 2007 Pre-NDA meeting that was held by teleconference with representatives of the Division of Neurology Products and the Division of Psychiatry Products. At this time, we are submitting minutes of that meeting as ATTACHMENT 1.

We wish to thank both Divisions for a productive meeting and we are targeting submission of the NDA for the end of November 2007. If there are any comments or questions regarding this submission please contact me at (919) 483-3627 or by email at eric.b.benson@gsk.com. Thank you.

Sincerely,

Eric B. Benson
Senior Director
US Regulatory Affairs

Trade secret and/or confidential commercial information contained in this submission is exempt from public disclosure to the full extent provided under law.

FDA Desk Copy (1): Dr. Jacqueline Ware, Division of Neurology Products

ATTACHMENT 1

GlaxoSmithKline Memo GlaxoSmithKline Telecon

Author: Eric B. Benson **Call Date:** 01-Oct-07

Pre-IND 077440; Lamictal ODT
General Teleconference: Other; Pre-NDA Meeting

Call From

Eric B. Benson, Senior Director, US Regulatory Affairs
Jonathan Bullman, Clinical Pharmacokineticist, Clinical Pharmacology and Discovery Medicine, Clinical Pharmacokinetics
Ruth Dixon, Director, Discovery Medicine, Clinical Pharmacology and Discovery Medicine
Sarah Job, Senior Statistician, Drug Development Sciences, Clinical Pharmacology Statistics & Programming
Kay Maltby, Clinical Research Program Manager, Clinical Pharmacology and Discovery Medicine, Clinical Science & Study Operations
Tom Thompson, Director, Clinical Development, Psychiatry
John Messenheimer, Senior Director, Clinical Development, Neurosciences
Julie Varner, Manager, US Regulatory Affairs
GlaxoSmithKline CMC
Kathleen Church, Asst. Director, Global CMC Regulatory Affairs
Simon Summers, Team Manager, Pharmaceutical Development
Alison Potts, Principal Scientist, Pharmaceutical Development
Paul Coleman, Principal Scientist, Pharmaceutical Development
Eurand, Inc. – CMC
Bhanu Balasubramaniam, Manager, Regulatory Affairs
Jin Wang Lai, Director, Formulations and Process Development
Mike Markham, Assistant Director, Analytical R&D
Phil Stevens, Formulation Scientist, Formulations

Call To

Russell G. Katz, Director, Division of Neurology Products (DNP)
Tom Laughren, Director, Division of Psychiatry Products (DPP)
Jaqueline Ware, Project Manager, DNP
Mitchell Mathis, DPP Deputy Director
Ni Aye Khin, DPP Clinical Team Leader
John Feeney, DNP Clinical Team Leader
Gwen Thornberg, DPP Acting Clinical Team Leader
Cara Alfaro, DPP Medical Reviewer
Danita Tandon, Reviewer, Office of Clinical Pharmacology
Mark Hyman, Pharmaceutical Assessment Lead, ONDQA
Wendy Wilson, ONDQA Chemistry Reviewer
Tina Kasliwal, Pharmacy Student
Mona Patel, Pharmacy Student

Description of Conversation

BACKGROUND:

Representatives of GSK and Eurand met via teleconference with the representatives of the FDA's Division of Neurology Products (DNP) and Division of Psychiatry Products (DPP) from 10:05 to 10:45 AM on Monday October 1, 2007 to agree the format and content of the NDA for Lamictal® (lamotrigine) Orally Disintegrating Tablets (ODT). The basis for approval of the NDA will be demonstrated bioequivalence with Lamictal Tablets that are approved for use in the treatment of epilepsy and as maintenance treatment of patients with Bipolar I disorder.

In preparation for the meeting, a Briefing Document that included detailed proposals for the format and content of the NDA, preliminary data from the pivotal bioequivalence study and questions for the FDA was submitted to the Division of Neurology under Pre-IND #077440 on August 29, 2007. The FDA review team provided preliminary responses to GSK in an email dated September 26, 2007.

PRE-NDA MEETING

After introductions, it was agreed that the meeting would use the FDA's September 26 document as a basis for discussion and that GSK/Eurand would seek clarification regarding the FDA's preliminary responses as necessary. The questions were organized into Clinical, CMC and Administrative categories. The GSK questions are restated below followed by the FDA's preliminary comments followed in turn by a summary of additional discussion at the Pre-NDA meeting when this occurred.

Clinical Questions

GSK Question 1. The NDA will include final clinical study reports for the following two clinical studies; the pilot BA/BE study, LBI108614 and the "pivotal" BA/BE study, LBI108617. Does the Agency concur with this proposal?

FDA Preliminary Response:

We concur that these are the relevant final clinical study reports to be included in the NDA.

Discussion at Pre-NDA meeting:

GSK stated that no further discussion regarding this and the following clinical question is necessary.

GSK Question 2. Does the Agency concur with the proposal to include a Module 2.7.1 but in the spirit of ICH, our proposal to NOT provide the Clinical Pharmacology and Biopharmaceutics Review Aid as an Appendix to 2.7.1?

FDA Preliminary Response:

We concur.

Administrative Questions

GSK Question 1. Does the Agency grant a waiver for the conduct of pediatric studies with this formulation?

FDA Preliminary Response:
Given that the Lamictal ODT is likely to be used for some patients in the pediatric age range, a deferral of pediatric studies rather than a waiver will be granted. Of particular note, a study of Lamictal ODT in bipolar patients ages 10-17 years will be needed.

Discussion at Pre-NDA meeting:
GSK stated its concerns with the potential requirement for pediatric studies. Dr. Messenheimer pointed out that for epilepsy, the CD tablet had been studied extensively in pediatric patients and was approved for adjunctive use in partial seizures down to age 2. In addition, an adjunctive study has also been carried out in infants as young as one month of age demonstrating excellent acceptance of this formulation in this age group. As noted in the briefing document, pediatric dosing below the age of 13 requires the use of 2, 5 and 25 mg CD tablets to achieve accurate mg/kg dosing necessary in this age group. In most cases this requires the administration of multiple 2, 5 or 25 mg tablets to achieve the correct dose. Despite the need for multiple tablets the use of the CD formulation permits administration of the required dose by a single administration in liquid. The ODT formulation is bioequivalent with immediate-release Lamictal. Even if lower ODT tablet doses were made available, dosing in this age group would require the administration of multiple tablets at once. The ODT tablet would not provide any benefit over the CD tablet in this age group. Dr. Messenheimer noted ethical concerns regarding the performance of a clinical trial in this age group using an ODT formulation that is bioequivalent to the Lamictal compressed tablet that has already been tested extensively. Moreover, there are ethical concerns with repeating any placebo controlled studies that were a basis for approval with a bioequivalent formulation. Dr. Katz recommended that GSK present our rationale for waiver in the NDA and that it would be a matter of review. He pointed out that if some younger patients may benefit from the ODT formulation it may be necessary for GSK to develop dose strengths lower than 25mg.

With respect to the FDA's preliminary comment requiring a study in pediatric patients 10 to 17 years of age with bipolar disorder, Dr. Thompson noted that GSK was in the process of initiating a study of Lamictal compressed tablets in adolescents 13 to 17 years of age in order to fulfill the FDA's previous request for a study with the compressed tablets. He pointed out that in June 7, 2007 correspondence the Psychiatry Division agreed to the lower age limit of 13 for this study and questioned the lower age limit of 10 years. A brief discussion regarding the rationale of the lower age limit ensued. Dr. Laughren stated that the Psychiatry Division has determined in consultation with experts in the field that bipolar pediatric studies should be conducted in patients 10 to 17 years of age and this is the age limit that has been specified in its Pediatric Written Requests to other sponsors. He was surprised to learn that the Division had recently concurred with a lower age limit of 13 years. Dr. Laughren acknowledged that it would not be

appropriate to repeat the study with a bioequivalent formulation and it was agreed that GSK would follow up with the Psychiatry Division to agree the design of a single study to assess the efficacy of Lamictal in pediatric bipolar disorder.

GSK Question 2. The NDA will be submitted in eCTD format according to the April 2006 "Guidance for Industry: Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications". Does the Division agree that this format is acceptable?

FDA Preliminary Response:

We agree, but you should also contact the Office of Business Process Support (OBPS) directly to confirm the acceptability of this proposal.

Discussion at Pre-NDA meeting:
GSK indicated that it would contact OBPS to address this and the other electronic CTD formatting questions where OBPS consultation is recommended.

GSK Question 3. The specifications and file formats that we propose to use will be described in the Briefing Document. These items are fully consistent with FDA's guidance document. Does the Division agree that these specifications and file formats are acceptable for this NDA?

FDA Preliminary Response:

We agree, but you should also contact OBPS directly to confirm the acceptability of this proposal.

GSK Question 4. Does the Division concur with our proposal to submit all required datasets in the 1999 standard structure, rather than the standard Study Data Tabulation Model (SDTM) structure?

FDA Preliminary Response:

We defer response to this question to OBPS. Please contact OBPS directly to confirm the acceptability of this proposal.

GSK Question 5. Regarding information previously submitted to NDA 20-241 and incorporated by cross reference, it is our understanding from the April 2006 "Guidance for Industry: Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications", Section G, page 5, that this cross-referencing approach would be acceptable. Does the Agency concur?

FDA Preliminary Response:

We agree, but you should also contact OBPS directly to confirm the acceptability of this proposal.

GSK Question 6. Does the Division concur with our proposal to continue existing expedited safety reporting processes after NDA submission with subsequent submission to the eCTD?

FDA Preliminary Response:
Existing expedited safety reporting processes regarding Lamictal products must continue as previously required by the Division. Periodic reports of dispensing errors and liver cases should also continue.

GSK Question 7. Does the Division concur with the proposal for inclusion of case report forms and narratives for all patients in the clinical studies reported in the NDA who died or discontinued due to an adverse event or experienced a serious adverse event?

FDA Preliminary Response:
We concur with this proposal.

GSK Question 8. Is there any additional information that can be provided to facilitate the Division's review in order to help achieve approval of this single bioequivalence study based NDA at the 10-month action date?

FDA Preliminary Response:
Please provide the following information in the Biopharmaceutics summary with hyperlinks to the CMC section:

- *Dissolution (in multiple media) and composition comparisons of all strengths to justify biowaiver of lower strengths.*
- *In vitro and in vivo disintegration times.*

Discussion at Pre-NDA meeting:
Ms. Church stated that hyperlinks to the CMC section within the GSK NDA will not be possible as this information does not reside in GSK's CMC section. As noted previously, only sections P3.1 and P7 will be included in the GSK's CMC section and all other CMC information will be located in Eurand's DMF. She further stated that the dissolution in multiple media and the composition comparison of all strengths (which is Eurands proprietary information) will be provided in a Section 2.7.1 in Eurands DMF. The reviewer indicated that this approach was acceptable and to provide two desk copies of Eurand's module 2.7.1 to Dr. Jacqueline Ware at the Silver Spring address in addition to the one desk copy of the entire DMF.

The in vitro disintegration times will also be presented in the Eurand DMF and are (b) (4) (b) (4) as specified in the April 2007 Draft Guidance for Orally Disintegrating Tablets. GSK expressed surprise regarding the request for **in vivo** disintegration times and pointed out that the protocols for both the pilot and the pivotal biostudies that will be included in the NDA did not specify collection of these data. Despite this, the CRO conducting the pilot study did collect some in vivo disintegration data on their own volition that will now be presented in the Biopharm summary as requested. The

reviewer indicated she was interested in seeing any in vivo data that was collected but the agency has no particular expectations regarding these data.

CMC Questions

GSK Question 1. The lamotrigine microcap (b) (4) (which may be stored for up to 6 months) is (b) (4) (b) (4) We have 6 months holding time (stability) data on the microcaps stored in warehouse conditions. Furthermore, in support of this, we intend to process one of the aged microcap batches into tablets and include the release data as part of the NDA. Does the Agency agree with the proposal?

FDA Preliminary Response:
In addition to the release data, provide stability data for the aged microcap tablet batches. Your justification should demonstrate that the drug product stability is the same, irrespective of the age of the microcap batch used. The final determination of the basis for the date of manufacture will be data driven and determined during the review.

Discussion at Pre-NDA meeting:
Ms. Balasubramaniam from Eurand stated that only release data will be available at the time of submission for the tablet batches manufactured with the aged microcap (b) (4). However, 3 months accelerated data would be available at the time Eurand provides a stability update on the NDA stability batches during review and therefore would like to propose submitting stability data on the tablet batches manufactured with the aged microcap (b) (4) at this time as well. Dr. Wilson responded that they are not agreeable with this approach and they expect both release and stability data at the time of submission, not during review.

In regard to the FDA's preliminary response on providing a justification that should demonstrate that the drug product stability is the same irrespective of the age of the microcap batch used, Ms. Balasubramaniam stated that Eurand will present data that compares 3 months of accelerated stability data for tablet batches using the aged microcap versus tablet batches that did not use the aged microcap. Dr. Wilson stated that a comparison at accelerated conditions would not be acceptable. She stated that they expect to see a comparison at the long-term condition. Ms. Balasubramaniam asked how much long-term data would be acceptable and Dr. Wilson responded that they would want sufficient long-term stability to support the proposed expiry.

(b) (4)

(b) (4)

Furthermore, Ms. Balasubramaniam acknowledged that the final determination for the date of manufacture will be data driven and determined during the review.

GSK Question 2. Magnesium stearate and polyethylene are considered processing aids and are present in trace amounts in the tablets. Does the Agency agree that these can be omitted from the inactive ingredient listing in the prescribing information (PI)?

FDA Preliminary Response:
It is our expectation that all inactive ingredients will be included in the prescribing information. You may provide justification for omitting this information in the NDA, including actual content levels for magnesium stearate and polyethylene in the final drug product. The final decision will be based on the merit of your proposal and the data submitted to support your position.

Discussion at Pre-NDA meeting:
Ms. Balasubramaniam agreed that Eurand will provide a justification for omitting this information from the prescribing information in their DMF.

As a point of clarification, she noted that the actual content levels for PE are tested on the microcap (b) (4) and not the final drug product. However, Eurand can provide a *calculated* amount of PE in the final drug product for the NDA stability batches based on the amount of actual PE content in the microcap and the tablet strength. Dr. Wilson responded that this was acceptable.

GSK Question 3. Since Magnesium stearate, polyethylene, (b) (4) (b) (4) are processing aids, we propose to include CMC information on these four components as part of P2 (Pharmaceutical Development) as opposed to P.4 (Control of Excipients). Does the Agency agree with this proposal?

FDA Preliminary Response:
It is our expectation that the CMC information for all inactive ingredients, including processing aids, will be provided in Section P4 Control of Excipients.

Discussion at Pre-NDA meeting:
Ms. Balasubramaniam agreed to provide this information in section P4 of Eurand's DMF.

GSK Question 4. In this pre-NDA briefing package we have prepared a justification to support the use of Polyethylene (b) (4) as a processing aid in the manufacture of Lamictal ODT. Does the Agency agree that the continued use of polyethylene is acceptable based on the information and justification provided?

FDA Preliminary Response:
The use of polyethylene appears reasonable. However, this is a review issue. Provide data on the residual amounts of polyethylene in the final drug product and provide a

comparison of these levels to the allowable polyethylene amounts in food products. The final decision will be based on the merit of your proposal.

Discussion at Pre-NDA meeting:
Ms. Balasubramaniam agreed to provide data on the *calculated* amounts of residual PE in the final drug product and provide a comparison to the allowable PE amounts in food products. Dr. Wilson stated that this was acceptable.

GSK Question 5. The proposed specification tests are suitable to control the quality of Lamictal ODT Tablets for commercial supply, including the proposal for no drug-related impurities testing at release. Does the Agency agree with this proposal?

FDA Preliminary Response:
The proposed specifications, with the exception of drug related impurities appear reasonable. Due to the potential for formulation or manufacturing specific impurities as well as the limited commercial experience manufacturing the drug product, we advise you to include drug related impurities at release. We would like to remind you that in accordance with 21 CFR 206.10, unique identifiers are needed for each tablet strength. The final drug product description should reflect the unique identification for each tablet strength. Because this is an ODT formulation and the final drug product is not coated, we recommend including friability testing at release and during stability.

Discussion at Pre-NDA meeting:
Ms. Balasubramaniam agreed to provide drug product related impurities testing at release. In addition, in regards to the tablets needing a unique identifier, she stated that this was raised at the End of Phase II meeting on April 26, 2007 and confirmed that Eurand would uniquely identify the commercial tablets indicating strength.

Furthermore, she stated that a discussion on conducting friability testing at release and during stability was discussed at the End of Phase II meeting as well. At that meeting she described that friability testing was performed as an in-process test as part of every tabletting run. It was noted that throughout the tabletting run at suitable intervals, samples are tested for friability. Therefore, Eurand believes that this provides a more accurate representation of the entire run and is more predictive since multiple samples are tested as opposed to when it is done simply as part of end product testing wherein a single composite sample is taken. At the End of Phase II meeting, the agency agreed that in-process testing only is suitable. Ms. Balasubramaniam asked if the Agency was still in agreement with this approach and Dr. Wilson stated that this was sufficient and Eurand can continue to conduct friability testing during in-process only.

Ms. Balasubramaniam also stated that friability testing is being conducted on the NDA stability batches and that six months worth of stability data which will include friability testing will be provided in Eurand's DMF. In addition, Eurand will also include any available friability data on stability on the pilot batches as well. She stated that based on this data, Eurand will justify not performing friability on an annual basis in the NDA. Dr. Wilson agreed that providing a justification in the NDA was acceptable.

GSK Question 6. The Agency's official End of Phase II meeting minutes dated May 10, 2007 states that our proposal to submit 6 months stability data at the time of submission and to update with 9 months during review was acceptable. Does the Agency further agree with our proposal to submit the stability update and statistical package, if applicable within 6 months of the NDA submission date without impacting the NDA review time?

FDA Preliminary Response:
Stability updates received within 5 months of the original NDA submission will be reviewed in the first cycle. We cannot guarantee first cycle review of stability updates received after the 5 month time point. The expiry determination will be data driven and will be determined during the review.

Additionally, does the Agency agree with our proposal to include the 6 month data on the (b) (4) samples as a separate amendment to the DMF that would be submitted within one month of the initial DMF amendment submission to support GSK's NDA?

FDA Preliminary Response:
We have no objections at this time.

Discussion at Pre-NDA meeting:
Ms. Balasubramaniam agreed that Eurand will provide updated information within the timeframes provided.

GSK Question 7. The CMC section of GSKs NDA will provide a cross-reference for drug substance information to approved NDA 20-241 (LAMICTAL (lamotrigine) Tablets). In addition, CMC information on the drug product will be provided in module 3, sections P.3 (manufacturers) and P.7 (container/closure) only. All other drug product information will be cross-referenced to Eurand's DMF. Does the Agency agree with this proposal?

FDA Preliminary Response:
In your NDA submission, identify the manufacturing and testing sites for both the drug substance and drug product. Include the specification and a summary of justification of specification for both the drug substance and drug product. Provide CoA results for the drug substance batches used to manufacture the NDA stability batches as well as the NDA stability drug product batches.

Discussion at Pre-NDA meeting:
Ms. Church from GSK agreed to provide the CoAs for the drug substance batches used to manufacture the NDA stability batches as well as the CoAs for the NDA stability drug product batches in GSK's NDA.

She stated however that in regards to the FDA's request for drug substance information, that in order to not duplicate existing approved information and to provide the FDA with the most current information on the Lamictal drug substance, that GSK prefers to provide a cross-reference to NDA 20-241 and all associated supplements which is in alignment

with the cross-reference provided for the recent Lamictal XR NDA. Dr. Wilson stated that this was not acceptable and she requested that GSK provide the drug substance information in our NDA. She stated that this is important for the fields to have the information available to them in a standalone document.

Ms. Church stated that in regards to the FDA's request to provide manufacturing and testing sites for the drug product, that GSK agreed that this will be provided in GSK's NDA. However, she stated that the drug product specification and justification of specification will be located in Eurand's DMF since they are the owner of this information. GSK would prefer not to duplicate any of Eurand's information provided in their DMF in our NDA. Dr. Wilson stated that they disagreed to this approach and stated that they needed the information in GSKs NDA for the drug product as well.

GSK Question 8. GSK's NDA will be submitted as an eCTD via the electronic gateway whereas Eurand's DMF will be submitted in CTD format via paper. GSK intends to submit the NDA electronically shortly (1-2 days) after Eurand's DMF is submitted via paper. GSK would like to confirm that this timing is acceptable to the Agency given the possibility that the NDA might arrive and become available to reviewers prior to Eurand's DMF?

FDA Preliminary Response:
We recommend that you confirm that the amendment has been delivered to the Agency before submitting your NDA submission.

Discussion at Pre-NDA meeting:
Ms. Balasubramaniam stated that Eurand planned on delivering their DMF by Fed Ex and asked if confirmation of delivery by FedEx prior to submitting the GSK NDA via the gateway was acceptable. Dr. Wilson stated that this was acceptable.

GSK Question 9. Eurand will submit one field copy of the DMF containing the drug product information to both the Cincinnati and Atlanta field offices. Likewise, GSK will submit a field copy letter to both the Cincinnati and Atlanta offices. Does the Agency agree with this proposal?

FDA Preliminary Response:
We have no objection at this time.

Discussion at Pre-NDA meeting:
Agreed, no further discussion at the meeting.

GSK Question 10. All analytical methods related to the drug product will be provided in Eurand's DMF. Please advise on how we should provide a methods validation package.

FDA Preliminary Response:
We cannot conduct an analytical methods validation based on a DMF submission. Submit a methods validation package as part of your NDA submission.

Discussion at Pre-NDA meeting:
Ms. Church stated that none of the information used to build a method validation package will be included in GSK's NDA and that as noted previously, only sections P.3.1 and P7 will be in GSKs NDA. All other CMC information will be located within Eurand's DMF. She requested that rather than extracting information from Eurand's DMF and generating the methods validation package electronically in GSK' NDA, if the Agency was agreeable that GSK hold back the package and provide it upon request by the labs. Dr. Wilson stated this was not acceptable and GSK needs to include the method validation package in their NDA.

Ms. Church then proposed if it was acceptable to extract information from Eurand's DMF as pdf files and provide electronically in GSKs NDA without also duplicating in a section P5 which currently doesn't' exist in GSKs CMC section. Dr. Wilson agreed that this was acceptable however she requested that GSK include a section P5 which links to the method validation package.

GSK Question 11. Eurand intends to provide one desk copy of the DMF amendment as a review copy. Is this acceptable to the Agency?

FDA Preliminary Response:
We have no objections at this time. We advise you to include a statement with the desk copy certifying that the information included in the desk copy is the same as the information submitted in the DMF amendment.

Discussion at Pre-NDA meeting:
Ms. Balasubramaniam agreed that Eurand will include the statement as suggested.

GSK Question 12. Eurand's DMF will include one representative executed batch record for the lamotrigine microcap (b) (4), the blend, and for each tablet strength manufactured for NDA stability purposes. All batch records will be available on site for review during an inspection. Does the Agency agree with this proposal?

FDA Preliminary Response:
Since the drug product is dose-proportional and all tablet strengths are compressed from one common blend, we recommend submitting one representative executed batch record that reflects the commercial manufacturing process from the initial process step through packaging and labelling. The choice of tablet strength represented is the executed batch record is at your discretion.

Discussion at Pre-NDA meeting:
Ms. Balasubramaniam stated that the executed batch record will reflect the commercial manufacturing process, however it does not include the debossing step. This step will be provided in the blank Master Batch Record provided in Eurand's DMF. Dr. Wilson stated that this was acceptable and confirmed that they want the packaging and labeling batch records as well.

Additional FDA CMC Comment: In an effort to facilitate dissolution specification determination, we recommend that you provide the individual dissolution results for 12 tablets in addition to the mean and range values. We also recommend that you provide separate result tables for the biobatches and the NDA stability batches. The determination of the dissolution specification will be determined as part of the NDA review and will be data driven.

Discussion at Pre-NDA meeting:

Ms. Balasubramaniam agreed that Eurand would provide the individual dissolution results as recommended. As a point of clarification she stated that the biobatch is the same as one of the 200mg NDA stability batches and therefore separate result tables will not be provided. Dr. Wilson acknowledged this and agreed.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 76,557

GlaxoSmithKline
Attention: Maria Wagner, Ph.D.
Senior Director, Psychiatry and Neurology
P.O. Box 13398
Five Moore Drive
Research Triangle Park, North Carolina 27709-3398

Dear Dr. Wagner:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (lamotrigine) orally disintegrating tablets.

We also refer to the teleconference between representatives of your firm, Eurand, and the FDA on April 26, 2007. The purpose of the meeting was to provide division feedback on the development program for this formulation of lamotrigine.

The official minutes of the meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Doris J. Bates, Ph.D., Regulatory Project Manager, at (301) 796-2260, or email her at doris.bates@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Thomas P. Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

Meeting Minutes
IND 76,557 Lamotrigine ODT-- Bipolar Disorder
GlaxoSmithKline (GSK) / Eurand
Type B [End of Phase 2] Meeting
PreMeeting April 12, 2007; Teleconference with Firm April 26, 2007

Participants –
FDA: April 12, 2007:
T. Laughren, M.D., Division Director, DPP
M. Mathis, M.D., Deputy Director; DPP
N. Khin, M.D., Clinical Team Leader; DPP
C. Alfaro, Pharm.D., Clinical Reviewer; DPP
R. Baweja, Ph.D., Team Leader; Office of Clinical Pharmacology
K. Kumi, Ph.D., Reviewer; OCP
T. Oliver, Ph.D., Pharmaceutical Assessment Lead; Office of New Drug Quality Assessment
W. Wilson, Ph.D., Chemistry Reviewer; ONDQA
D. Bates, Ph.D., Regulatory Project Manager; DPP
S. Goldie, Regulatory Project Manager, ONDQA

FDA, April 26, 2007:
T. Laughren, M.D., Division Director, DPP
M. Mathis, M.D., Deputy Director; DPP
N. Khin, M.D., Clinical Team Leader; DPP
M. Mehta, Ph.D., Director, OCP Division I
R. Baweja, Ph.D., Team Leader; OCP
T. Oliver, Ph.D., Pharmaceutical Assessment Lead; ONDQA
W. Wilson, Ph.D., Chemistry Reviewer; ONDQA
D. Bates, Ph.D., Regulatory Project Manager; DPP
S. Goldie, Regulatory Project Manager, ONDQA

GSK, April 26, 2007:
J. Bullman, Clinical Pharmacokineticist, Clinical Pharmacology and Discovery Medicine, Clinical Pharmacokinetics
R. Dixon M.D., Director, Discovery Medicine, Clinical Pharmacology and Discovery Medicine
S. Job, Senior Statistician, Drug Development Sciences, Clinical Pharmacology Statistics & Programming
K. Maltby, Clinical Research Program Manager, Clinical Pharmacology and Discovery Medicine, Clinical Science & Study Operations
M. Wagner, Ph.D., Senior Director, Regulatory Affairs
S. Watson, Director, Global CMC Regulatory Affairs
K. Church, Manager, Global CMC Regulatory Affairs
S. Summers, Team Manager, Pharmaceutical Development
A. Potts, Ph.D., Principal Scientist, Product Development
P. Coleman, Principal Scientist, Product Development

Eurand, April 26, 2007:
B. Balasubramaniam, Regulatory Affairs Manager
J. Wang Lai, Ph.D., Director Formulations and Process Development
M. Markham, Assistant Director, Analytical R&D
M. Gosselin, Ph.D., Formulation Scientist II

Background: Lamotrigine has been approved in the US as Lamictal Tablets [NDA 20-241, December 1994] and Lamictal Chewable Dispersible Tablets {NDA 20-764].

Approved neurological indications are: partial seizures (adjunctive therapy, adults); Lennox-Gastaut Syndrome (generalized seizures, adjunctive therapy, pediatric); monotherapy in adults receiving therapy with a single enzyme-inducing antiepileptic drug; adjunctive treatment for partial seizures (pediatric); conversion to monotherapy from valproate in adults with partial seizures, and primary generalized tonic-clonic seizures in both adult and pediatric patients.

The currently approved psychiatric indication is long-term treatment of mood episodes in bipolar I disorder; lamotrigine is not currently approved for the acute treatment of bipolar disorder, whether manic, mixed, or depressed.

IND 76,557 was submitted November 15, 2006. This IND provides for an orally disintegrating tablet formulation of lamotrigine. Eurand is the contract manufacturer for the dosage form development program. The intended market strengths are 25, 50, 100 and 200 mg tablets.

The purpose of this meeting is to obtain division feedback on the sponsor's development program for the ODT formulation of this drug.

Questions:

Clinical.

Question 1. Would the Division accept the data from a single study that is designed to evaluate bioavailability, bioequivalence, the effect of administration with food and with water as being adequate to support the approval of lamotrigine formulated as an orally disintegrating tablet (ODT), with the reference standard being the currently marketed immediate-release compressed tablet? (*Clinical information in support of Question 1 can be found in Section 8.1, Proposed Study Design for LBI108617 [protocol in Attachment 1]*, with supporting data summarized in *Section 7, Preliminary Data from Pilot Pharmacokinetic Study: LBI108614).*

> All relevant nonclinical and clinical safety and efficacy data from approved NDA 20-241 (immediate-release compressed tablet formulation; serving as the reference standard) and approved NDA 20-764 (chewable dispersible tablet formulation; previously shown as being bioequivalent to the compressed tablet formulation) would be incorporated by reference.

Information related to drug substance would be incorporated by reference to the approved NDAs for LAMICTAL, and information relevant to drug product would be provided by Eurand Inc., the developer of the ODT formulation and holder of Type II DMF #19909.

Preliminary Comments: Yes.

Safety and efficacy of the drug have been established in the bipolar indication with approval of Lamictal Tablets for the long-term treatment of mood episodes in bipolar I disorder. Therefore, this Division would accept data from a single study as described to support a new NDA for the ODT formulation in this indication. With regard to the indications approved in the Division of Neurology Products, an IND should be opened for the ODT formulation to allow for submission of any adverse event information to that Division as well as to DPP. Any plans for submission of an NDA for the neurology indications should be discussed with DNP.

Discussion at Meeting: No further discussion.

Question 2. Does the Division concur with the proposal for a parallel-group design? (*Clinical information in support of Question 2 can be found in Section 8.1, Proposed Study Design for LBI108617 [protocol in Attachment 1*])

Preliminary Comments: Yes. A parallel group design is acceptable.

Discussion at Meeting: No further discussion.

Question 3. Does the Division concur with the evaluation of the 25mg and 200mg strength of tablets? (*Clinical information in support of Question 3 can be found in Section 8.1, Proposed Study Design for LBI108617; [protocol in Attachment 1*]

Preliminary Comments: Yes. You can evaluate the 200 mg strength in the proposed study. Since the 25 mg strength is compositionally proportional to the 200 mg strength, (as are the 50 mg and 100 mg ODT tablet strengths), and, as all strengths are manufactured from one common blend, you can eliminate the two treatment arms of the 25 mg dose (viz., ODT and IR) in the study.

Discussion at Meeting: The sponsor mentioned that they would like to keep the two treatment arms of 25 mg in the study because their program may also be submitted to the Division of Neurology. OCP explained that even if their program were to be submitted to Neurology, from an OCP perspective the same reasoning as provided for here for the elimination of the two treatment arms of the 25 mg dose, would apply. The sponsor said that the feedback was helpful and that they would take it into consideration.

Question 4. Does the Division concur with the evaluation of the effect of food at one dose strength (i.e., 200mg)? (*Clinical information in support of Question 4 can be found in Section 8.1, Proposed Study Design for LBI108617; [protocol in Attachment 1*])

Preliminary Comments: Yes.

Discussion at Meeting: No further discussion.

Question 5. Does the Division concur with the evaluation of the effect of administration with water at one dose strength (i.e., 200mg)? (*Clinical information in support of Question 5 can be found in Section 8.1, Proposed Study Design for LBI108617; [protocol in Attachment 1*])

Preliminary Comments: Yes.

Discussion at Meeting: No further discussion.

Question 6. Does the Division agree with proposed analysis to determine the definitive bioavailability, bioequivalence, the effect of administration with food and the effect of administration with water on the bioavailability for lamotrigine formulated as an ODT? (*Clinical information in support of Question 6 can be found in Section 8.2, Proposed Analysis for LBI108617; [protocol in Attachment 1*])

Preliminary Comments: Analysis of the study results is a matter of review.

Discussion at Meeting: No further discussion.

Chemistry, Manufacturing and Controls - Drug Product

Information specific to CMC-related questions can be found in Eurand's amended DMF#19909; amendment submitted 7 March 2007, under separate cover, by Eurand Inc.

Question 7. The specification tests are suitable to control the quality of LAMICTAL ODT Tablets for the pivotal study, NDA stability and support of the commercial product. Does the Division agree? (*CMC information in support of Question 7 can be found in Eurand's DMF#19909 Section II.3.1 and II.3.2*)

Preliminary Comments: Friability testing should be added as part of your release testing. The moisture specification limits will need to be justified in your NDA submission. It should be noted that your tablets need to be uniquely identified or an exemption provided (21 CFR 206). Actual disintegration times (b) (4) will need to be submitted in the NDA. Justification of the residual polyethylene limit for Lamotrigine Microcaps should be included in your NDA. Ultimately, the adequacy of the specification limits will be determined as part of the review.

Discussion at Meeting:
The actual disintegration times should be reported instead of (b) (4). The sponsor indicated that their intention was to report the times as (b) (4). FDA stated that sponsors are asked to report the actual data as a way of observing trends. We mentioned

we may be open to having the data reported in "tiers" (e.g., 0-5 secs), but the sponsor would need to make an argument for the need to report data in that fashion. The sponsor should ensure that the polyethylene used meets the current CFR standards. In addition, we asked for justification of the residual polyethylene limit in Lamotrigine Microcaps.

Question 8. The dissolution method and specification are suitable for the pivotal study, NDA stability, and support of commercial product of LAMICTAL ODT. Does the Division agree? *(CMC information in support of Question 8 can be found in Eurand's DMF#19909 Section II.3.3)*

Preliminary Comments: The dissolution profiles (for release and stability) and supportive information on the development of the dissolution method (e.g., speed and medium) should be submitted as part of the NDA. The adequacy of the dissolution method and determination of the specification limit will be part of the review.

Discussion at Meeting:
We recommend that data be collected at multiple time points for dissolution at release and on stability to better assess the dissolution behavior of the drug product. We reserve final judgment of the adequacy of the dissolution method and the determination of the specification limit until the review of the NDA.

Question 9. The proposed drug product stability protocol for long-term, accelerated, and stress testing is sufficient to support the NDA. Does the Division agree? *(CMC information in support of Question 9 can be found in Eurand's DMF#19909 Section II.5)*

Preliminary Comments: This question will need to be discussed further at the meeting. Friability testing should be added as part of your stability testing. The moisture specification limit will need to be justified in your NDA submission.

Discussion at Meeting:
Reference was made to Appendix I, page 3. The stability protocol (25^{o}C/60%RH Lamictal ODT) appears adequate for the 25 mg [(b) (4) bottle & blisters (left column)] and the 200 mg [(b) (4) bottles and blisters (right column). However, there is not enough coverage for the 50 mg and 100 mg strengths as currently proposed. Currently, there is no blister representation and no justification for why there is no 30 ct representation. FDA agreed that the stability protocol issues could be revisited in a "Special Protocol-Stability" submission.

Question 10. The drug product NDA stability batches consist of (b) (4) (lamotrigine Microcaps® and lamotrigine ODT blend) that are each manufactured at commercial scale, at the commercial site, according to the commercial process. The drug product NDA stability batches are subsequently tabletted at least at (b) (4) commercial scale, at the commercial site, according the commercial process. *(CMC information in support of Question 10 can be found in Eurand's DMF#19909 Section II.5)*

a.) Does the Division accept the proposal to submit the NDA with 6-month stability data on these three drug product batches with a 9-month update during review with no impact on the review clock, in support of an 18-month shelf life?

Preliminary Comments: This question will need to be discussed further at the meeting. Your proposal to submit 6 months of stability data at the time of submission is accepted (for tablets currently described in the briefing package). It should be noted that stability updates received within 6 months of the original NDA submission will be reviewed in the first cycle. We cannot guarantee first cycle review of stability updates received after that 6 month time point. An excipient compatibility study should be performed to support stability and the data submitted as part of your NDA. The expiry determination will be data driven and will be determined during the review.

Discussion at Meeting:
The sponsor indicated that the commercial tablets would be debossed. FDA stated that the primary stability batches would be considered to be the commercially manufactured product. The stability generated with the non debossed tablets would be supportive data. Release data (CoA) from one batch of each commercial tablet strength will need to be submitted in the NDA (preferably at the time of submission). The sponsor should clearly highlight how the drug product used to generate the supportive stability data differs from the proposed commercial product. The expiry determination will be data driven and will be determined during the review.

b.) Following NDA approval, ongoing stability data from these drug product NDA stability batches will be reported in the Annual Report. Does the Division agree that real-time data from these drug-product NDA stability batches may be used to extend the shelf life as provided for in 21 CFR 314.70(d)(5)?

Preliminary Comments: This question will need to be discussed further at the meeting.

Discussion at Meeting:
This issue should be revisited as part of the NDA review. The sponsor will need to place one batch of each strength (commercial drug product) on stability according to the proposed protocol (refer to 10c).

c.) Does the Division accept the proposal that three additional production batches will not be placed on stability post-approval (a stability commitment to test one production batch each year that the product is manufactured post-approval will be stated in the NDA)?

Preliminary Comments: This question will need to be discussed further at the meeting.

Discussion at Meeting:
In addition to the stability batches outlined in the briefing documents, one batch of each strength (commercial drug product) will need to be placed on stability according to the agreed protocol.

Additional Comment: **DPP strongly recommends prior consultation with the Division of Neurology Products regarding the establishment of an IND for this dosage form if approval in any neurological indication is likely to be sought.**

DPP does not have authority to address neurological indications, and there are issues relevant to clinical safety/adverse event reporting, the Pediatric Research Equity Act, and User Fees which should be clarified well in advance of any planned NDA submission to either Division.

Conclusions:
Minutes will be provided to the sponsor. These minutes are the official minutes of the meeting. The sponsor is responsible for notifying FDA of any significant differences in understanding they have regarding the meeting outcomes.

Doris J. Bates, Ph.D.
Regulatory Project Manager

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

/s/

Thomas Laughren
5/10/2007 02:19:11 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-251

Proprietary Name: Lamictal Orally Disintegrating Tablets
Established Name: lamotrigine
Strengths: 25mg, 50mg, 100mg, and 200mg

Applicant: SmithKline Beecham (d/b/a GlaxoSmithKline)
Agent for Applicant (if applicable): n/a

Date of Application: 11/28/07
Date of Receipt: 11/28/07
Date clock started after UN: n/1
Date of Filing Meeting:
Filing Date: 1/18/08
Action Goal Date (optional): User Fee Goal Date: 9/28/08

Indication(s) requested: same as that for already approved lamotrigine products (Lamictal Tablets/N20-241 & Lamictal Chewable Dispersible Tablets/N20-764)

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. 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). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☒ NO ☐
  If yes, explain: NDA 20-241 and NDA 20-764 carry 3 yr exclusivity for the primary generalized tonic clonic indication. Both NDAs also carry pediatric exclusivity.

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☒

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☒

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

  1. This application is a paper NDA YES ☐

  2. This application is an eNDA or combined paper + eNDA YES ☐
     This application is: All electronic ☐ Combined paper + eNDA ☐
     This application is in: NDA format ☐ CTD format ☐
     Combined NDA and CTD formats ☐

     Does the eNDA, follow the guidance?
     (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☐ NO ☐

     If an eNDA, all forms and certifications must be in paper and require a signature.

     If combined paper + eNDA, which parts of the application were submitted in electronic format?

     Additional comments:

  3. This application is an eCTD NDA. YES ☒
     If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒
NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) 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 . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
YES ☒ NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
(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.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☒ NO ☐

- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: All clinical and
IND 23,793 (lamotrigine tablets), IND 43,551 (lamotrigine dispersible tablets), IND 49,916 (lamotrigine for the treatment of bipolar disorder), IND 69,254 (lamotrigine extended-release tablets), IND 76,557 (lamotrigine orally disintegrating tablet), pre-IND 077440

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) 4/26/07 NO ☐

If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 10/1/07 NO ☐
  If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) 7/26/07 & 7/30/07 for CMC Stability NO ☐
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. 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 Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☐ NO ☒

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☒ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☒ YES ☐ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☒

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐

If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐
- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☒

ATTACHMENT

MEMO OF FILING MEETING

DATE: 1/18/08

NDA #: 22-251

DRUG NAMES: Lamictal ODT (lamotrigine) Orally Disintegrating Tablets

APPLICANT: GlaxoSmithKline

BACKGROUND:
The purpose of this New Drug Application is to seek approval of LAMICTAL ODT Orally Disintegrating Tablets (25mg, 50mg, 100mg and 200mg dose strengths). The application is based on the demonstration of bioequivalence between the currently marketed LAMICTAL Tablets and the LAMICTAL ODT Orally Disintegrating Tablets. The design of the pivotal bioequivalence study, Study LBI018617, was discussed and agreed with the Agency at the End-of Phase 2 meeting held on April 26, 2007 and the format and content of the NDA were agreed with the Agency at the Pre-NDA meeting that was held by teleconference on October 1, 2007.

ATTENDEES: J. Ware, R. Katz, N. Hershkowitz, M. Heimann, R. Uppoor, P. Sheridan

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	**Reviewer**
Medical:	Phil Sheridan
Pharmacology:	Ed Fisher
Chemistry:	Wendy Wilson
Biopharmaceutical:	Carol Noory
DSI:	C. T. Viswanathan
Regulatory Project Management:	Jackie Ware

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☐ NO ☒
  If no, explain: Only a bioequivalence study submitted.
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- 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?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☒ FILE ☐ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? ☒ NO ☐
  YES

PHARMACOLOGY/TOX N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☐

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Sterile product? YES ☐ NO ☒
  If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments: none

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☒ No filing issues have been identified.
- ☐ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. ☒ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Jacqueline H. Ware, Pharm.D.
Senior Regulatory Project Manager
Division of Neurology Products, Office of Drug Evaluation I

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

/s/

Jackie Ware
12/24/2008 08:29:45 AM
CSO

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 22251 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type: Type 3: new dosage form
Proprietary Name: Lamictal ODT Established/Proper Name: Lamotrigine Orally Disintegrating Tablets Dosage Form: ODT tablets		Applicant: SmithKline Beecham Corporation d/b/a Glaxo SmithKline Agent for Applicant (if applicable): Eric B Benson
RPM: Sulin Sun		Division: DNP

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) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ If no listed drug, check box and 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 Sept 28, 2008 (paid)	☐ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval, were promotional materials received? Note: For 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 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.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 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

Comments:

❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No n/A
• Press Office notified of action (by OEP)	☐ Yes ☐ No n/A
• 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.)*	☐ No ☐ Yes n/a If yes, NDA # and date exclusivity expires:
• (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.)*	☐ No ☐ Yes n/a If yes, NDA # and date exclusivity expires:
• (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.)*	☐ No ☐ Yes n/a If yes, NDA # and date exclusivity expires:
• 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 ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ 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.	21 CFR 314.50(i)(1)(*i*)(A) ☒ Verified n/a 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [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
• [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? ☐ Yes ☐ No 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)? ☐ Yes ☐ No 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? ☐ Yes ☐ No 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)? ☐ Yes ☐ No 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.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[3]	Yes
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
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s)
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.	Sept 25, 2009
• Original applicant-proposed labeling	May 8, 2009
• Example of class labeling, if applicable	

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

❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in ttrack-changes format.	March 2009
• Original applicant-proposed labeling	
• Example of class labeling, if applicable	
❖ 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	Sept 2008
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	July 2007
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM ☐ DMEPA ☒ DRISK March 25,2009 ☐ DDMAC ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	Dec 24, 2008
❖ 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 in on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☐ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: Ped Deferral request granted (ready for approval for use in adult before pediatric studies are completed • Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☐ Included
❖ 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)*	Included
❖ Internal memoranda, telecons, etc.	Included

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ 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)*	☐ N/A or no mtg Jan 18, 2008
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg Oct 1, 2007
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg April 26, 2007
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None Dec 7, 2008 & May 7, 2009
Division Director Summary Review *(indicate date for each review)*	☐ None
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None Dec 17, 2008
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)* see CTD review	Dec 3, 2008
• Clinical review(s) *(indicate date for each review)*	
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None Feb 03,2010
❖ 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)*	Nov 1, 2007
❖ 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
❖ 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)*	Feb. 3, 2010 March 25, 2009 Sept 26, 2008; March 16, 2009 Dec. 23, 2008 ☐ None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested Sept 8, 2008
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 ☒ None	

[5] Filing reviews should be filed with the discipline reviews.

❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None
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)*	☐ None ~~Dec 12, 2008~~ Aug. 28, 2008
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None Dec 12, 2008 & 1/17/08
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☐ None ~~Nov 12, 2008~~ Dec. 1, 2008
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 Sept 15, 2008
❖ 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 Sept 16, 2008
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None Sept 15, 2008 & Dec. 10, 2007
❖ 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)*	Feb 13, 2008
☐ 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)* See cmc review pg 28	Date completed: July 30, 2008 ☑ Acceptable ☐ Withhold recommendation
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed

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.