

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER:  
22-509**

**OTHER REVIEW(S)**

**NDA/BLA REGULATORY FILING REVIEW**  
(Including Memo of Filing Meeting)

<b>Application Information</b>		
NDA # 22509 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Lamictal XR Established/Proper Name: Lamotrigine Dosage Form: tablet Strengths: (b) (4) 300mg		
Applicant: Glaxo Smith Kline Agent for Applicant (if applicable):		
Date of Application: 3/31/09 Date of Receipt: 3/31/09 Date clock started after UN:		
PDUFA Goal Date: 1/31/10	Action Goal Date (if different):	
Filing Date: 5/20/09 Date of Filing Meeting: 5/20/09		
Chemical Classification: (1,2,3 etc.) (original NDAs only) 6		
Proposed Indication(s): Adjunctive treatment of Primary Generalized Tonic-Clonic Seizures (PGTC) seizures in subjects ≥13 years of age		
Type of Original NDA: AND (if applicable)	<input checked="" type="checkbox"/> 505(b)(1)	
Type of NDA Supplement:	<input type="checkbox"/> 505(b)(2)	
<b>Refer to Appendix A for further information.</b>	<input type="checkbox"/> 505(b)(1)	
	<input type="checkbox"/> 505(b)(2)	
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease Priority review voucher was submitted, review classification defaults to Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority	
	<input type="checkbox"/> Tropical disease Priority review voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>		
Resubmission after refuse to file? <input type="checkbox"/>		
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR	

601.42)	
Collaborative Review Division (if OTC product):	
List referenced IND Number(s): 69254	
PDUFA and Action Goal dates correct in tracking system?  <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
Are all classification codes/flags (e.g. orphan, OTC drug, pediatric data) entered into tracking system?  <i>If not, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Application Integrity Policy</b>	
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ora/compliance_ref/aiplist.html">http://www.fda.gov/ora/compliance_ref/aiplist.html</a>  If yes, explain:  If yes, has OC/DMPQ been notified of the submission?  Comments:	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>User Fees</b>	
Form 3397 (User Fee Cover Sheet) submitted	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
User Fee Status  Comments:	<input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required
<i>Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. It is expected that all 505(b) applications, whether 505(b)(1) or 505(b)(2), will require user fees unless otherwise waived or exempted (e.g., business waiver, orphan exemption).</i>	
<b>Exclusivity</b>	

<p>Does another product have orphan exclusivity for the same indication? <i>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></i></p> <p><b>If yes</b>, is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES # years requested: 3 <input type="checkbox"/> NO
<p>If the proposed product is a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>):</p> <p>Did the applicant (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b) request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>	<input checked="" type="checkbox"/> Not applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	
<ol style="list-style-type: none"> <li>1. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>2. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).</li> <li>3. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug (see 21 CFR 314.54(b)(2))?</li> </ol>	<input type="checkbox"/> Not applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i></p>	
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<p>4. Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? <b>Check the Electronic Orange Book at: <a href="http://www.fda.gov/cder/ob/default.htm">http://www.fda.gov/cder/ob/default.htm</a></b></p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO																
<p><b>If yes, please list below:</b></p> <table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td>20764</td> <td>Lamictal CD</td> <td>Ped</td> <td>March 22, 2010</td> </tr> <tr> <td>22115</td> <td>Lamictal XR</td> <td>NDF</td> <td>May 29, 2012</td> </tr> <tr> <td>20241</td> <td>Lamictal tab</td> <td>PED</td> <td>March 22, 2010</td> </tr> </tbody> </table>			Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	20764	Lamictal CD	Ped	March 22, 2010	22115	Lamictal XR	NDF	May 29, 2012	20241	Lamictal tab	PED	March 22, 2010
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															
20764	Lamictal CD	Ped	March 22, 2010															
22115	Lamictal XR	NDF	May 29, 2012															
20241	Lamictal tab	PED	March 22, 2010															
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																		
<b>Format and Content</b>																		
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> <p><b>Comments:</b></p>		<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)																
<p><b>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</b></p>																		
<p><b>If electronic submission:</b>  <u>paper</u> forms and certifications signed (non-CTD) or <u>electronic</u> forms and certifications signed (scanned or digital signature)(CTD)?</p> <p><i>Forms include: 356h, patent information (3542a), financial disclosure (3454/3455), user fee cover sheet (3542a), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i></p> <p><b>Comments:</b></p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO																
<p><b>If electronic submission, does it follow the eCTD guidance?</b>  <a href="http://www.fda.gov/cder/guidance/7087rev.pdf">http://www.fda.gov/cder/guidance/7087rev.pdf</a></p> <p><b>If not, explain (e.g., waiver granted):</b></p>		<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO																

<p><b>Form 356h:</b> Is a signed form 356h included?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. agent must sign the form.</i></p> <p>Are all establishments and their registration numbers listed on the form?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p>Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:</p> <p><input checked="" type="checkbox"/> legible  <input checked="" type="checkbox"/> English (or translated into English)  <input checked="" type="checkbox"/> pagination  <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)</p> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>Controlled substance/Product with abuse potential:</b></p> <p>Abuse Liability Assessment, including a proposal for scheduling, submitted?</p> <p>Consult sent to the Controlled Substance Staff?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BLAs/BLA efficacy supplements only:</b></p> <p>Companion application received if a shared or divided manufacturing arrangement?</p> <p><b>If yes, BLA #</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	
<p>Patent information submitted on form FDA 3542a?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Debarment Certification</b>	
<p>Correctly worded Debarment Certification with authorized signature?</p> <p><i>If foreign applicant, <b>both</b> the applicant and the U.S. Agent must</i></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>sign the certification.</b></p> <p><i>Note: Debarment Certification should use wording in FD&amp;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...”</i></p> <p><b>Comments:</b></p>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	
<p>Field Copy Certification: that it is a true copy of the CMC technical section (<i>applies to paper submissions only</i>)</p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	<p><input checked="" type="checkbox"/> Not Applicable (<i>electronic submission or no CMC technical section</i>)</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Financial Disclosure</b>	
<p>Financial Disclosure forms included with authorized signature?</p> <p><i>Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an Agent.</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Pediatrics</b>	
<b>PREA</b>	
<p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	
<p>Are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p><b>If no</b>, is a request for full waiver of pediatric studies OR a request for partial waiver/deferral and a pediatric plan included?</p> <ul style="list-style-type: none"> <li>• <i>If no, request in 74-day letter.</i></li> <li>• <b>If yes</b>, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</li> </ul>	<p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<b>Comments:</b>	

<b>BPCA (NDAs/NDA efficacy supplements only):</b>	
Is this submission a complete response to a pediatric Written Request?  <i>If yes, contact PMHS (pediatric exclusivity determination by the Pediatric Exclusivity Board is needed).</i>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Comments:</b>	
<b>Prescription Labeling</b>	
Check all types of labeling submitted.  <b>Comments:</b>	<input type="checkbox"/> <b>Not applicable</b> <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> MedGuide <input type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)
Is electronic Content of Labeling submitted in SPL format?  <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
Package insert (PI) submitted in PLR format?  <b>If no</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If before</b> , what is the status of the request?  <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Comments:</b>	
MedGuide or PPI (plus PI) consulted to OSE/DRISK? ( <i>send WORD version if available</i> )	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>Comments:</b>	
REMS consulted to OSE/DRISK?	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	
Carton and immediate container labels, PI, PPI, and proprietary name (if any) sent to OSE/DMEDP?	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Comments:</b>	

<b>OTC Labeling</b>	
<p>Check all types of labeling submitted.</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> <b>Not Applicable</b> <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)
<p>Is electronic content of labeling submitted?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Are annotated specifications submitted for all stock keeping units (SKUs)?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>If representative labeling is submitted, are all represented SKUs defined?</p> <p><i>If no, request in 74-day letter.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p>Proprietary name, all labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEDP?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<b>Meeting Minutes/SPA Agreements</b>	
<p>End-of Phase 2 meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO
<p>Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)?</p> <p><i>If yes, distribute minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES Date(s): August 27, 2007 <input type="checkbox"/> NO
<p>Any Special Protocol Assessment (SPA) agreements?</p> <p><i>If yes, distribute letter and/or relevant minutes before filing meeting.</i></p> <p><b>Comments:</b></p>	<input type="checkbox"/> YES Date(s): <input checked="" type="checkbox"/> NO

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** May 20, 2009

**NDA/BLA #:** 022509

**PROPRIETARY/ESTABLISHED NAMES:** Lamictal (lamotrigine) Extended Release

**APPLICANT:** GlaxoSmithKline

**BACKGROUND:** This is the second NDA submitted for Lamictal XR ( the original, NDA 22-115, is still under review). The overall clinical development for Lamictal XR is found under IND 69,254.

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Dorothy Demczar	y
	CPMS/TL:	Robbin Nighswander	y
Cross-Discipline Team Leader (CDTL)	Norman Hershkowitz		y
Clinical	Reviewer:	Steve Dinsmore	y
	TL:	Norman Hershkowitz	y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
Labeling Review ( <i>for OTC products</i> )	Reviewer:		
	TL:		
OSE	Reviewer:		
	TL:		
Clinical Microbiology ( <i>for antimicrobial products</i> )	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Ta-Chen Wu	y
	TL:	Veneeta Tandon	
Biostatistics	Reviewer:	Steve Bai	y
	TL:	Kun Jin	y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Ed Fisher	y
	TL:	Lois Freed	
Statistics, carcinogenicity	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Wendy Smith	y
	TL:	Martha Heimann	y
Facility ( <i>for BLAs/BLA supplements</i> )	Reviewer:		
	TL:		
Microbiology, sterility ( <i>for NDAs/NDA efficacy supplements</i> )	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:	Tony El Hage	
	TL:		
Other reviewers			

**OTHER ATTENDEES:**

505(b)(2) filing issues?  <b>If yes, list issues:</b>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
Per reviewers, are all parts in English or English translation?  <b>If no, explain:</b>	<input type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>Electronic Submission comments</b></p> <p><b>List comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable
<p><b>CLINICAL</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason:
<ul style="list-style-type: none"> <li>• 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?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<b>Comments:</b>	<input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<b>BIOSTATISTICS</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<b>PRODUCT QUALITY (CMC)</b>  <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no</b>, was a complete EA submitted?</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> </ul> <ul style="list-style-type: none"> <li>Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Sterile product?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO

<p><b>If yes, was Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>FACILITY (BLAs only)</b></p> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>REGULATORY PROJECT MANAGEMENT</b></p>	
<p><b>Signatory Authority:</b> Russell Katz, MD -division director</p> <p><b>GRMP Timeline Milestones:</b></p> <p><b>Comments:</b></p>	
<p><b>REGULATORY CONCLUSIONS/DEFICIENCIES</b></p>	
<input type="checkbox"/>	<p>The application is unsuitable for filing. Explain why:</p>
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional):</p> <p><input checked="" type="checkbox"/> Standard Review</p> <p><input type="checkbox"/> Priority Review</p>
<p><b>ACTIONS ITEMS</b></p>	
<input checked="" type="checkbox"/>	<p>Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into tracking system.</p>
<input type="checkbox"/>	<p>If RTF action, notify everybody who already received a consult request, OSE PM., and Product Quality PM. Cancel EER/TBP-EER.</p>
<input type="checkbox"/>	<p>If filed and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.</p>
<input type="checkbox"/>	<p>If BLA or priority review NDA, send 60-day letter.</p>
<input checked="" type="checkbox"/>	<p>Send review issues/no review issues by day 74</p>
<input type="checkbox"/>	<p>Other</p>

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-22509

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ORIG-1

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SMITHKLINE  
BEECHAM CORP  
DBA  
GLAXOSMITHKLIN  
E

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LAMICTAL  
XR(LAMOTRIGINE)ORAL  
TABLETS

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/s/  
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DOROTHY J DEMCZAR  
01/25/2010

**M E M O R A N D U M**

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

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**CLINICAL INSPECTION SUMMARY**

DATE: January 18, 2010

TO: Dorothy Demczar, Regulatory Health Project Manager  
Steve Dinsmore, D.O., Medical Officer  
Division of Neurology

THROUGH: Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-509

APPLICANT: GlaxoSmithkline

DRUG: Lamictal XR (lamotrigine)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of primary generalized tonic-clonic seizures

CONSULTATION REQUEST DATE: May 21, 2009

DIVISION ACTION GOAL DATE: January 31, 2010

PDUFA DATE: January 31, 2010

## I. BACKGROUND:

The Sponsor, GlaxoSmithKline, has submitted a supplemental New Drug Application for the use of lamictal extended-release (LTG XR) a new enteric-coated, extended-release Lamictal XR (lamotrigine) formulation that may allow subjects with seizures to be on a once daily dosing regimen. This formulation would allow for a reduction in daily trough-to-peak fluctuations in lamotrigine serum concentrations compared to Lamictal IR and may improve compliance due to once a day compared to twice a day dosing. The current study was conducted to investigate the efficacy and safety of adjunctive therapy with LTG extended release in subjects with primary generalized tonic-clonic seizures. The duration of the study for all phases was 24 weeks, open-label 45 weeks and taper/follow-up phase 3-6 weeks.

The review division requested inspection of Protocol LAM100036: “A multi-center, randomized, double-blind, parallel-group, evaluation of Lamictal extended-release adjunctive therapy in subjects with primary generalized tonic-clonic seizures.” The sponsor submitted results from Protocol LAM100036 in support of NDA 22-509.

The primary objective of study Protocol LAM 100036 was to assess the efficacy of once daily adjunctive therapy with LTG extended-release in subjects with primary generalized tonic-clonic (PGTC) seizures. The primary endpoint was to determine the percent change from Baseline in PGTC seizure frequency during the entire double-blind treatment phase. The inspection targeted one domestic clinical investigator and two foreign investigators who enrolled a relatively large number of subjects.

## II. RESULTS (by protocol/site):

Name of CI, site # and location	Protocol and # of subjects	Inspection Dates	Final Classification
Rupam Borgohain, M.D Department of Neurology Nizam’s Institute Punjagutta, Hyderabad- 050082, Andhra, India <b>Site # 12924</b>	Protocol LAM100036 24 subjects	9/7-11/09	Pending (preliminary classification VAI)
Shamsher Dwivede, M.D. Vidyasager Institute of Mental Health Institutional Nehru Nagar, New Delhi 110065, India <b>Site # 12927</b>	Protocol LAM100036 18 subjects	8/31-9/4/09	Pending (Preliminary classification VAI)
David B. Kudrow, M.D. 2001 Santa Monica Blvd., Suite 880 W Santa Monica CA90404 <b>Site #1230</b>	Protocol LAM100036 9 subjects	7/6-14/09	VAI

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations for regulations. Data unreliable.

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

Protocol LAM100036

**1. Rupam Borgohain, M.D.  
Andhra Pradesh, India**

**Note:** Observations noted below are based on an e-mail summary statement from the FDA field investigator; the EIR for this inspection is currently pending. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the EIR.

At this site, a total of 26 subjects were screened; 26 subjects were randomized and 24 completed the study.

The medical records/source data for 26 subjects were reviewed for inclusion/exclusion criteria, adverse events, drug accountability, the use of concomitant medications, informed consent, and source documents were compared to case report forms and data listings for primary efficacy endpoints and adverse events.

At the end of the inspection, a Form FDA 483 was issued. Our investigation found that for 5 subjects, blood urine tests and physical exams were not done, inadequate records in that transcription errors in recording seizure count were noted for Subjects 1527, 1536, 1540 and 1562, no seizure diary for Subject 1540 at Visit 3 and 4, the ECG for Subject 1572 was not done for visit 8. In addition, our investigation found inadequate record keeping in that minor discrepancies were found between progress notes and what was recorded in the case report forms. For example, six (6) subjects experienced nystagmus at certain visits (1532, 1533, 1540, 1564, 1570 and 1567), five (5) subjects experienced memory impairment, impaired intellect, confusion at baseline and Visit 4 (1533, 1543, 1561, 1562 and 1572), Subject 1545 had fever and received paracetamol, and Subject 1566 had gaze tremor and these were not recorded in their respective case report forms. The clinical investigator acknowledged the inspectional findings and stated that the inspection served as a learning experience.

The medical records reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the records reviewed were found to be verifiable. There were no known limitations to this inspection.

Assessment of Data Integrity

Although minor violations were noted, the findings are unlikely to impact data integrity; however, the review division may choose to consider the AEs as outlined above that were not reported on the CRFs in their assessment of safety. The data appear acceptable in support of the pending application.

2. **Shamsher Dwivedee, M.D.**  
**Nehru Nagar, India**

**Note:** Observations noted below are based on an e-mail summary statement from the field investigator; the EIR for this inspection is currently pending. An inspection addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

At this site, a total of 18 subjects were screened; 18 subjects were randomized and completed the study.

The medical records/source data for 14 subjects were reviewed for inclusion/exclusion criteria, adverse events, drug accountability, the use of concomitant medications, informed consent and source documents were compared to data listings for primary efficacy endpoints and adverse events.

At the end of the inspection, a Form FDA 483 was issued. Our investigation found that for 3 subjects, pregnancy tests were not done as no documentation that the tests were done were found, inadequate records in that transcription errors in recording seizure counts were noted for Subjects 1511, 1517, 1518, the EEG for Subject 1518 was done 6 month after randomization and minor discrepancies between progress notes and what was recorded in the case report forms for at least 5 subjects who experienced sleepiness (1511), mild gum hypertrophy (1517), loss of nystagmus (1521, 1524), and mild memory impairment (1519, 1521). The clinical investigator acknowledged the inspectional findings and stated that the inspection served as a learning experience.

The medical records reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the records reviewed were found to be verifiable. There were no known limitations to this inspection.

Assessment if Data Integrity

Although minor violations were noted, the findings are unlikely to impact data integrity; however, the review division may choose to consider the AEs as outlined above that were not reported on the CRFs in their assessment of safety. The data appear acceptable in support of the pending application.

**3. David B. Kudrow, M.D.  
Santa Monica, CA 90404-2196**

At this site, a total of 9 subjects were screened and consented, nine (9) subjects were randomized, 9 subjects completed the study and 6 subjects entered the extension phase of the study. One subject withdrew consent and one subject became pregnant and was terminated due to rash. Informed consent for all subjects was verified and signed by subjects prior to enrollment.

The medical records/source documents for 9 subjects were reviewed for inclusion/exclusion criteria consent forms, case report forms, drug accountability records, concomitant medications, and source documents were compared to data listings for primary efficacy endpoints and adverse events. Adverse events experienced by study subjects were not reported to the sponsor and IRB in a timely manner.

At the end of the inspection, a Form FDA 483 was issued. Our investigation found that for 3 subjects, a Spanish consent form was signed initially and later an English consent was signed by the same subjects. The clinical investigator explained that he became aware that the subjects were bilingual. Therefore, Dr. Kudrow re-consented the subjects with the English version. The clinical investigator acknowledged the inspectional observation and this observation was not reiterated in the letter to the CI. However, in review of the Informed Consent Document, it was noted that one of the elements required in the ICD was not appropriately listed, as per the item noted in the letter.

The medical records reviewed disclosed no adverse findings that would reflect negatively on the reliability of the data. In general, the study records reviewed were accurate in terms of data entries and reporting of adverse events. There were no known limitations to this inspection.

Assessment of Data Integrity

The data from Dr. Kudrow's site appear acceptable and reliable in support of the pending application.

**III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL  
RECOMMENDATIONS**

Two foreign clinical investigators and one domestic clinical investigator were inspected in support of this application. Although regulatory violations were noted, it is unlikely that the inspectional findings would significantly impact data integrity; however, the review division should consider the unreported AEs as outlined above for the inspections of Drs. Borgoghain and Dwivedee in their evaluation of safety. In general, the data are considered reliable in support of the application.

**Note:** Observations noted for Drs. Borgohain and Dwivedee are based on e-mail summary statements from the FDA field investigators; the EIRs for these inspections are currently pending. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the EIRs.

*{See appended electronic signature page}*

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

CONCURRENCE:

*{See appended electronic signature page}*

Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22509	ORIG-1	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLIN E	LAMICTAL XR(LAMOTRIGINE)ORAL TABLETS

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ANTOINE N EL HAGE  
01/20/2010

TEJASHRI S PUROHIT-SHETH  
01/20/2010