CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-115s000

CHEMISTRY REVIEW(S)

NDA 22-115

Lamotrigine Extended Release Tablets

SmithKline Beecham d/b/a GlaxoSmithKline

Wendy I. Wilson, Ph.D.
Office of New Drug Quality Assessment
for Division of Neurology Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA: 22-115
2. REVIEW: 01
3. REVIEW DATE: 15-JUN-2007
4. REVIEWER: Wendy I. Wilson, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	22-Nov-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	SmithKline Beecham d/b/a GlaxoSmithKline Kline
Address:	One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19101
Representative:	Elizabeth A. McConnell, Pharm. D.
Telephone:	919-483-6466

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Lamictal® XR™ Tablets

b) Non-Proprietary Name (USAN): Lamotrigine Extended Release Tablets

c) Code Name/# (ONDQA only): N/A.

d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)
10. PHARMACOL. CATEGORY: Anti-convulsant
11. DOSAGE FORM: Extended Release Tablet
12. STRENGTH/POTENCY: 25, 50, 100, or 200 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: _X__Rx ___OTC

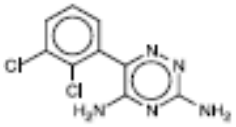
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine
Mol. Formula: $C_9H_7N_5Cl_2$
Mol. Weight: 256.09



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)		1	Adequate.	15-JUN-07	
	III			4	N/A		
	III			3	Adequate.	01-FEB-07	
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			3	Adequate.	09-JAN-07	
	III			4	Adequate.		
	III			4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20-241	Lamictal® Tablets
NDA	20-764	Lamictal® Chewable Tablets
IND	23,793	Lamictal® Tablets
		(b) (4)
IND	69,254	Lamotrigine Extended Release Tablets
		(b) (4)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Acceptable.	15-AUG-2007	Tristan Massie
EES	Acceptable.	16-AUG-2007	S. Adams
Pharm/Tox	N/A	-	-
Biopharm	Acceptable.	05-SEP-2007	Veneeta Tandon
LNC	N/A	-	-
Methods Validation	No samples for FDA method validation.	02-JUL-2007	Wendy Wilson
DMETS	No objections to proprietary name. Minor revisions to labeling format and tablet printing.	03-MAY-2007 02-AUG-2007	Kimberly Culley-Pedersen Todd Bridges
EA	No significant impact.	29-APR-2007	Raanan Bloom
Microbiology	N/A	-	-

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Executive Summary

Chemistry Review for NDA 22-115

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC perspective, this application is approved. The sponsor demonstrated the capacity to manufacture drug product with adequate quality and stability.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no CMC Phase 4 activity recommendations.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Lamotrigine is an antiepileptic drug of the phenyltriazine class. Lamotrigine is a white to pale cream colored powder with a pK_a of 5.7. Lamotrigine is very slightly soluble in water (0.17 mg/mL at 25°C) and slightly soluble in 0.1 M HCl (4.1 mg/mL at 25°C). Lamotrigine is classified as a BCS Class II drug. This drug substance was initially approved under NDA 20-241 on 27-DEC-1994.

Lamictal® XR tablets are round, biconvex, film-coated tablets for oral administration of 25, 50, 100, or 200 mg of lamotrigine. The tablets are ~ 9 mm in diameter for the 25 and 50 mg strengths and ~ 10 mm in diameter for the 100 and 200 mg strengths. Each tablet has a white to off-white aperture present in the enteric coating on both faces of the tablet. Colored sub-coats differentiate the various tablet strengths.

Lamotrigine requires an extended release delivery system with differential control mechanisms in the gastric and intestinal regions to overcome its pH-dependent solubility. GSK manufactures Lamictal® XR tablets using conventional pharmaceutical excipients typical of those used for extended release tablets. The sponsor achieves extended release using their DiffCORE drug delivery technology. The tablet cores contain a modified-release, eroding matrix formulation. The tablet sub-coat is a (b) (4)® (b) (4) and the clear enteric coat is a (b) (4) GSK drills apertures on both faces of the coated tablets, enabling a controlled release of the drug in the acidic environment of the stomach.

The aperture size and surface area limit the drug release rate in the stomach. In the gastric phase, the DiffCORE tablet slows drug release and the drug release profile becomes independent of the fasted or fed state. Once the DiffCORE tablet leaves the stomach and reaches pH > 5.5, the enteric coat dissolves, revealing the tablet hypromellose matrix. The increased surface area of the matrix exposed to higher pH environment triggers matrix erosion and the release of the drug at a controlled rate.

Lamictal® XR tablet manufacturing uses conventional processes except the aperture drilling process. The overall control strategy for the product consists of standard controls with additional process specific controls incorporated for the drilling operation. Development of all of the unit processes ensures a robust, reliable, and repeatable process that meets the commercial manufacturing needs. The 25 and 50 mg strength Lamictal® XR tablets are (b) (4). The 100 and 200 mg strength Lamictal® XR tablets include a (b) (4) The process validation results demonstrate that the proposed manufacturing processes consistently produce quality drug product.

The common drug product specifications across all strengths are identification (HPLC and UV), lamotrigine content, uniformity of dosage units, and drug related impurities. The description specification varies based on the sub-coat color. The tablet core tests include weight, hardness, and thickness as in-process controls. The tablet aperture tests include presence, size, position, depth, and tablet weight loss as in-process controls. The proposed dissolution specifications correlate with the proposed IVIVC for the drug product. The dissolution sampling time points differ for the 25/50 mg strength tablets compared to the 100/200 mg strength tablets. All of the NDA stability batches met the proposed specifications. We agree with the finished drug product specifications at release as well as on stability.

GSK proposes two packaging presentations, blister packs and 30-count, 60 cc HDPE bottles. The sponsor proposes a storage condition of 25°C with excursions permitted in the range of 15°C – 30°C. For 25 mg strength tablets packaged in blister packs, GSK proposes an 18 month shelf life. For 25 mg strength tablets packaged in HDPE bottles, GSK proposes a 24 month shelf-life. GSK proposes a 36 month shelf-life for the 50, 100, and 200 mg strength tablets in blisters and HDPE bottles. The real-time stability data support the expiries for the 25 mg strength tablets in blisters and bottles. The statistical evaluation supports the 36 month expiration date for the remaining tablet strengths in blisters and bottles. We concur with the proposed 18 month expiration for the 25 mg strength tablets packaged in blisters and the 24 month expiration for the 25 mg strength tablets packaged in HDPE bottles. We also concur with the proposed 36 month expiration for the 50, 100, and 200 mg strength tablets packaged in both blisters and HDPE bottles.

B. Description of How the Drug Product is Intended to be Used

The proposed Lamictal® XR indication is an adjunctive therapy for partial onset seizures with or without secondary generalization in patients ≥ 13 years of age. Safety and effectiveness has not been established for use in patients below the age of 13 years. The drug product provides extended release of lamotrigine to reduce the number and frequency of tablets taken. The drug product also provides improved lamotrigine absorption. The sponsor provides Lamictal® XR as bulk tablets in HDPE bottles for dispensing, starter kits in blisters for titration, and sample kits in blisters for physicians.

The current dosing recommendation in the US for lamotrigine immediate-release (IR) tablets is twice daily for concurrent administration with EIAEDs or as monotherapy and once or twice daily administration with VPA. Table 1 includes the proposed dosing regimen for Lamictal® XR:

Table 1 – Lamictal® XR Dosing Regimen

	For Patients Taking Valproate	For Patients Taking AEDs Other Than Carbamazepine, Phenytoin, Phenobarbital, Primidone, or Valproate	For Patients Taking Carbamazepine, Phenytoin, Phenobarbital, Primidone and Not Taking Valproate
Weeks 1 and 2	25mg every *other* day	25mg every day	50mg every day
Weeks 3 and 4	25mg every day	50mg every day	100mg every day
Week 5	50mg every day	100mg every day	200mg every day
Week 6	100mg every day	150mg every day	300mg every day
Week 7	150mg every day	200mg every day	400mg every day
Maintenance Range (Week 8 and onward)	150-250mg every day	200-400mg every day	400-600mg every day

Lamictal® XR offers patients with seizures a once daily dosing regimen, with titration to efficacy using the same starting dose, dose titration, and comparable maintenance doses as currently approved for IR lamotrigine. The proposed tablet strengths provide required titration and maintenance doses, up to 200 mg, in one tablet. Patients requiring more than 200 mg lamotrigine will need multiple tablets of various tablet strengths to achieve the proposed dosing.

The data shows dose proportionality over the proposed tablet strength range but decreased relative bioavailability of DiffCORE formulations compared to IR formulations. The results also show increased absorption rates for DiffCORE formulations but decreased extents of absorption in environments with chronically elevated gastric pH. Consideration should be given to the disease state, other medicines, and diet of patients prescribed Lamictal XR® to ensure optimal therapeutic effect. The major benefits of therapy using this drug product are decreased variation in steady-state lamotrigine plasma-levels and reduced dosing to achieve therapeutic plasma levels.

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, this application is approved. The drug substance was determined to be safe, effective, and manufactured with inherent quality in NDA 20-241, approved 27-DEC-1994. The sponsor identified CQA and established controls to ensure the quality of the drug product. The batch analysis results confirm adequate quality of the drug product at release. The data demonstrated adequate stability of the drug product and support the proposed expiration dates. The intended commercial packaging presentations provide adequate protection of the drug product and ensure drug product quality over the proposed shelf-life. From a CMC perspective, the labeling is adequate.

III. Administrative

A. Reviewer's Signature

Wendy I. Wilson

B. Endorsement Block

WWilson: 06-SEP-2007
MHeimann: 10-SEP-2007
RSood: 12-SEP-2007

C. CC Block

SGoldie

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/s/

Wendy I. Wilson
9/12/2007 11:24:49 AM
CHEMIST

Ramesh Sood
9/12/2007 01:23:09 PM
CHEMIST