

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-251

CHEMISTRY REVIEW(S)

CMC BRANCH CHIEF MEMORANDUM

To: NDA 22-251
From: Ramesh Sood, Ph.D., Branch Chief, ONDQA
Date: 16-Sep-2008
Drug: Lamictal (lamotrigine) Orally Disintegrating Tablets
Route of administration: Oral
Strength: 25 mg, 50 mg, 100 mg and 200 mg.
Subject: **Approval** recommendation for NDA 22-251

Introduction: Lamotrigine (chemical name: 3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine) is currently approved for adjunctive treatment of partial seizures and Lennox-Gastault Syndrome, and for maintenance treatment of Bipolar I Disorder. Two immediate-release dosage forms are available, conventional compressed tablets (25 mg, 100 mg, 150 mg and 200 mg) and chewable-dispersible tablets (2 mg, 5 mg and 25 mg). An approvable letter for the applicant's NDA 22-115, which provides for an extended release tablet formulation, was issued on 21-Sep-2007. The current NDA provides for a lamotrigine orally disintegrating tablet formulation to be available in four strengths, 25 mg, 50 mg, 100 mg and 200 mg. The recommended adult dosages for treatment of epilepsy and bipolar disorder are, respectively, 100 mg-500 mg/day and 100 mg-400 mg/day. Dosages for both indications require adjustment based on concomitant medications.

Drug Substance: Lamotrigine is a white to pale cream colored powder with a pKa 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. It is a well characterized small molecule with molecular formula C₉H₇N₅Cl₂ and molecular weight 256.09. The bulk drug substance is manufactured under currently approved NDA 20-241, which is cross-referenced for CMC information. Information in the current NDA is limited to a summary of the manufacturing facilities and drug substance specification approved under NDA 20-241 and certificates of analysis for drug substance batches used to manufacture primary stability batches of the ODT formulations.

Drug product: Lamictal® ODTs are white to off-white, round, flat-faced radius edge tablets. The tablets are immediate-release (IR) and intended for oral administration. All four strengths are dose-proportional and manufactured from one common blend with different tablet weights. All tablets are the same color, shape, and flavor. The tablet size, combined with the distinct tablet debossing, differentiates the four different tablet strengths. The target product profile includes an ODT formulation of lamotrigine – available in 25 mg, 50 mg, 100 mg, and 200 mg strengths – that effectively masks the taste of lamotrigine and disintegrates (b) (4). The sponsor references DMF 19,909 (EUR-1048 Orally Disintegrating Tablets, Eurand, Inc.) for information in support of the drug product, except the container closure system. A second (b) (4) DMF (b) (4) is also referenced. (b) (4) is a proprietary excipient pre-mix that is intended for use, (b) (4), to manufacture multiple products. These two DMFs were reviewed and found to be adequate to support the current NDA. Appropriate quality controls at the various stages of manufacturing and product testing have been included to assure the final product quality and consistency.

One intended commercial container closure is opaque, white, HDPE bottles sealed (b) (4). The HDPE bottles contain desiccant and polyester headspace filler. The other intended commercial container closure is blister strips (b) (4) and sealed (b) (4).

(b) (4) also manufactures cherry placebo ODTs. The placebo ODTs are white to off-white, round, flat-faced radius edge tablets, with a characteristic cherry odor and no debossing. These tablets are demonstration tablets, used by the practitioner to train the patient on proper administration. The cherry placebo ODTs are available in four tablet sizes – 7 mm, 9 mm, 11 mm, and 14 mm. Each placebo matches a corresponding lamotrigine ODT.

An 18-month expiration date is assigned for the drug product stored at 25 °C (77 °F) with excursions permitted to 15-30 °C (59-86 °F) (USP Controlled Room Temperature) based on the evaluation of provided stability data.

The Office of Compliance has provided an overall acceptable recommendation for the manufacturing sites.

Recommendation: All CMC related issues had been resolved for this application. The application is recommended for “Approval” from CMC perspective.

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/s/

Ramesh Sood
9/16/2008 11:06:31 AM
CHEMIST

NDA 22-251

Lamotrigine Orally Disintegrating Tablets

SmithKline Beecham d/b/a GlaxoSmithKline

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

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Chemistry Review Data Sheet

1. NDA: 22-251
2. REVIEW: 01
3. REVIEW DATE: 15-SEP-2008
4. REVIEWER: Wendy I. Wilson, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
None	N/A

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	28-NOV-2007
Amendment	31-JAN-2008
Amendment	01-MAY-2008
Amendment	09-SEP-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	SmithKline Beecham d/b/a GlaxoSmithKline
Address:	One Franklin Plaza 200 North 16 th Street Philadelphia, PA 19102
Representative:	Eric B. Benson Senior Director US Regulatory Affairs
Telephone:	919-483-3627

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Lamictal® ODT (lamotrigine) Orally Disintegrating Tablets
b) Non-Proprietary Name (USAN): Lamotrigine
c) Code Name/# (ONDQA only): BW430C
d) Chem. Type/Submission Priority (ONDQA only):
 • Chem. Type: 3
 • Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Epilepsy and Bipolar Disorder

11. DOSAGE FORM: Tablet, Orally Disintegrating

Chemistry Review Data Sheet

12. STRENGTH/POTENCY: 25 mg, 50 mg, 100 mg, 200 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

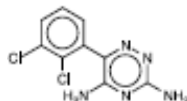
Not a SPOTS product

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

Chemical Name: 3,5-diamino-6-(2,3-dichlorophenyl)-as-triazine

Mol. Formula: C₉H₇N₅Cl₂

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)	III			(b) (4)	4	N/A	
	III			4	N/A		
	III			3	Adequate	19-NOV-2007	For NDA 22-181
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			4	N/A		
	III			3	Adequate	19-NOV-2007	For NDA 22-181
19909	II	Eurand, Inc.	Lamotrigine Orally Disintegrating Tablets	1	Adequate	15-SEP-2008	
(b) (4)	IV			(b) (4)	1	Adequate	01-JUL-2008

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
IND	23,793	Lamictal® (lamotrigine) Tablets
IND	43,551	Lamictal® (lamotrigine) Dispersible Tablets
IND	49,916	Lamictal® (lamotrigine) Tablets for the Treatment of Bipolar Disorder
IND	69,254	Lamotrigine Extended Release Tablets
IND	(b) (4)	Lamotrigine Orally Disintegrating Tablet (ODT)
NDA	20-241	Lamictal® (lamotrigine) Tablets
NDA	20-764	Lamictal® (lamotrigine) Chewable Dispersible Tablets
NDA	22-115	Lamictal® XR (lamotrigine) Extended-Release Tablets
(b) (4)		


18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable	05-AUG-2008	S. Adams
Pharm/Tox	Pending.		J. Edward Fisher
Biopharm	Acceptable, pending DSI recommendation	28-AUG-2008	C. Noory
LNC	N/A	N/A	N/A
Methods Validation	Method validation not needed.	08-JUL-2008	W. Wilson
DMEDP	Pending.		Z. Oleszczuk
EA	Categorical exclusion under 21 CFR 25.31 (b) granted	13-FEB-2008	R. Bloom
Microbiology	N/A	N/A	N/A

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Chemistry Review for NDA 22-251

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

Based on our review, we recommend approval of Lamictal® ODT, pending labeling.

Approval Letter Comment: Based on our review of stability data, we grant an 18 month expiry for all four tablet strengths of Lamictal® (lamotrigine) Orally Disintegrating Tablets when packaged in the commercial container closures (30-count HDPE bottles (b) (4) HDPE bottles, and (b) (4) blister packs) and stored at controlled room temperature [20°C – 25°C (68 F – 77 F)], with excursions permitted between 15°C – 30°C (59°F – 86°F).

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

There are no CMC recommendations for Phase IV commitments.

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and Drug Substance(s)**

Lamotrigine is a phenyltriazine, indicated as an adjunctive treatment of partial seizures and Lennox-Gastaut Syndrome as well as a maintenance treatment for Bipolar I Disorder. The drug substance is a well-characterized, small molecule. 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. Lamotrigine is indicated as adjunctive epilepsy therapy in patients ≥ 2 years of age in the treatment of partial seizures, primary generalized tonic-clonic seizures, or generalized seizures of Lennox-Gastaut syndrome. Lamotrigine is also indicated as a monotherapy in patients ≥ 16 years of age. Lamotrigine is also indicated as a maintenance treatment of Bipolar I Disorder in patients ≥ 18 years of age to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy.

Lamictal® ODTs are white to off-white, round, flat-faced radius edge tablets. The proposed tablet strengths are 25 mg, 50 mg, 100 mg and 200 mg. The tablets are immediate-release (IR) and intended for oral administration. All four strengths are dose-proportional and manufactured from one common blend with different tablet weights. All tablets are the same color, shape, and flavor. The tablet size, combined with the tablet debossing, differentiates the four different tablet strengths. The target product profile includes an ODT formulation of lamotrigine – available in 25 mg, 50 mg, 100 mg, and 200 mg strengths – that effectively masks the taste of lamotrigine and disintegrates within (b) (4). The sponsor refers to MF 19909 for information concerning the chemistry, manufacturing, and control of Lamictal® ODT. Our review found this MF adequate to support this NDA. We grant an 18 month expiry for all tablet strengths of Lamictal® ODT in both HDPE bottles and in (b) (4) blister packs.

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

Lamictal® ODT is designed for administration without the aid of water. However, GSK's clinical study LBII08617 showed that swallowing the ODT whole with water did not affect the pharmacokinetics of lamotrigine. The ODT serves as an alternative dosage form that offers an ease of use for patients that experience difficulty in swallowing. Lamotrigine dosing is based on concomitant medications, indication, and patient age.

Executive Summary Section

Table 1 - Escalation Regimen for LAMICTAL in Patients Over 12 Years of Age With Epilepsy

	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	25 mg every <i>other</i> day	25 mg every day	50 mg/day
Weeks 3 and 4	25 mg every day	50 mg/day	100 mg/day (in 2 divided doses)
Week 5 to maintenance	Increase by 25 to 50 mg/day every 1 to 2 weeks	Increase by 50 mg/day every 1 to 2 weeks	Increase by 100 mg/day every 1 to 2 weeks
Usual Maintenance Dose	100 to 400 mg/day (1 or 2 divided doses) 100 to 200 mg/day with valproate alone	225 to 375 mg/day (in 2 divided doses)	300 to 500 mg/day (in 2 divided doses)

Table 2 - Escalation Regimen for LAMICTAL in Patients With Bipolar Disorder

	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	25 mg every <i>other</i> day	25 mg every day	50 mg/day
Weeks 3 and 4	25 mg every day	50 mg/day	100 mg/day (in 2 divided doses)
Weeks 5	50 mg daily	100 mg daily	200 mg daily, in divided doses
Week 6	100 mg daily	200 mg daily	300 mg daily, in divided doses
Week 7	100 mg daily	200 mg daily	Up to 400 mg daily, in divided doses

One intended commercial container closures is opaque, white, HDPE bottles sealed (b) (4) (b) (4). The HDPE bottles contain desiccant and polyester headspace filler. The other intended commercial container closure is blister strips (b) (4) and sealed (b) (4) (b) (4)

(b) (4) also manufactures cherry placebo ODTs. The placebo ODTs are white to off-white, round, flat-faced radius edge tablets, with a characteristic cherry odor and no debossing. These tablets are demonstration tablets, used by the practitioner to train the patient on proper administration. The cherry placebo ODTs are available in four tablet sizes – 7 mm, 9 mm, 11 mm, and 14 mm. Each placebo matches a corresponding lamotrigine ODT.

C. Basis for Approvability or Not-Approval Recommendation

We recommend approval of Lamictal® ODT, pending labeling. The MF supporting the commercialization of this drug product is adequate. The facilities inspections found all sites associated with Lamictal® ODT acceptable.

III. Administrative

A. Reviewer’s Signature

Wendy I. Wilson

B. Endorsement Block

WWilson: 15-SEP-2008
 MHeimann: 15-SEP-2008
 RSood: 15-SEP-2008

C. CC Block

SGoldie
 BFraser
 JWare
 NDA22-251

19 Page(s) Withheld

X Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Wendy I. Wilson
9/15/2008 05:06:16 PM
CHEMIST

Ramesh Sood
9/16/2008 07:33:02 AM
CHEMIST

Initial Quality Assessment
Branch I
Pre-Marketing Assessment Division I

OND Division: Division of Neurology Products
NDA: 22-251
Applicant: SmithKline Beecham d/b/a GlaxoSmithKline (GSK)
Stamp Date: 28-Nov-2007
PDUFA Date: 28-Sep-2008
Trademark: Lamictal® ODT
Established Name: lamotrigine
Dosage Form: Orally disintegrating tablet
Route of Administration: Oral
Indication: Epilepsy, Treatment of bipolar disorder

PAL: Martha R. Heimann, Ph.D.

	Yes	No
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input type="checkbox"/>	<input checked="" type="checkbox"/>

Summary and Critical Issues:

Summary

Lamotrigine (chemical name: 3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine) is currently approved for adjunctive treatment of partial seizures and Lennox-Gastault Syndrome, and for maintenance treatment of Bipolar I Disorder. Two immediate-release dosage forms are available, conventional compressed tablets (25 mg, 100 mg, 150 mg and 200 mg) and chewable-dispersible tablets (2 mg, 5 mg and 25 mg). An approvable letter for the applicant's NDA 22-115, which provides for an extended release tablet formulation, was issued on 21-Sep-2007. The current NDA provides for a lamotrigine orally disintegrating tablet formulation to be available in four strengths, 25 mg, 50 mg, 100 mg and 200 mg. The recommended adult dosages for treatment of epilepsy and bipolar disorder are, respectively, 100 mg-500 mg/day and 100 mg-400 mg/day. Dosages for both indications require adjustment based on concomitant medications.

Drug Substance

The active ingredient in Lamictal ODT, lamotrigine, is a well characterized small molecule with molecular formula C₉H₇N₅Cl₂ and molecular weight 256.09. The bulk drug substance is manufactured under NDA 20-241, which is cross-referenced for CMC information. Information in the current NDA is limited to a summary of the manufacturing facilities and drug substance specification approved under NDA 20-241 and certificates of analysis for drug substance batches used to manufacture primary stability batches of the ODT formulations.

Drug Product

The sponsor references DMF 19,909 (EUR-1048 Orally Disintegrating Tablets, Eurand, Inc.) for information in support of the drug product, except the container closure system. The DMF was previously referenced to support studies under IND (b) (4) and a DMF amendment to support the commercial product was submitted on 27-Nov-2007. A second (b) (4) DMF (b) (4) (b) (4) is also referenced. (b) (4) is a proprietary excipient pre-mix that is intended for use, (b) (4), to manufacture multiple products. Per discussion at the pre-NDA teleconference [01-Oct-2007] all manufacturing sites are identified in the NDA submission and a copy of the Methods Validation Package (copied from the DMF (b) (4)) is included in the NDA.

Critical issues for review

Drug Substance: No critical issues can be identified based on information provided in the NDA. The appropriateness of the drug substance specification, with respect to product quality, should be evaluated during review of the DMF.

Drug Product: No critical issues can be identified based on information provided in the NDA.

Additional issues

Administrative: As the Lamictal ODT is a new dosage form, approval of this application may be expected to increase use of the active moiety, lamotrigine. The firm has submitted a claim for categorical exclusion under 25.31(b) which states that use of this product will not cause the concentration of the drug substance active moiety to be one part per billion (1 ppb) or greater at the point of entry into the aquatic environment. It is noted, however, that in the recent NDA for Lamictal XR Tablets (NDA 22-115, currently “approvable”) the applicant submitted an updated environmental assessment, which cross-referenced documentation previously submitted to NDA 20-241 (Lamictal Tablets) and NDA 20-274 (Lamictal Chewable Dispersible Tablets) in which the firm projected an expected introduction concentration that exceeded the 1 ppb threshold. As the information submitted in the current application is not consistent with information previously submitted by the same applicant, it is recommended that this be consulted to the OPS/PARS staff for review.

Establishment Evaluation: A full list of facilities involved in the manufacture, packaging and testing of Lamictal XR Tablets is provided in the submission. The facilities listed in Attachment Facility information were entered into EES on 06-Dec-2007.

Labeling/Established Name: The active ingredient in Lamictal ODT, lamotrigine, is the free base. Therefore, there is no issue of consistency between the USAN name and the labeled potency. It is noted, however, that all CMC-related labeling information regarding the dosage form will need to be verified based on the drug product DMF.

Comments for 74-Day Letter

There are no comments for the 74 day letter

Review, Comments and Recommendation:

The NDA is fileable from a CMC perspective. The drug substance is manufactured under an approved NDA. Assignment of the NDA to a single reviewer is recommended.

Martha R. Heimann, Ph.D.
Pharmaceutical Assessment Lead

12/10/07
Date

Ramesh Sood, Ph.D.
Branch Chief

12/10/07
Date

ATTACHMENT

Manufacturing Establishment for Lamictal ODT Tablets

Primary GSK contact for scheduling of pre-approval inspections is Diane Sevigny, RTP, North Carolina, (919) 483-8974

Facility Information	Function
(b) (4)	
SmithKline Beecham Corporation d/b/a GlaxoSmithKline 1011 North Arendell Avenue Zebulon North Carolina 27597 Registration No. 1033964 Site Contact: Allen Moss (Director of QA) Tel. No. 919 269-1045	Primary and secondary packaging of drug product.
Eurand, Inc. 845 Center Drive Vandalia, Ohio 45377 Registration No. 1525864 Site Contact: Bill Webb (Director of Quality) Tel. No. 937 898-9669, Ext. 313	Manufacture, quality control, bulk packaging of commercial product. Testing and stability storage of commercial stability batches.
(b) (4)	

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/s/

Martha Heimann
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Ramesh Sood
12/10/2007 01:37:49 PM
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