CENTER FOR DRUG EVALUATION AND RESEARCH

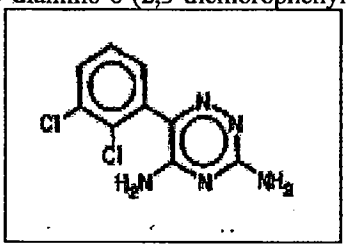
APPLICATION NUMBER:

20-764/S-011
20-241/S-017

CHEMISTRY REVIEW(S)

CHEMIST REVIEW
OF **SUPPLEMENT**

1. ORGANIZATION: HFD-120
2. NDA: **20-241**
3. SUPPLEMENT NUMBERS/ DATES: **SE1-017 Response to AE letter**
   letter date: April 21, 2003
   stamp date: April 23, 2003
4. AMENDMENTS/REPORTS/DATES:
5. RECEIVED BY CHEMIST: June 3, 2003
6. APPLICANT NAME & ADDRESS: SmithKline Beecham Corporation d/b/a GlaxoSmithKline
   One Franklin Plaza
   P.O. Box 7929
   Philadelphia, PA 19101
7. NAME OF DRUG: Lamictal (lamotrigine) tablets
8. NONPROPRIETARY NAME: Lamotrigine
9. CHEMICAL NAME/STRUCTURE: 3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine



10. DOSAGE FORM(S): Tablets
11. POTENCY: 25, 50, 100, 150, 200 and 250 mg
12. PHARMACOLOGICAL CATEGORY: Anticonvulsant
13. HOW DISPENSED: X (R_X) _____ (OTC)
14. RECORDS & REPORTS CURRENT: X Yes _____ No
15. RELATED IND/NDA/DMF: NA

SUPPLEMENT PROVIDES FOR:.Complete response to the Approvable (AE) letter dated April 4, 2003 including clinical, labeling and final safety update.

COMMENTS: The sponsor, GSK, not only provided a complete response to the AE letter but also included minor changes to the carton and container labeling. The background color has been changed from yellow to orange; certain footnotes have been moved to emphasize patient population and additional wording has been added to increase the safe use of the product. All the changes to container closure are minor and increase the safe usage of the product (see review notes for details). In addition, GSK has adopted the editorial changes recommended for the "HOW SUPPLIED" section of package insert in the FDA's AE letter of April 4, 2003. Based on the acceptable labeling changes and minor carton and container labeling modifications, the response to AE letter is acceptable from the CMC standpoint.

CONCLUSIONS & RECOMMENDATIONS: APPROVAL from CMC standpoint

Cc: NDA 20-241/SE1-017
DISTRICT OFFICE
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HFD-120/GGill-Sangha/TOliver/JWare
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REVIEW NOTES:

GSK provides a complete response to the FDA's AE letter dated April 4,2003. In this response GSK provides clinical, labeling and final safety updates.

Labeling:

GSK accepts the editorial changes recommended in the FDA's AE letter of April 4, 2003 for the "HOW SUPPLIED" section in order to increase clarity.

Evaluation: Acceptable since GSK incorporated the editorial changes recommended for "HOW SUPPLIED" section.

Container Closure:

Minor revisions to the artwork for Sample and Trade packs are proposed.

- The background color has been modified from yellow to orange.
- On the front panel of Sample and Trade packs, the footnotes have been moved below the dark blue bar that contains the description of the patient populations being treated (i.e., "For Patients TAKING valproate*" and For Patients TAKING enzyme-inducing drugs* and NOT TAKING valproate† and "For Patients NOT TAKING enzyme-inducing drugs* or valproate†") to further emphasize the patient population treatment information.
- The following wording has been added to the bottom left of the inside face cards on the Sample and Trade packs: "To remove tablets, push through back of card." This wording is a necessary part of the Child-Resistant Packaging Testing in older adults and was inadvertently omitted in the earlier draft artwork.

Evaluation: Acceptable since the changes to the Sample and Trade packs are minor and do not affect the product safety.

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/s/

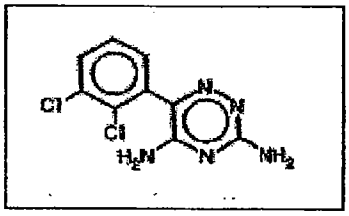
Gurpreet Gill-Sangha
6/9/03 09:32:56 AM
CHEMIST

Review for N20-241/SE1-017 AE letter

Thomas Oliver
6/9/03 09:43:51 AM
CHEMIST

CHEMIST REVIEW
OF **SUPPLEMENT**

1. ORGANIZATION:	HFD-120
2. NDA:	**20-241 and 20-764**
3. SUPPLEMENT NUMBERS/ DATES:	**SE1-017 and SE1-011 respectively** **Efficacy Supplements**
letter date:	June 5, 2002
stamp date:	June 10 and June 7, 2002 respectively
4. AMENDMENTS/REPORTS/DATES:	
5. RECEIVED BY CHEMIST:	June 13, 2002
6. APPLICANT NAME & ADDRESS	SmithKline Beecham Corporation d/b/a GlaxoSmithKline One Franklin Plaza Po Box 7929 Philadelphia, PA 19101
7. NAME OF DRUG:	Lamictal (lamotrigine) tablets – N20-241 Lamictal (lamotrigine) Chewable Dispersible Tablets – N20-764
8. NONPROPRIETARY NAME:	Lamotrigine
9. CHEMICAL NAME/STRUCTURE:	3,5-diamino-6-(2,3-dichlorophenyl)-*as*-triazine



10. DOSAGE FORM(S):	Tablets for N20-241 Chewable Dispersible Tablets for N20-764		
11. POTENCY:	25, 50, 100, 150, 200 and 250 mg for N20-241 2, 5, 25, 100 mg for N20-764		
12. PHARMACOLOGICAL CATEGORY:	Anticonvulsant		
13. HOW DISPENSED:	X	(R_X)	(OTC)
14. RECORDS & REPORTS CURRENT:	X	Yes	No
15. RELATED IND/NDA/DMF:	NA		

SUPPLEMENT PROVIDES FOR:.Use of Lamictal tablets and chewable dispersible tablets as long term management of Bipolar I Disorder to delay the relapse/recurrence of depressive episodes as a new indication.

COMMENTS: All the CMC information regarding the drug substance and drug product sections remains unchanged form the approved NDA's 20-241 and 20-764 for this efficacy supplement. Only the package insert includes three new kits and the package insert is reviewed and the necessary changes are recommended in this review for clarity of the label.

CONCLUSIONS & RECOMMENDATIONS: N20-241/SE1-017 and N20-764/SE1-011 are recommended for APPROVAL from CMC standpoint with the recommended changes to the HOW SUPPLIED section of the package insert.

Cc: NDA 20-241/SE1-017 and NDA 20-764/SE1-011
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HFD-120/GGill-Sangha/TOliver/JWare
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REVIEW NOTES:

1. DRUG SUBSTANCE

GSK references NDA 20-241 for drug substance lamotrigine and states that all the CMC information for NDA 20-241 remains unchanged for this efficacy supplement.

Evaluation: Acceptable, since NDA 20-241 was approved on December 27, 1994.

2. DRUG PRODUCT

GSK references NDA 20-241 for Lamictal tablets and NDA 20-764 for Lamictal Chewable Dispersible tablets and states that all the CMC information for NDA 20-241 remains unchanged for this efficacy supplement

Evaluation: Acceptable, since NDA 20-241 was approved on December 27, 1994 and NDA 20-764 was approved on August 24, 1998.

3. PACKAGE INSERT AND LABELING

GSK is adding three kits in the HOW SUPPLIED section of the label.

Evaluation: The revised HOW SUPPLIED section of the label is attached at the end of this review with the changes highlighted to the HOW SUPPLIED section. The changes are proposed for increasing clarity to the label based on the information gathered from approved lables in the PDR (Physician's Desk Reference). The label with its highlighted changes was also submitted directly to the Project Manager, Jackie Ware and Dr. Thomas Laughren, Deputy Division Director, Division of Neuropharmacological Drugs. There are no changes in the DESCRIPTION section of the package insert.

4. ENVIRONMENTAL ASSESSMENT

GSK requests for a categorical exclusion in accordance with 21 CFR Part 25.31(b). GSK claims that based on reviewed market forecasts, indications and dosage informaiton the concentration of drug substance active moiety will not increase more than 1 ppb at the point of entry into the aquatic environment. Further, GSK states that it does not have knowledge of any extraordinary circumstances that might cause this action to have a significant affect on the quality of the human environment.

Evaluation: Acceptable. Based on 21 CFR 25.31(b) a categorical exclusion is granted since the concentration of the lamotrigine will be less than 1 ppb.

LAMICTAL®
(lamotrigine)
Tablets

PRESCRIBING INFORMATION

LAMICTAL®
(lamotrigine)
Chewable Dispersible Tablets

HOW SUPPLIED

—**LAMICTAL Tablets, 25-mg,**
wWhite, scored, shield-shaped tablets debossed with "LAMICTAL" and "25", bottles of 100 (NDC 0173-0633-02).
—*Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature] in a dry place.*

—**LAMICTAL Tablets, 100-mg,**
pPeach, scored, shield-shaped tablets debossed with "LAMICTAL" and "100", bottles of 100 (NDC 0173-0642-55).
—**LAMICTAL Tablets, 150-mg,**
eCream, scored, shield-shaped tablets debossed with "LAMICTAL" and "150", bottles of 60 (NDC 0173-0643-60).
—**LAMICTAL Tablets, 200-mg,**
bBlue, scored, shield-shaped tablets debossed with "LAMICTAL" and "200", bottles of 60 (NDC 0173-0644-60).
—*Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature] in a dry place and protect from light.*

—**LAMICTAL Chewable Dispersible Tablets, 2-mg,**
wWhite to off-white, round tablets debossed with "LTG" over "2", bottles of 30 (NDC 0173-0699-00). ORDER DIRECTLY FROM GLAXO WELLCOME INC. 1-800-334-4153.
—**LAMICTAL Chewable Dispersible Tablets, 5-mg,**
wWhite to off-white, caplet-shaped tablets debossed with "GX CL2", bottles of 100 (NDC 0173-0526-00).
—**LAMICTAL Chewable Dispersible Tablets, 25-mg,**
wWhite, super elliptical-shaped tablets debossed with "GX CL5", bottles of 100 (NDC 0173-0527-00).
—*Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature] in a dry place.*

—**LAMICTAL Starter Kit for Patients Taking Valproate,**
25-mg, wWhite, scored, shield-shaped tablets debossed with "LAMICTAL" and "25", blisterpack of 35 tablets (NDC 0173-0633-10).
—*Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature] in a dry place.*

—**LAMICTAL Starter Kit for Patients Taking Enzyme-Inducing Drugs and Not Taking Valproate,**
25 mg, ~~,~~ ~~w~~White, scored, shield-shaped tablets debossed with "LAMICTAL" and "25" and 100 mg, peach, scored, shield-shaped tablets debossed with "LAMICTAL" and "100", blisterpack of 84, 25-mg tablets and 14, 100-mg tablets (NDC 0081-0594-01)
Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature] in a dry place and protect from light.

—**LAMICTAL Starter Kit for Patients Not Taking Enzyme-Inducing Drugs or Valproate**
~~,~~25 mg, white, scored, shield-shaped tablets debossed with "LAMICTAL" and "25" and 100 mg, peach, scored, shield-shaped tablets debossed with "LAMICTAL" and "100", blisterpack of 42, 25-mg tablets and 7, 100-mg tablets (NDC 0173-0594-02).
—*Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature] in a dry place and protect from light.*

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/s/

Gurpreet Gill-Sangha
11/7/02 10:34:28 AM
CHEMIST

CMC review for two efficay supplements

Thomas Oliver
11/7/02 11:05:32 AM
CHEMIST