CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-710

Chemistry Review(s)

NDA 21-710

[ ]

(Carbamazepine)
Extended-Release Capsules

Shire Laboratories, Inc.

Chhagan G. Tele, Ph.D.

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

Table of Contents

Appears This Way
On Original

Chemistry Review Data Sheet

1. **NDA 21-710**

2. **REVIEW #:** 1

3. **REVIEW DATE: 08-NOV-2004**

4. **REVIEWER: Chhagan G. Tele, Ph.D.**

5. **PREVIOUS DOCUMENTS:**

Previous Documents	Document Date

6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
Original NDA	13-FEB-2004
Amendment 002 N(BC)	08-MAR-2004
Amendment 002 N(BC)	12-MAR-2004
Amendment 003 N(C)	12 MAR-2004
Amendment 006 N(BC)	06-OCT-2004

7. **NAME and ADDRESS OF APPLICANT:**

Name:	**Shire Laboratories, Inc.**
Address:	1550 East Gude Drive Rockville, MD 20850
Representative:	Rick Lilley, Sr. Vice President, Regulatory Affairs
Telephone:	(240) 453-6447

8. **DRUG PRODUCT NAME/CODE/TYPE:**

a) Proprietary Name: [ ]
b) Non-Proprietary Name (USAN): Carbamazepine
c) Code Name/#: SPD417
d) Chem. Type/Submission Priority:

- Chem. Type: 6
- Submission Priority: S

9. **LEGAL BASIS FOR SUBMISSION:** 505 (b) (2); The RLDs are Carbatrol® (carbamazepine) Extended-release Capsules, 100 mg, 200 mg, and 300 mg, Shire Laboratories, Inc. NDA 20-712 and Tegretol® (carbamazepine) Extended-release Capsules, 100 mg, 200 mg, and 400 mg, Novartis pharmaceuticals NDA 16-608.

10. **PHARMACOLOGICAL CATEGORY:**

Treatment of acute manic or mixed episodes associated with Bipolar I Disorder.

11. **DOSAGE FORM:** Capsules

12. **STRENGTH/POTENCY:** 100 mg, 200 mg, and 300 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:**

USAN Name: 5*H*-Dibenz[b,f]azepine-5-carboxamide

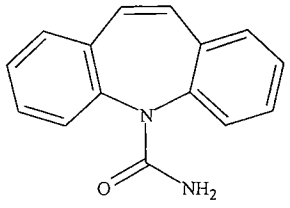
Non-Proprietary Name: Carbamazepine

Chemical Formula: $C_{15}H_{12}N_2O$

Molecular Weight: 236.27

CAS registry #: 298-46-4

Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED
[redacted]	II	[redacted]	Drug Substance	3	Adequate	16-OCT-96 Dr. Martha R. Heimann
[redacted]	II	[redacted]	Drug Substance	3	Adequate	22-FEB-02 Dr. Thomas F. Oliver

[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	20-712	Carbatrol® Capsules
NDA	16-608	Tegretol® Capsules
IND	59,050	Commercial IND (Treatment of bipolar disorder)

Chemistry Review Data Sheet

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	-	-
EES	Overall Recommendation Acceptable	20-OCT-04	S. Ferguson (HFD-322)
Pharm/Tox	Pending	-	-
Biopharm	Pending	-	-
LNC	USAN available	1965	-
Methods Validation	Pending	-	-
DMETS	Unacceptable	09-JUL-2004	Charlie Hoppes, R.Ph., M.P.H.
EA	Acceptable	As per this review	Chhagan Tele, Ph.D.
Microbiology	N/A	-	-

The Chemistry Review for NDA 21-710

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 21-710 for [redacted]® (carbamazepine) is recommended **APPROVAL** from the CMC standpoint.

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

N/A

II. Summary of Chemistry Assessments

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

[redacted]® (carbamazepine, USP) extended-release capsules are indicated for the treatment of acute manic or mixed episodes associated with Bipolar I Disorder. Numerous effects of carbamazepine have been described in published literature. It deceases turnover and weakly blocks norepinephrine, up-regulates rather than down-regulates β-adrenergic receptors, indirectly decreases dopamine turnover and enhances serotonin levels, increases gamma-aminobutyric acid (GABA) turnover, inhibits collapse of sensory neuron growth cones and increases the growth cone area in vitro and protects against neuronal damage in vivo. Carbamazepine, therefore, has a variety of effects upon neurotransmitter systems, intracellular signal transduction systems and may provide protection against neuronal damage. One or more of these effects may provide the basis for the efficacy of carbamazepine in bipolar disorder. Their exact mechanism of action is unknown.

Carbamazepine was originally approved in 1997, under NDA 20-712, as extended-release oral capsules (Carbatrol® Capsules, 100 mg, 200 mg, and 300 mg strengths) manufactured and distributed by Shire Laboratories, Inc. in the treatment of epilepsy and trigeminal neuralgia and approved in 1968, under NDA 16-608, as extended-release oral tablets (Tegretol® Tablets, 100 mg, 200 mg, and 400 mg strengths) manufactured and distributed by Novartis Pharmaceuticals as an anticonvulsant. The proposed product, [redacted]® extended-release capsules, is to be marketed as an oral dosage form in strengths of 100 mg, 200 mg and 300 mg by Shire US Manufacturing Inc., Owings Mills, MD facility. The commercial manufacturing process for [redacted] Extended-Release Capsule is a multi-component formulation consisting of three different types of pellets: immediate-release (IMA), sustained-release (IMB), and enteric-release (IMC) pellets. These pellets will be manufactured using the same commercial process and at the same commercial location (Shire US Manufacturing Inc., Owings Mills, MD). However, the 100 mg finished drug product will be encapsulated, packaged, and labeled at [redacted] The inactive ingredients used in the formulation are all USP/NF Grade (citric acid, colloidal silicon dioxide, lactose monohydrate, microcrystalline cellulose, polyethylene glycol, povidone, sodium lauryl

sulfate, talc, triethyl citrate) with the exception of [ ]. The specifications and test methods for the [ ] were adopted from the manufacturer, [ ] and have not changed from what was previously filed and approved for Carbatrol®. The specifications and test methods for the hard gelatin capsules were adopted from [ ]. Hard gelatin capsules provided by [ ] meets the FDA September 1997 Guidance for Industry for " The Sourcing and Processing of Gelatin to Reduce the Potential Risk Posed by Bovine Spongiform Encephalopathy (BSE) in FDA-Regulated Products for Human Use". Hard gelatin capsule Size #3, Size #1 Elongated, and Size #0 Elongated used for [ ] extended-release capsules, 100 mg, 200 mg, and 300 mg, respectively. The proposed capsule shells for the 100 mg strength is a light blue green opaque body with a yellow opaque cap, for the 200 mg strength, blue opaque body with a yellow opaque cap, and for the 300 mg strength, blue body with a yellow opaque cap. The applicant indicated that the capsule shell colors for SPD417 extended-release capsules are achieved by [ ] of coloring agents used in the current approved capsule shells for Carbatrol® and will be imprinted with the same imprinting ink (White [ ]. The applicant cross-referenced currently approved NDA 20-712 for the finished product specifications and test methods for testing Carbatrol®, with exception of two differences. The appearance differences between SPD417 extended-release capsules and Carbatrol® (extended-release capsules) are the [ ]. The applicant indicated that all analytical methods for the release of the finished product were validated.

Since, the [ ] the capsule shells is possible after exposure to the light and long-term storage. In telecon dated 05-MAR-04 with Zohra Lomri, Senior Manager, Regulatory Affairs was asked to provide photostability data of the drug product. Shire Provided (amendment #003 dated 12-MAR-04) photostability data of SPD417 extended release capsules, 100, 200, and 300 mg strengths to evaluate the capsule shell's resistance to light. The stability studies were performed on drug product manufactured at commercial site, Shire Laboratories, Inc., Rockville, MD site and tested at commercial testing site, Shire US Manufacturing Inc., Owings Mill, MD in the same container/closure system currently approved as the US commercial trade dress for Carbatrol® (extended-release capsules). The applicant conducted [ ] tests for the photostability studies using commercial analytical methods. The applicant indicated that [ ] where the cap and body of the capsule overlap for the unprotected light chamber samples of 100 mg and 200 mg. The 300 mg capsules did not exhibit fading in either the protected or the unprotected light chamber samples. No [ ] was noted in the pellets of the 200 mg and 300 mg samples for all conditions. The 100 mg capsules [ ]. In telecon dated 03-NOV-04 with Ms. Zohra Lomri from Shire and Dr. Tom Oliver and Dr. Chhagan Tele, the issue [ ] in the areas where the cap and body of the capsule overlaps for the unprotected light chamber samples of 100 mg and 200 mg was discussed. We recommended the applicant add a "Protect from light" statement in the storage condition "Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature] in the labeling of [ ] extended-release capsules. The statement "Protect from light" could potentially be removed in the future if real time stability data demonstrates that [ ] is not a problem. In fax dated 03-NOV-04, Shire committed to include a

"Protect from light" statement in the trade dress and physician sample bottles labels for all strengths of SPD417 extended release capsules.

The batch analysis was provided for one batch of each strength of [ ]® extended-release capsules, 100 mg, 200 mg, and 300 mg. The release and stability specifications for the drug product are identical.

The drug substance, carbamazepine, is a white to off-white powder (USP 27, 2004, pp. 322). There are [ ] of Carbamazepine. Carbamazepine [

] . Shire indicated that it [ ] Carbamazepine (supplied by [ ] and uses a drug product formulation and process that does not [to the drug substance. The [ ] drug substance was determined by] according to the current USP method. The [

] The drug substance, carbamazepine, is manufactured and supplied to the applicant by two approved sites, [ ] approved in the original application for Carbatrol® (extended release capsules), NDA 20-712 and [ ] approved as an alternate manufacturing site for Carbamazepine in NDA 20-712/S-015 (approved on 21-FEB-2002). A retest date of [ ] years has been established for the bulk carbamazepine drug substance.

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

[ ] extended-release capsules, 100 mg strength, will be marketed in 120-count 100 cc and 14-count physician samples in 75 cc HDPE bottles (currently approved trade bottle and cap configurations described in NDA 20-712/S-007, approved on 22-DEC-99). Similarly, the 200 mg and 300 mg strengths will be marketed in 120-count 150 cc and 30-count physician samples in 75 cc HDPE bottles currently approved trade bottle and cap configuration described in NDA 20-712, NDA 20-712/S-006 (approved on 28-JUN-99), NDA 20-712/S-008 (approved on 08-NOV-99), and the annual report, dated 03-MAR-03.

The maximum recommended total daily dose is 1600 mg/day, given in divided doses, twice daily. The applicant has requested a 24 month expiration period (shelf life) for all strengths packaged in bottles on the basis of approved Carbatrol® (extended-release capsules) stability data. The proposed expiration dating period of 24 months is not supported by sufficient long-term stability data for the commercial batches of SPD417 extended-release capsules, 100 mg, 200mg, and 300 mg strengths. Based on the available stability data on Carbatrol® (extended-release capsules), 100 mg, 200mg, and 300 mg, we will accept a tentative 24 month expiration dating period until additional real time data is collected.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-710 for [ ] extended release capsules is recommended to be granted **Approval** status from CMC standpoint.

III. Administrative

A. Reviewer's Signature

See electronic signatures in DFS.

B. Endorsement Block

See electronic signatures in DFS.

C. CC Block

See DFS.

45 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

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

/s/

Chhagan Tele
11/8/04 01:19:59 PM
CHEMIST

Thomas Oliver
11/8/04 05:08:45 PM
CHEMIST

FIELD COPY CERTIFICATION

On behalf of Shire Laboratories, Inc. (Shire), I hereby certify that the field copy is a true copy of the Chemistry, Manufacturing, and Controls Section 21 CFR §314.50(d)(1) contained in the archival and review copies of this New Drug Application for SPD417.

R.J. Lilley

Rick Lilley, Ph.D.
Senior Vice President
Regulatory Affairs

12 February 2004
Date

IV. ENVIRONMENTAL ASSESSMENT

CLAIM FOR CATEGORICAL EXCLUSION

The carbamazepine drug product, SPD417 (extended-release capsules) 100mg, 200mg and 300mg, consist of a mixture of immediate-release (IMA) pellets, sustained-release (IMB) pellets, and enteric-release (IMC) pellets. The pellets mixture is encapsulated to provide an extended-release solid oral dosage form. The manufacturing sites identified for the manufacturing of SPD417 drug product are listed in Table 30 below:

Table 30: SPD417 Drug Product Manufacturing Sites

Manufacturing	Strengths	Manufacturing site	Location

All wastes generated as a result of the proposed action will be disposed of in full compliance with local, state and Federal (US) regulations of the Environmental Protection Agency (EPA).

Shire Laboratories Inc. claims a categorical exclusion to the environmental analysis requirements in accordance with categorical exclusion criteria 21 CFR Part 25.31(b) for action on an NDA. The estimated concentration of the substance at the point of entry into the aquatic environment will be below [redacted] part per billion in the fifth year of marketing after approval. Shire laboratories Inc. claims that to the best of its knowledge, no extraordinary circumstances exist that might cause this action to have a significant effect on the quality of the human environment.

Prepared by: Zohra Lomri
Sr. Manager, Regulatory Affairs

The undersigned official certifies that the information presented is true, accurate and complete to the best of Shire Laboratories Inc.'s knowledge.

Richard A. Couch 11-Feb-04

Richard A. Couch, Ph.D. Date
Senior Vice President
Pharmaceutical Sciences
Shire Laboratories Inc.