CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202810Orig1s000

CHEMISTRY REVIEW(S)

TO: **CMC MEMO-TO-FILE**

FROM: **P. Shiromani, Ph.D**

SUBJECT: **NDA 202810: OXCARBAZEPINE EXTENDED RELEASE TABLETS**

DATE: **11-Sep-2012**

The attached Summary Report from the Office of Compliance was received on 10-Sep-2012, with an 'Acceptable' overall recommendation. There are no other CMC pending issues. Accordingly, this NDA is recommended for approval from a CMC perspective. The CMC Review was submitted to DARRTS on 28-Aug-2012.

ATTACHMENT:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 202810/000

Sponsor:

SUPERNUS PHARMS

Org. Code: Priority:

120

3

1550 EAST GUDE DR ROCKVILLE, MD 20850

Stamp Date: 19-DEC-2011

Brand Name:

OXCARBAZEPINE EXTENDED RELEASE TABLETS

PDUFA Date: Action Goal: District Goal:

19-OCT-2012

20-AUG-2012

Estab. Name: Generic Name:

Product Number; Dosage Form; Ingredient; Strengths

001; TABLET, EXTENDED RELEASE; OXCARBAZEPINE; 150MG
002; TABLET, EXTENDED RELEASE; OXCARBAZEPINE; 300MG
003; TABLET, EXTENDED RELEASE; OXCARBAZEPINE; 600MG

FDA Contacts: T. BOUIE

M. HEIMANN

Project Manager

Team Leader

3017961649

3017961678

Overall Recommendation:	ACCEPTABLE	on 10-SEP-2012	by M. STOCK	(HFD-320)	3017964753
	PENDING	on 06-JAN-2012	by EES_PROD		
	PENDING	on 06-JAN-2012	by EES_PROD		

Establishment:

CFN:

(b) (4)

FEI:

(b) (4)

(b) (4)

DMF No:

(b) (4)

AADA:

Responsibilities:

(b) (4)

Profile:

Last Milestone:

(b) (4) "ALSO" (DRUGS)
OC RECOMMENDATION

OAI Status:

NONE

Milestone Date:

06-JAN-2012

Decision:

ACCEPTABLE

Reason:

BASED ON PROFILE

Establishment:

CFN:

(b) (4)

FEI:

(b) (4)

(b) (4)

(b) (4)

DMF No: (b) (4)

AADA:

Responsibilities:

(b) (4)

Profile:

(b) (4)

OAI Status:

NONE

Last Milestone: Milestone Date:

OC RECOMMENDATION

10-SEP-2012

Decision:

ACCEPTABLE

Reason:

DISTRICT RECOMMENDATION

Establishment:

CFN:

(b) (4)

FEI:

(b) (4)

(b) (4)

DMF No:

(b) (4)

AADA:

Responsibilities:

(b) (4)

Profile:

Last Milestone:

(b) (4) "ALSO" (DRUGS)
OC RECOMMENDATION

OAI Status:

NONE

Milestone Date:

06-JAN-2012

Decision:

ACCEPTABLE

Reason:

BASED ON PROFILE

Establishment:

CFN:

(b) (4)

FEI:

(b) (4)

(b) (4)

DMF No:

(b) (4)

AADA:

Responsibilities:

(b) (4)

Profile:

Last Milestone:

(b) (4) "ALSO" (DRUGS)

OC RECOMMENDATION

OAI Status:

NONE

Milestone Date:

06-JAN-2012

Decision:

ACCEPTABLE

Reason:

BASED ON PROFILE

Establishment:

CFN:

(b) (4)

FEI:

(b) (4)

(b) (4)

DMF No:

(b) (4)

AADA:

Responsibilities:

(b) (4)

Profile:

TABLETS, EXTENDED RELEASE

OAI Status:

NONE

Last Milestone: Milestone Date:

OC RECOMMENDATION

23-MAR-2012

Decision:

ACCEPTABLE

Reason:

DISTRICT RECOMMENDATION

Establishment:

CFN:

(b) (4)

FEI:

(b) (4)

(b) (4)

DMF No:

(b) (4)

AADA:

Responsibilities:

(b) (4)

Profile:

Last Milestone:

(b) (4) "ALSO" (DRUGS)
OC RECOMMENDATION

OAI Status:

NONE

Milestone Date:

06-JAN-2012

Decision:

ACCEPTABLE

Reason:

BASED ON PROFILE

Establishment:

CFN:

FEI:

(b) (4)

(b) (4)

DMF No:

(b) (4)

AADA:

Responsibilities:

(b) (4)

Profile:

Last Milestone:

(b) (4) "ALSO" (DRUGS)
OC RECOMMENDATION

OAI Status:

NONE

Milestone Date:

06-JAN-2012

Decision:

ACCEPTABLE

Reason:

BASED ON PROFILE

Establishment:

CFN:

FEI:

3005209462

SUPERNUS PHARMACEUTICALS INC

DMF No:

ROCKVILLE, , UNITED STATES 208501339

AADA:

Responsibilities:

(b) (4)

Profile:

CONTROL TESTING LABORATORY

OAI Status:

NONE

Last Milestone: Milestone Date:

OC RECOMMENDATION

06-JAN-2012

Decision:

ACCEPTABLE

Reason:

BASED ON PROFILE

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

/s/

PRAFULL K SHIROMANI
09/11/2012

RAMESH K SOOD
09/11/2012

NDA 202-810

SPN8040-Oxcarbazepine Extended Release Tablets 150mg, 300mg & 600mg

Supernus Pharmaceuticals Inc.

Prafull Shiromani Ph.D.

Division of Pre-Marketing Assessment 1
Division of Neurology Products
Office of New Drug Quality Assessment

Table of Contents

Chemistry Review Data Sheet

1. NDA 202-810

2. REVIEW #: 1

3. REVIEW DATE: 27-Aug-2012

4. REVIEWER: Prafull Shiromani Ph.D.

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA	19-Dec-2011
Supplement S0012: Applicant's Response to FDA CMC IR Letter	21-Jun-2012
Supplement S0015: Applicant's Response to FDA CMC IR Letter	26-Jul-2012
Supplement S0018: Applicant's Response to FDA CMC IR Letter	13-Aug-2012
Supplement S0019: Applicant's Response to ONDQA Biopharm IR Letter.	22-Aug-2012

7. NAME & ADDRESS OF APPLICANT:

Name: Supernus Pharmaceuticals, Inc.

Chemistry Review Data Sheet

Address:	1550 East Gude Drive, Rockville, MD 20850
Representative:	Tami Martin, RN, Esq, Vice-President, Regulatory Affairs
Telephone:	301-838-2500

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: (b) (4)
b) Non-Proprietary Name (USAN): Oxcarbazepine
c) Code Name/# (ONDC only): SPN8040
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b) (2)

10. PHARMACOL. CATEGORY: Antiepiletic

11. DOSAGE FORM: Extended release tablet

12. STRENGTH/POTENCY: 150mg, 300mg & 600mg

13. ROUTE OF ADMINISTRATION: Oral

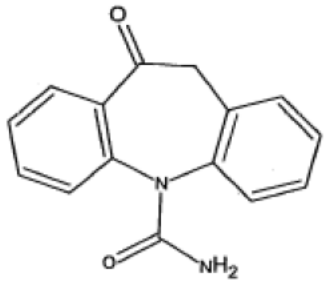
14. Rx/OTC DISPENSED: ___Rx ___OTC

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: 10,11-dihydro-10-oxo-5*H*-dibenz[*b,f*]azepine-5-carboxamide; 5*H*-dibenz[*b,f*]azepine-5-carboxamide, 10,11-dihydro-10-oxo-

CAS Number: 28721-07-5

Molecular Formula: $C_{15}H_{12}N_2O_2$

Molecular Mass: 252.27

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED		COMMENTS LOA Date
(b) (4)	II	(b) (4)	Oxcarbazepine	3	Adequate	26-Apr-2012		02-N0v-2011
	IV		(b) (4)	4				20-May-2008
	III			4				02-Jun-2008
	III			4				11-Aug-2011
	III			4				12-Sep-2011
	III			4				11-Aug-2011

(b) (4)		(b) (4)					
	III		4				11-Aug-2011
	III		4				10-Aug-2011
	III		4				30-Aug-2011
	III		4				02-Jul-2011
	III		4				11-Aug-2011
	III		4				11-Aug-2011
	III		4				02-Jul-2011

[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: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER

Chemistry Review Data Sheet

Biometrics	N/A		
EES	Pending		
Pharm/Tox	Pending		
Biopharm	Approval	23-Aug-2012	S. Saurez
LNC			
Methods Validation	Samples of the DS, DP and reference compounds are available.	14-Aug-2012	Validation is not required since the analytical methods are conventional.
OPDRA			
EA	Their claim for categorical exclusion is acceptable.	14-Aug-2012	P. Shiromani
Microbiology	N/A		

The Chemistry Review for NDA 202-810

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has provided adequate responses to the FDA CMC IR letters. Additionally, the ONDQA Biopharm review has been satisfactorily completed and submitted into DARRTS; revised drug product dissolution specifications are recommended therein, which are acceptable to the applicant. There are no CMC pending issues. However, OC's overall acceptable recommendation based on site inspection is pending and when received will be entered into DARRTS as a Memo-to-File. Once this acceptable recommendation is received the NDA will be recommended for approval from a CMC perspective.

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)

Oxcarbazepine was originally developed by Novartis Pharmaceuticals for treatment of epilepsy. It is marketed, under the trade name Trileptal®, as 150 mg, 300 mg and 600 mg immediate release tablets (NDA 21-014) and a 60 mg/mL oral suspension (NDA 21-285); generic versions of both products are also available.

Supernus Pharmaceuticals has developed extended release (XR) tablet formulations of the DS. In the current NDA, the firm proposes marketing of oxcarbazepine XR tablets for adjunctive therapy in the treatment of partial seizures in adults and children (b)(4) 17 years. Three strengths are proposed, 150 mg, 300 mg, and 600 mg. The products are intended for once daily treatment versus twice daily dosing for the immediate release products currently available. The recommended dose is 1200mg to 2400 mg per day.

The active ingredient, oxcarbazepine, is a neutral molecule. Therefore, there is no issue of consistency between the established name (oxcarbazepine extended release tablets) and the labeled potency.

DRUG SUBSTANCE

The active ingredient, oxcarbazepine (chemical name: 10,11-dihydro-10-oxo-5*H*-dibenz[*b,f*]-azepine-5-carboxamide), is a well characterized, neutral, small molecule with molecular formula C15H12N2O2 and molecular weight 252.27. The bulk drug substance is an off-white to yellow crystalline powder that is practically insoluble in water over the pH range 1 to 8. Oxcarbazepine exhibits (b) (4) have been listed in the literature (US Patent 7,183,272).

The bulk drug substance is manufactured by (b) (4) under DMF (b) (4), which is cross-referenced for CMC information. The DMF has been reviewed previously and found adequate (M. Bennett, 26-Apr-2012). Limited manufacturing and control information is provided in the NDA itself including a brief description of the final (b) (4) step, which the applicant indicates is not described in the drug substance manufacturer's DMF.

(b) (4) The proposed regulatory specification appears generally consistent with the USP, with additional testing including related substances (not included in USP monograph), identification by (b) (4), and particle size. It is noted, however, that the proposed assay/related substances HPLC method differs from the USP HPLC assay method. The USP monograph method uses a C18 column, methanol-acetonitrile-phosphate buffer pH 6.8 mobile phase, and UV detection at 215 nm. The applicant's method uses a C18 column, methanol-water mobile phase, and UV detection at 220 nm. Additionally, the USP monograph requires determination of (b) (4) while the applicant proposes use of a loss on drying test (USP <731>). In response to the CMC IR Letter, the applicant has implemented the USP methods as regulatory methods, as evident in the revised DS specification table.

The DS has been assigned a (b) (4) re-test date by the DMF holder.

The applicant has responded satisfactorily to DS comments in the Agency CMC IR Letter.

DRUG PRODUCT

The proposed dosage form is a matrix type, film-coated, extended release tablet containing 150 mg, 300 mg or 600 mg of oxcarbazepine. All tablet strengths are presented as modified oval shaped tablets which are differentiated by size, color and imprint. 150 mg tablets are yellow andimprinted with "150" on one side, along the long axis, with black ink. 300 mg tablets are brown and imprinted with "300" and 600 mg tablets are brownish-red, imprinted with “600”.

The tablet (b) (4) formulations are qualitatively similar, but not directly proportional. The relative proportions of oxcarbazepine, (b) (4) SLS, povidone, and magnesium stearate (b) (4) The percentage of (b) (4) microcrystalline cellulose in the tablet (b) (4) increases with increasing tablet strength; the percentage of hypromellose (b) (4).

The applicant presents an empirical approach to development of the product formulations and manufacturing process; however detailed information on development is provided in the Pharmaceutical Development Section. Oxcarbazepine extended release tablets will be manufactured by a contract manufacturer, (b) (4). The manufacturing process involves conventional unit processes such as (b) (4), film-coating and printing.

The ONDQA Biopharm review has been satisfactorily completed and submitted into DARRTS (23-Aug-2012). The following dissolution method and revised dissolution acceptance criteria are acceptable for Oxcarbazepine ER tablets, 150 mg, 300 mg and 600 mg:

USP Apparatus/RPM	Medium	Volume	Acceptance Criteria
II/75 rpm	De-ionized water with 1% (w/v) SLS	900 mL	2 hrs: (b) (4)% 4 hrs: (b) (4)% 8 hrs: > (b) (4)%

The revised drug product specifications are included in the applicant's supplement dated 22-Aug-2012 (S0019) and are included in this review.

The applicant has accepted the Agency's recommendation to include tests for moisture and microbial limits in the DP specification.

The applicant has responded satisfactorily to DP comments in the Agency CMC IR Letter.

Two packaging configurations are proposed. The trade configuration is 100-count HDPE bottles containing (b) (4) coil and desiccant canister. The bottles are inductively sealed (b) (4) closures. Physician samples will be packaged in (b) (4) blisters.

The NDA stability package includes long-term stability data through 24 months and accelerated data through 6 months for three commercial-scale batches per tablet strength packaged in HDPE bottles and (b) (4) blisters. The proposed commercial expiration dating period of 36 months is supported by the statistical analysis of individual batches for oxcarbazepine extended-release tablets, 150mg, 300mg, and 600mg in 100-count bottles and 5-count blister packs, in conformance to ICH Q1E and hence, is acceptable.

The firm has submitted a claim for categorical exclusion under 21 CFR 25.31(b) which states that the estimated concentration of the active moiety at the point of entry into the aquatic environment will be below one part per billion (1 ppb). Their request is granted by this reviewer.

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

- The recommended daily dose is 1200 to 2400 mg/day
- Adjunctive Therapy/Adults: initiated with a dose of 600 mg/day, given in once a-day regimen. Maximum increments of 600 mg/day at approximately weekly intervals
- Adjunctive Therapy/Children: (Aged (b) (4) 17 Years): target maintenance dose should be increased by no more than 600 mg/week
- Patients may be converted to once/day dosing with clinical oversight.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has provided adequate responses to the FDA CMC IR letters. Additionally, the ONDQA Biopharm review has been satisfactorily completed and submitted into DARRTS; revised drug product dissolution specifications are recommended therein, which are acceptable to the applicant. There are no CMC pending issues. However, OC's overall acceptable recommendation based on site inspection is pending and when received will be entered into DARRTS as a Memo-to-File. Once this acceptable recommendation is received the NDA will be recommended for approval from a CMC perspective.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Chemist Name/Date: Prafull Shiromani Ph.D.
Chemistry Team Leader Name/Date: Ramesh Sood, Ph.D.
Project Manager Name/Date: S. Parancutt

C. CC Block

221 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

PRAFULL K SHIROMANI
08/27/2012

RAMESH K SOOD
08/28/2012

Initial Quality Assessment
Branch I
Division of New Drug Quality Assessment I

OND Division:	Division of Neurology Products
NDA:	202810
Applicant:	Supernus Pharmaceuticals, Inc.
Stamp Date:	19-Dec-2011
PDUFA Date:	19-Oct-2012
Trademark:	TBD
Established Name:	Oxcarbazepine
Dosage Form:	Extended release tablet
Route of Administration:	Oral
Indication:	Antiepileptic
CMC Lead:	Martha R. Heimann, Ph.D.

	Yes	No
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☒	☐

Summary and Critical Issues:

Summary

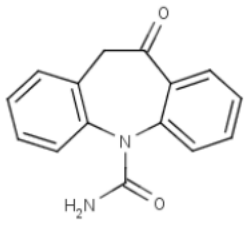
Oxcarbazepine was originally developed by Novartis Pharmaceuticals for treatment of epilepsy. It is marketed, under the trade name Trileptal®, as 150 mg, 300 mg and 600 mg immediate-release tablets (NDA 21-014) and a 60 mg/mL oral suspension (NDA 21-285); generic versions of both products are also available.

Supernus Pharmaceuticals has developed extended release (XR) tablet formulations of oxcarbazepine. In the current NDA, the firm proposes marketing of oxcarbazepine XR tablets for adjunctive therapy in the treatment of partial seizures in adults and children (b) (4) 17 years. Three strengths are proposed, 150 mg, 300 mg, and 600 mg. The products are intended for once daily treatment versus twice daily dosing for the immediate release products currently available. The recommended dose is 1200mg to 2400 mg per day.

Drug Substance

The active ingredient, oxcarbazepine (chemical name: 10,11-dihydro-10-oxo-5*H*-dibenz[*b*,*f*]-azepine-5-carboxamide), is a well characterized, neutral, small molecule with molecular formula $C_{15}H_{12}N_2O_2$ and molecular weight 252.27. The bulk drug substance is an off-white to yellow crystalline powder that is practically insoluble in water over the pH range 1 to 8. Oxcarbazepine exhibits (b) (4) have been listed in the literature (US Patent 7,183,272).

The chemical structure of oxcarbazepine is:



The bulk drug substance is manufactured by [redacted] (b) (4) under DMF [redacted] (b) (4), which is cross-referenced for CMC information. The DMF has been reviewed previously and found adequate (M. Bennett, 20-Jan-2012). Limited manufacturing and control information is provided in the NDA itself. An outline of the manufacturing process for [redacted] (b) (4) oxcarbazepine is provided in Module 3.2.S.2.2 and reproduced in Applicant's Figure 1 below. Module 3.2.S.2.2 also includes a brief description of the final [redacted] (b) (4) step, which the applicant indicates is not described in the drug substance manufacturer's DMF.

[redacted] (b) (4)

Figure 1: Flow Diagram of Oxcarbazepine Synthetic Route [redacted] (b) (4)

The drug substance manufacturer's release specification, which is designated as the regulatory specification, is reproduced below [**Table 1: Oxcarbazepine Regulatory Specifications** (b) (4)]. The applicant also proposes Oxcarbazepine Incoming Specifications (testing limited to identification by FTIR, potency, and examination of certificate of analysis), and Oxcarbazepine Qualification Specifications (full testing equivalent to the drug substance manufacturer's release testing).

Table 1: Oxcarbazepine Regulatory Specifications (b) (4)

Test	Method Type (Method Number)	Acceptance Criteria
Description	Physical observations (QCD/GTP/011) [a]	Off-white to yellow crystalline powder.
Solubility	Dissolve 0.1 gram of sample in 3.0 and 10mL of chloroform (QCD/GTP/014) [a]	Sparingly soluble in chloroform.
Identification IR absorption	IR, USP<197K> (QCD/MH/FP/OXB/001) [a]	IR absorption spectrum in KBr dispersion of sample should be concordant with that of working standard.
Identification HPLC	HPLC/UV (QCD/MH/FP/OXB/001) [a]	Retention time of the sample should be same as that of working standard in the assay method.
Identification X-ray diffraction	X-Ray, USP<941> (QCD/MH/FP/OXB/001) [a]	X-ray diffraction pattern of sample should be concordant with that of working standard.
(b) (4)		

Test	Method Type (Method Number)	Acceptance Criteria
Related substances by HPLC	HPLC/UV (QCD/MH/FP/OXB/001) [a]	(b) (4)
Assay (dry basis)	HPLC/UV (QCD/MH/FP/OXB/001) [a]	
Residual Solvents	GC headspace (QCD/MH/FP/OXB/001) [a]	
Cyanide content	UV-VIS spectroscopy (QCD/MH/FP/OXB/001) [a]	
Particle size distribution [b]	Laser diffraction (QCD/MH/PS/OXC/001) [c]	

NMT: not more than

(b) (4)

(b) (4) The proposed regulatory specification appears generally consistent with the USP, with additional testing including related substances (not included in USP monograph), identification by (b) (4), and particle size. It is noted, however, that the proposed assay/related substances HPLC method differs from the USP HPLC assay method. The USP monograph method uses a C18 column, methanol-acetonitrile-phosphate buffer pH 6.8 mobile phase, and UV detection at 215 nm. The applicant's method uses a C18 column, methanol-water mobile phase, and UV detection at 220 nm. Additionally, the USP monograph requires determination of water content by direct titration (USP <921> Method 1a) while the applicant proposes use of a loss on drying test (USP <731>). The applicant will be asked to provide justification for the proposed methods.

Drug Product

The proposed dosage form is a matrix type, film-coated, extended release tablet containing 150 mg, 300 mg or 600 mg of oxcarbazepine. All tablet strengths are presented as modified oval shaped tablets which are differentiated by size, color and imprint. 150 mg tablets are yellow and imprinted with "150" on one side, along the long axis, with black ink. 300 mg tablets are brown and imprinted with "300" and 600 mg tablets are brownish-red, imprinted with "600".

The unit compositions of Oxcarbazepine Extended-Release Tablets are shown in the tables below which are taken from the respective 3.2.P.1 modules. It is noted that the tablet (b) (4) formulations are qualitatively similar, but not directly proportional. The relative proportions of oxcarbazepine, (b) (4), SLS, povidone, and magnesium stearate (b) (4). The percentage of (b) (4) microcrystalline cellulose in the tablet (b) (4) increases with increasing tablet strength; the percentage of hypromellose (b) (4).

Table 1: Theoretical Composition of Oxcarbazepine Extended-Release Tablets, 150mg

Component and Quality Standard (and Grade, if applicable)	Function	Strength (label claim)	
		Oxcarbazepine Extended-Release Tablets, 150mg	
		Quantity per unit (mg)	% w/w
Oxcarbazepine	Drug substance	150.00	58.25
(b) (4) Microcrystalline Cellulose, NF (b) (4)			(b) (4)
Methacrylic Acid Copolymer (b) (4) (b) (4)			
Sodium Lauryl Sulfate, NF (b) (4) (b) (4)			
Hypromellose (b) (4) USP (b) (4)			
Povidone, USP (b) (4)			
Magnesium Stearate, NF (b) (4) (b) (4)			
(b) (4) Yellow (b) (4)			
Ink, Black (b) (4)			
Purified Water, USP			
Purified Water, USP			
Total		257.50	100.0

(b) (4)

Table 1: Theoretical Formulation Composition of Oxcarbazepine Extended-Release Tablets, 300mg

Component and Quality Standard (and Grade, if applicable)	Function	Strength (label claim)	
		Oxcarbazepine Extended-Release Tablets, 300mg	
		Quantity per unit (mg)	% w/w
Oxcarbazepine	Drug substance	300.0	58.25
Silicified Microcrystalline Cellulose, NF (b) (4)	(b) (4)		
Methacrylic Acid Copolymer (b) (4) (b) (4)			
Sodium Lauryl Sulfate, NF (b) (4) (b) (4)			
Hypromellose (b) (4) USP (b) (4)			
Povidone, USP (b) (4)			
Magnesium Stearate, NF (b) (4) (b) (4)			
(b) (4) Brown (b) (4)			
Ink, Black (b) (4)			
Purified Water, USP			
Purified Water, USP			
Total		515.0	100.0

(b) (4)

Table 1: Theoretical Formulation Composition of Oxcarbazepine Extended-Release Tablets, 600mg

Component and Quality Standard (and Grade, if applicable)	Function	Strength (label claim)	
		Oxcarbazepine Extended-Release Tablets, 600mg	
		Quantity per unit (mg)	% w/w
Oxcarbazepine	Drug substance	600	58.25
Silicified Microcrystalline Cellulose, NF (b) (4)	(b) (4)		
Methacrylic Acid Copolymer (b) (4) (b) (4)			
Sodium Lauryl Sulfate, NF (b) (4) (b) (4)			
Hypromellose (b) (4) USP (b) (4)			
Povidone, USP (b) (4)			
Magnesium Stearate, NF (b) (4) (b) (4)			
(b) (4) Red (b) (4)			
Ink, Black (b) (4)			
Purified Water, USP			
Purified Water, USP			
Total		1030	100.0

The applicant presents an empirical approach to development of the product formulations and manufacturing process; however detailed information on development is provided in the Pharmaceutical Development Section.

Oxcarbazepine extended release tablets will be manufactured by a contract manufacturer, (b) (4). The manufacturing process involves conventional unit processes such as (b) (4) film-coating and printing.

The proposed regulatory specifications for Oxcarbazepine Extended-Release Tablets, 150 mg are summarized in the applicant's Table 1 below. The proposed acceptance criteria for the 300 mg and 600 mg strengths are the same, except for appearance, as for 150 mg tablets.

Table 1: Proposed Commercial Release Specifications for Oxcarbazepine Extended-Release Tablets, 150mg

Test	Method	Specification
Appearance	Visual Inspection (Inspect 10 tablets) AS-LAB003	Yellow modified oval shaped tablets printed "150" on one side, along the long axis, with black ink.
Identification A	HPLC/UV TM-804-102	Chromatographic retention time of oxcarbazepine in sample differs from that in the standard by not more than 0.5 minutes.
Identification B	HPLC/PDA TM-804-102	UV spectra extracted at oxcarbazepine retention time for the sample test solution and the standard solution exhibit maxima and minima at the same wavelengths.
Average Content	HPLC/UV TM-804-102	(b) (4) of label claim
Non-Parent Peaks (Degradation Products)	HPLC/UV TM-804-102	(b) (4)
Dissolution [a]	USP <711> Apparatus 2, 75rpm, 900mL, de-ionized water with 1% (w/v) SLS, HPLC/UV TM-804-201	Time (hours): 2, 4, 8 — % Dissolved: (b) (4)
Uniformity of Dosage Units (Weight Variation) [b]	USP <905>	Meets current USP<905> requirements.

[a] Report dissolution results at 2, 4, and 8 hours. Acceptance criteria for dissolution follow the current USP Section <711> including level L2 and L3 testing, where applicable.

[b] Acceptance criteria for Weight Variation follow current USP Section <905> including 30 unit testing, where applicable.

The proposed test parameters are typical for an extended-release formulation. The analytical procedures appear relatively straight-forward and are adequately described to permit substantive review. A single isocratic, (b) (4) HPLC method is used for identification, assay, related substances and content uniformity. The method is similar to that used for the bulk drug substance. Dissolution results are quantitated using a separate, unrelated HPLC method. With respect to the proposed dissolution acceptance criteria, it is noted that the applicant proposes relatively broad acceptance criteria (b) (4) but has not established an in vitro/in vivo correlation (IVIVC). Acceptability of the proposed dissolution method and limits is deferred to the Biopharmaceutics reviewer.

Two packaging configurations are proposed. The trade configuration is 100-count HDPE bottles containing (b) (4) coil and desiccant canister. The bottles are inductively sealed (b) (4) closures. Physician samples will be packaged in (b) (4) blisters.

The NDA stability package includes long-term stability data through 24 months and accelerated data through 6 months for three commercial-scale batches per tablet strength packaged in HDPE

bottles and (b) (4) blisters. Additionally, per Agency agreement (reference preliminary meeting responses for Type B pre-NDA meeting held on 23 May 2011), batch release data and a stability commitment are provided for a fourth commercial scale batch of 600 mg tablets manufactured using a different tablet press. A 36 month expiry is proposed.

Critical issues for review

Drug Substance:

No critical issues can be identified based on information provided in the NDA. However, as noted above, the applicant will asked to acknowledge USP compendial methods as regulatory methods and to provide justification for use of alternate methods.

Drug Product:

No critical issues were identified during the initial assessment. However, the rationale for varying the relative proportions of (b) (4) microcrystalline cellulose and hypromellose in the tablet (b) (4) changes should be examined.

Additional issues

Administrative: 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 oxcarbazepine to be one part per billion (1 ppb) or greater at the point of entry into the aquatic environment.

Establishment Evaluation: A complete list of manufacturers is appended to the signed copy of the 356h. Manufacturing and testing sites requiring compliance evaluation were entered into EES on 06-Jan-2012.

Labeling/Established Name: The active ingredient, oxcarbazepine, is a neutral molecule. Therefore, there is no issue of consistency between the established name (oxcarbazepine extended release tablets) and the labeled potency.

Comments for 74-Day Letter/Fileability Issues

With respect to the drug substance specification we note inconsistencies with the current USP requirements for Oxcarbazepine. You propose use of an HPLC assay method that differs from the USP assay method. Additionally, the USP monograph requires (b) (4) Please acknowledge the USP methods as regulatory methods and provide justification for use of the proposed alternative methods.

Review, Comments and Recommendation:

It is recommended that the application be filed. It is recommended that a single CMC reviewer be assigned as the drug substance is not a new molecular entity and the drug product design (i.e., eroding matrix tablet) is not novel. The product is an extended-release tablet; therefore, a Biopharmaceutics review will be needed. Due to the simplicity of the product and

manufacturing process this application is not recommended for an office-level or division level regulatory briefing.

Martha R. Heimann, Ph.D. _____
CMC Lead Date

Ramesh Sood, Ph.D. _____
Branch Chief Date

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NDA Number:	**Supplement Number and Type:**	**Established/Proper Name:**
202810	N/A	Oxcarbazepine extended-release tablets
Applicant:	**Letter Date:**	**Stamp Date:**
Supernus Pharmaceuticals	19-Dec-2011	19-Dec-2011

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	X		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	X		
3.	Are all the pages in the CMC section legible?	X		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	X		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**	N/A		
7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		

8.	Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESSMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	X		Categorical exclusion claimed.

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	X		Cross-reference to DMF (b) (4)
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		Cross-reference to DMF
14.	Does the section contain information regarding the characterization of the DS?	X		Cross-reference to DMF
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		Cross-reference to DMF
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		X	
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?	X		
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?	X		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		X	
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	N/A		

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	II	(b) (4)	Oxcarbazepine	02-Nov-2011	
	IV		(b) (4)	20-May-2008	
	IV			02-Jun-2008	
	III			11-Aug-2011	
	III			11-Aug-2011	
	III			12-Sep-2011	
	III			11-Aug-2011	
	III			11-Aug-2011	
	III			10-Aug-2011	
	III			30-Aug-2011	
	III			02-Jul-2011	
	III			11-Aug-2011	
	III			11-Aug-2011	
	III			02-Jul-2011	

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**Is the product quality section of the application fileable?**	X		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	N/A		
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	X		Refer to 74 Day Letter comments above.

{See appended electronic signature page}
Martha R. Heimann, Ph.D.
CMC Lead, DNDQA-1, ONDQA

{See appended electronic signature page}
Ramesh Sood, Ph.D.
Branch Chief, DNDQA-1, ONDQA

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

/s/

MARTHA R HEIMANN
01/20/2012

RAMESH K SOOD
01/20/2012