CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022416Orig1s000

CHEMISTRY REVIEW(S)

Aptiom®
(eslicarbazepine acetate) Tablets
NDA 22-416

Summary Basis for Recommended Action
From Chemistry, Manufacturing, and Controls

Applicant: Sunovion Pharmaceuticals, Inc.
84 Waterford Drive
Marlborough, MA 01752-7010

Indication: Eslicarbazepine acetate is a novel voltage-gated sodium channel blocker. As a third-generation member of the first-line dibenz[b,f]azepine antiepileptic drugs represented by carbamazepine (first-generation) and oxcarbazepine (second-generation) it is intended for use as an adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy.

Presentation: Eslicarbazepine acetate tablets will be available as immediate release in 200 mg, 400 mg, 600 mg, and 800 mg strengths. All tablets are white, the 400 mg is round with no groove or score line, the 200 mg, 600 mg, and 800 mg are oblong with a groove on one side. The 200 mg tablet is embossed ESL 200 on one side, the 400 mg tablet is embossed ESL 400 on one side, the 600 mg is embossed ESL 600 on one side and the 800 mg is embossed ESL 800 on one side. The tablets come in white opaque HDPE bottles with (b) (4) caps and induction seal (200 mg: 30-count/45 cc, 60-count 30 cc bottle; 400 mg: 30-count/30 cc; 600 mg: 60-count/75 cc and 90-count/160 cc; 800 mg: 30-count/75 cc and 90-count/160 cc) or (b) (4) aluminum blister packaging (400 mg, 600 mg, and 800 mg: 7-count; and a starter pack containing a 7-count 400 mg with 7-count 800 mg).

EER Status: Acceptable, 1-Aug-2013

Consults: Methods Validation – Revalidation by Agency was not requested.
EA – Categorical exclusion granted under 21 CFR §25.31(c).
Pharm Tox – Acceptable, 6-Sep-2013 – C. Toscano
Biopharmaceuticals – Acceptable, 17-Oct-2013 – E. Chikhale

Post-Approval Agreements: None

A tertiary review was completed during the previous review cycle by Dr. Christine Moore (16-Apr-2010). During that review cycle, the CMC recommendation was for approval. In the current review cycle, a 200 mg dose strength is introduced to provide an additional titration dose. No changes have been made to the drug substance since the previous review cycle.

Drug Substance:
Eslicarbazepine acetate drug substance is a white to off-white, odorless, crystalline solid, manufactured by [redacted] (b) (4) for Bial of Portugal. CMC information on the drug substance was provided in this NDA in summary form and in detail in type II DMF No. 22026 (Bial-Portela & Ca S.A., Portugal). All CMC information provided in the DMF and an amendment to the DMF for the drug substance was adequate to support its approval for use in the drug product.

Conclusion: The drug substance is satisfactory.

Drug product:
The drug product is a conventional immediate release tablet of four strengths: 200, 400, 600 and 800 mg. Dosing of the drug product requires titration. Proposed dosing is approximately one week at 400 mg per day, then approximately one week at [redacted] (b) (4) 800 mg day. The normal dose is anticipated to be 800 mg per day, but can go up to 1200 mg day. Adequate data was provided to support divisibility of the 200mg, 600 mg and 800 mg strength tablets but not for the 400 mg strength. Consequently, the 400 mg tablet has no score line. A dose reduction is recommended in patients with moderate and severe renal impairment (i.e., creatinine clearance less than 50 mL/min). The recommended starting dose is 200 mg once daily for two weeks followed by 400 mg once daily. The dosage may be increased to a maximum of 600 mg once daily.

The drug product is manufactured using [redacted] (b) (4) eslicarbazepine acetate drug substance. The drug product formulation includes eslicarbazepine acetate drug substance, povidone [redacted] (b) (4), croscarmellose sodium [redacted] (b) (4), and magnesium stearate [redacted] (b) (4) The tablets are manufactured using [redacted] (b) (4)

The new, 200 mg dose strength [redacted] (b) (4) This issue has been resolved; refer to biopharmaceutics review by Dr. Elsbeth Chikhale (17-Oct-2013), which recommends approval.

Conclusion: Drug product is satisfactory, pending resolution of labeling.

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

The analytical methods used in the testing procedures (release, stability and in-process) are well known and widely used by the pharmaceutical industry, and the validation reports contained in the application were reviewed to verify this, so further validation by Agency laboratories is not requested.

Overall Conclusion: Approval from the CMC perspective is recommended.

Ali Al-Hakim
Acting Division Director, DPA I/ONDQA

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/s/

ALI H AL HAKIM
10/21/2013
Acting for Ramesh Sood

NDA 22-416

Aptiom®
(Eslicarbazepine Acetate) Tablets

Sunovion Pharmaceuticals, Inc.

Charles F. Jewell Jr.
Division of Neurology Products

Reference ID: 3393315

The Chemistry Review for NDA 22416

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is adequate from the chemistry, manufacturing and controls (CMC) perspective, and the manufacturing sites have received an overall acceptable rating from the CDER Office of Compliance (CDER-OC) as reported in the Establishment Evaluation System (EES). The previous review did not recommend approval because the 200 mg strength tablet did not qualify for a biowaiver [redacted] (b) (4), rendering its dissolution profile non-similar to the appropriate comparator. However, since then, the biopharmaceutics review team (Dr. Elsbeth Chikhale and Dr. Angelica Dorantes) found data in the application that supported the bioequivalence of a previously used 200 mg tablet in clinical studies, not the same formulation proposed for marketing, but similar, [redacted] (b) (4) and was shown to be bioequivalent with formulations relevant to the proposed marketing formulation. So a biowaiver was granted, providing that the applicant updated the dissolution specification for the 200 mg strength, to a single point Q = [redacted] (b) (4) at 15 minutes, to account for [redacted] (b) (4) The new specification in captured below in this revision of the CMC review.

If this application is approved, the following should be communicated to the applicant in the approval letter:

- Based on the available stability data, a 24-month expiration date is assigned to the 200 mg strength tablets and a 48-month expiration date is assigned to all configurations of the other three strengths. Drug product should be stored at 25°C (77°F); with temperature excursions in the range of 15°C to 30°C (59°F to 86°F) permitted.

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

None.

II. Summary of Chemistry Assessments

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

Eslicarbazepine acetate [(S)-10-acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide, ESL, BIA 2-093, SEP-0002093] is a novel voltage-gated sodium channel blocker. It can be considered a member of a third generation in an established family of dibenz[b,f]azepine antiepileptic drugs represented by carbamazepine (first-generation) and oxcarbazepine (second-

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generation). Unlike carbamazepine it is not metabolized to carbamazepine-10-11 epoxide and is not susceptible to auto-induction of its own metabolism. Unlike oxcarbazepine, it is not as readily metabolized into a racemic mixture of both eslicarbazepine and R-licarbazepine. The acetate is hydrolyzed to give mainly eslicarbazepine, the moiety responsible for the pharmacological effect.

The finished drug product, Aptiom® (eslicarbazepine acetate) Tablets are immediate release tablets of four different strengths, 200 mg, 400 mg, 600 mg and 800 mg. For the initial submission of this NDA, only three strengths were provided. The applicant has introduced a new 200 mg strength tablet in this resubmission. Previously the other three strengths were found adequate from the CMC perspective. All tablets are (b) (4) The proposed marketing configuration consists of tablets in bottles (HDPE with (b) (4) caps and an aluminum induction seal; oblong bottles are the preferred configuration but round bottles in cartons are an alternative configuration), or tablets in (b) (4)/ALU blisters. Blisters come in capacity of seven cards that are further packaged in cardboard wallets. The blisters are used for physician's samples and starter kits. The 200 mg, 600 mg and 800 mg strengths are white oblong tablets with a functional score on one side, and identifying engraving for substance and strength on the other side (ESL 200, ESL 600 or ESL 800). The score is demonstrated functional from the CMC and biopharmaceutics perspective. The 400 mg tablet is white round bi-convex with no score and engraved ESL 400 on one side.

The drug substance is a white to off-white, odorless crystalline solid, (b) (4) with a melting point of 184°C to 187°C (melts with decomposition). It is manufactured by (b) (4) under DMF 22026 for BIAL-Portela & C S.A. (Portugal) (BIAL is the DMF holder). It is only very slightly soluble in aqueous solvents. It is not ionizable under physiological conditions (pH = 1.2 to 7.4). It is not hygroscopic. Permeability studies indicate it is highly permeable, therefore it is expected to be easily absorbed by passive transport. The absorption rate will be directly proportional to its rate of dissolution. The drug substance is (b) (4) The drug substance has a demonstrated (b) (4) retest date supported by adequate stability studies at long term storage conditions (25°C / 60% RH).

Eslicarbazepine acetate is a single stereo-isomer, carbon-10 has the S-configuration. This assignment is experimentally supported from a single-crystal x-ray diffraction study of a derivative. A chiral chromatographic method was developed and used to verify the stereochemical purity of the drug substance. (b) (4)

The tablet manufacturing process was explored and developed by Bial and transferred to (b) (4) for scale-up to commercial scale. Early clinical studies were done with lower strength tablets. To obtain larger strengths, (b) (4) Once

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desired strengths were determined in clinical studies, (b) (4) was developed to produce all required strengths. The commercial formulation is designated formulation FP, to differentiate it from formulations FN (400 mg), FK (600 mg) and FC (800 mg) used in pivotal clinical studies. (b) (4)

Batches of tablets using the different formulations were found to be equivalent when compared by human bioavailability studies. *In vitro* dissolution profiles across three pH ranges demonstrated adequate similarity based on similarity factor f2. Overall, tablets from the commercial formulation demonstrate a better dissolution profile (b) (4) The dissolution assay used a two-point specification (dissolution reported at 15 minutes and 45 minutes) in order to differentiate dissolution profiles.

A biowaiver was granted for the 200 mg strength tablet as discussed above in section I A..

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

Eslicarbazepine acetate tablets are intended for use as an adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy. Treatment should be initiated with a once daily dose of 400 mg, for one week. Daily dosing may be increased at increments of 400 mg at approximately weekly intervals to a maximum recommended daily dose of 1200 mg once daily. The usual maintenance dose is 800 mg once daily. The 200 mg tablets are designed to be used in patients that required a lower starting dose than 400 mg per day (patients with renal impairment).

Eslicarbazepine acetate tablets will be available in the following commercial configurations:

- 200 mg strength
  - 30-count bottles (oblong, 45 cc bottle / 28 mm cap)
  - 60-count bottles (round, 30 cc bottle / 28 mm cap)
- 400 mg strength
  - 30-count bottles (oblong, 45 cc bottle / 28 mm cap)
  - 30-count bottles (round, 30 cc bottle / 28 mm cap)
  - 7-count blisters in wallet (sample presentation)
  - 7-count blisters with 7-count 800 mg strength blisters in wallet (starter pack)

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- 600 mg strength
  - 60-count bottles (oblong, 75 cc bottle / 33 mm cap)
  - 90-count bottles (oblong, 160 cc bottle / 38 mm cap)
  - 60-count bottles (round, 85 cc bottle / 33 mm cap)
  - 90-count bottles (round, 120 cc bottle / 38 mm cap)
  - 7-count blisters in wallet (sample presentation)
- 800 mg strength
  - 30-count bottles (oblong, 75 cc bottle / 33 mm cap)
  - 90-count bottles (oblong, 160 cc bottle / 38 mm cap)
  - 30-count bottles (round, 50 cc bottle / 33 mm cap)
  - 90-count bottles (round, 150 cc bottle / 38 mm cap)
  - 7-count blisters in wallet (sample presentation)
  - 7-count blisters with 7-count 400 mg strength blisters in wallet (starter pack)

Based on stability data, 24-months expiration dating is assigned to the 200 mg strength tablets and 48-months expiration dating is assigned to all configurations of the other three strengths. Drug product should be stored at 25°C (77°F); with temperature excursions in the range of 15°C to 30°C (59°F to 86°F) permitted.

The drug substance is designed to be rapidly metabolized to eslicarbazepine, the pharmacologically active moiety, and it is demonstrated that eslicarbazepine and (R)-licarbazepine are produced in approximately a (b) (4). Systemic exposure to eslicarbazepine acetate (the parent drug) is negligible in humans.

C. Basis for Approvability or Not-Approval Recommendation

The drug substance as manufactured was adequately characterized with respect to chemical purity, stereo-chemical purity, stability, impurity profile, physical properties and consistency in manufacture. The manufacturing process for the drug product was adequately studied and optimized to produce a controlled and consistent product. The drug product has adequate stability in the to-be-marketed packaging configurations as demonstrated by stability studies. This supports an approvability recommendation from the chemistry, manufacturing and controls perspective.

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

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Reviewer Comments: Below, the most up-to-date Establishment Evaluation System report is enclosed, which provides and overall acceptable recommendation from the Agency's Office of Compliance:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 22416/000	**Action Goal:**	
Stamp Date:	30-MAR-2009	**District Goal:**	12-SEP-2013
Regulatory:	11-NOV-2013		
Applicant:	SUNOVION	**Brand Name:**	SEP-0002093 ESLICARBAZEPINE ACETATE
	84 WATERFORD DR	**Estab. Name:**	
	MARLBOROUGH, MA 01752	**Generic Name:**	SEP-0002093 ESLICARBAZEPINE ACETATE
Priority:	1S	**Product Number; Dosage Form; Ingredient; Strengths**	
Org. Code:	120	002; TABLET; ESLICARBAZEPINE ACETATE; 600MG 001; TABLET; ESLICARBAZEPINE ACETATE; 400MG 003; TABLET; ESLICARBAZEPINE ACETATE; 800MG	

Application Comment: AS OF WRAP UP MEETING, LABELING AND CLINICAL ISSUES ONLY, LIKELY A CR LETTER TO BE ISSUED (on 10-MAR-2010 by JOHNSONE)

NDA IS FOR NEW MOLECULAR ENTITY, ESLICARBAZEPINE ACETATE. (on 10-APR-2009 by M. HEIMANN () 3017961678)

FDA Contacts:	C. JEWELL	Prod Qual Reviewer	3017964232
	T. BOUIE	Product Quality PM	3017961649
	S. SUN	Regulatory Project Mgr	3017960036
	M. HEIMANN	Team Leader	3017961678

Overall Recommendation:	ACCEPTABLE	on 01-AUG-2013	by R. SAFAAI-JAZI	()	3017964463
	PENDING	on 14-SEP-2012	by EES_PROD		
	PENDING	on 14-SEP-2012	by EES_PROD		
	ACCEPTABLE	on 30-SEP-2009	by EES_PROD		

October 18, 2013 2:14 PM **FDA Confidential - Internal Distribution Only** **Page 1 of 13**

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Establishment: **CFN:** **FEI:** 3007703969

BIAL PORTELA & C S.A.

A AVENIDA DA SIDERURGIA NACIONAL
S. MAMEDE DO CORONADO, , PORTUGAL 4745-4575

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE STABILITY TESTER

Establishment Comment: THIS FACILITY IS THE DMF HOLDER FOR DMF 22026 (ESLICARBAZEPINE ACETATE) (on 08-APR-2009 by D. HENRY () 3017964227)

THE US AGENT FOR THIS FACILITY IS SEPRACOR INC, 84 WATERFORD DRIVE; MARLBOROUGH MA 01752-7010. THE CONTACT PERSON IS KATHLEEN GRIM; 508-787-4020; EMAIL: KATHLEEN.GRIM@SEPRACOR.COM (on 10-APR-2009 by D. HENRY () 3017964227)

DRUG SUBSTANCE STABILITY TESTING (on 13-SEP-2012 by T. BOUIE () 3017961649)

Profile: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) **OAI Status:** NONE

Milestone Name / Comment	Milestone Date	Request Type	Planned Completion	Decision / Reason	Creator
SUBMITTED TO OC	10-APR-2009				HEIMANNM
SUBMITTED TO DO	13-APR-2009	Product Specific and GMP Inspection			STOCKM
ASSIGNED INSPECTION TO IB	15-APR-2009	Product Specific and GMP Inspection			JOHNSONE
INSPECTION SCHEDULED	11-AUG-2009		15-SEP-2009		IRIVERA
INSPECTION PERFORMED	15-SEP-2009		15-SEP-2009		JOHNSONE
DO RECOMMENDATION EI WAS NAI.	30-SEP-2009			ACCEPTABLE INSPECTION	JOHNSONE
OC RECOMMENDATION	30-SEP-2009			ACCEPTABLE DISTRICT RECOMMENDATION	JOHNSONE
SUBMITTED TO OC	14-SEP-2012				BOUIET
SUBMITTED TO DO GMP AC REC. WILL EXPIRE 15-SEP-2012. BASED ON APPLICATION, CR LETTER LIKELY.	14-SEP-2012	10-Day Letter			SAFAAIJAZIR
ASSIGNED INSPECTION TO IB	20-SEP-2012	GMP Inspection			PHILPYE
REQUEST CANCELLED	26-SEP-2012			HUMAN ERROR	BOUIET
SUBMITTED TO OC	01-MAR-2013				BOUIET
SUBMITTED TO DO PREVIOUSLY INSPECTED FOR PS+GMP. PROFILE STILL INITIAL.PDUFA GOAL DATE: 11-AUG-2013	04-MAR-2013	10-Day Letter			SAFAAIJAZIR
UNDER REVIEW	13-MAR-2013				PHILPYE
DO RECOMMENDATION	14-MAR-2013			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE

OC RECOMMENDATION	18-MAR-2013	ACCEPTABLE	SAFAAIJAZIR
		DISTRICT RECOMMENDATION	

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE PACKAGER

Establishment Comment: MANUFACTURE OF DRUG SUBSTANCE
PACKAGING OF DRUG SUBSTANCE. (b) (4)

Profile: (b) (4) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	10-APR-2009				HEIMANNM
SUBMITTED TO DO	13-APR-2009	Product Specific and GMP Inspection			STOCKM
DO RECOMMENDATION	15-APR-2009			ACCEPTABLE	JOHNSONE
10/2007 EI WAS VAI - 483 ISSUES WERE RELATED TO INADEQUATE SOPS AND INVESTIGATION PROCEDURES, ADEQUATE FIRM RESPONSE, ACCEPTABLE FOR (b) (4)				BASED ON FILE REVIEW	
OC RECOMMENDATION	15-APR-2009			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	14-SEP-2012				BOUIET
SUBMITTED TO DO	14-SEP-2012	Product Specific and GMP Inspection			SAFAAIJAZIR
ASSIGNED INSPECTION TO IB	20-SEP-2012	Product Specific and GMP Inspection			PHILPYE
REQUEST CANCELLED	26-SEP-2012				BOUIET
				HUMAN ERROR	
SUBMITTED TO OC	01-MAR-2013				BOUIET
SUBMITTED TO DO	04-MAR-2013	Product Specific and GMP Inspection			SAFAAIJAZIR
NME WITH NO PRIOR PS+GMP.PDUFA GOAL DATE: 11-AUG-2013					
DO RECOMMENDATION	12-MAR-2013			ACCEPTABLE	PHILPYE
				INSPECTION	
OC RECOMMENDATION	15-MAR-2013			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: PERFORMS RESIDUAL SOLVENTS TESTING FOR RELEASE OF DRUG SUBSTANCE (b) (4) (b) (4)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				**Reason**	
SUBMITTED TO OC	10-APR-2009				HEIMANNM
SUBMITTED TO DO	13-APR-2009	Product Specific and GMP Inspection			STOCKM
ASSIGNED INSPECTION TO IB	15-APR-2009	Product Specific and GMP Inspection			JOHNSONE
INSPECTION SCHEDULED	15-JUL-2009		29-JUL-2009		IRIVERA
INSPECTION PERFORMED	(b) (4)				DIGIULIOD

The current inspection did not reveal significant deficiencies regarding the NDAs and ANDAs covered or CGMP compliance. The Quality and Laboratory Systems were covered and correction to the previous inspection deficiencies was confirmed. Issues pertaining to QA were discussed with firm management. Deficiencies included the need to better document corrective actions on NCR reports and closing investigations in a timely manner. No FDA-483 was issued.

There were no samples collected and no refusals were experienced during the inspection.

INSPECTION PERFORMED	(b) (4)				JOHNSONE
DO RECOMMENDATION EI WAS NAI, ACCEPTABLE FOR CTL	02-SEP-2009			ACCEPTABLE INSPECTION	JOHNSONE
OC RECOMMENDATION	02-SEP-2009			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM
SUBMITTED TO OC	14-SEP-2012				BOUIET
SUBMITTED TO DO PAI PREVIOUSLY CONDUCTED	14-SEP-2012	GMP Inspection			SAFAAIJAZIR
ASSIGNED INSPECTION TO IB	20-SEP-2012	GMP Inspection			PHILPYE
REQUEST CANCELLED	26-SEP-2012			HUMAN ERROR	BOUIET

SUBMITTED TO OC	01-MAR-2013			BOUIET
SUBMITTED TO DO POAI. PDUFA GOAL DATE: 11-AUG-2013	04-MAR-2013	10-Day Letter		SAFAAIJAZIR
UNDER REVIEW	13-MAR-2013			PHILPYE
DO RECOMMENDATION	20-MAR-2013		ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION CTL	20-MAR-2013		ACCEPTABLE DISTRICT RECOMMENDATION	PRABHAKARAR

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: (b) (4)

Establishment Comment: (b) (4)

Profile: (b) (4) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	10-APR-2009				HEIMANNM
SUBMITTED TO DO	13-APR-2009	Product Specific and GMP Inspection			STOCKM
DO RECOMMENDATION 9/2008 EI WAS NAI	15-APR-2009			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	16-APR-2009			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM
SUBMITTED TO OC	14-SEP-2012				BOUIET
SUBMITTED TO DO (b) (4)	14-SEP-2012	10-Day Letter			SAFAAIJAZIR
UNDER REVIEW	20-SEP-2012				PHILPYE
REQUEST CANCELLED	26-SEP-2012			HUMAN ERROR	BOUIET
REQUEST CANCELLED	26-SEP-2012			HUMAN ERROR	BOUIET
SUBMITTED TO OC	01-MAR-2013				BOUIET
OC RECOMMENDATION	04-MAR-2013			ACCEPTABLE BASED ON PROFILE	SAFAAIJAZIR

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

FINISHED DOSAGE RELEASE TESTER

Establishment Comment: PERFORMS MICROBIOLOGICAL TESTING OF THE DRUG PRODUCT FOR RELEASE AND STABILITY TESTING (b) (4)
(b) (4)

PERFORMS THE FOLLOWING TESTS FOR RELEASE OF DRUG SUBSTANCE: IDENTIFICATION MELTING POINT, HEAVY METALS, RESIDUE ON IGNITION, ENANTIOMETRIC PURITY, HPLC ASSAY, PURITY, MICROBIAL. (b) (4)
(b) (4)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	10-APR-2009				HEIMANNM
SUBMITTED TO DO	13-APR-2009	Product Specific and GMP Inspection			STOCKM
DO RECOMMENDATION	23-APR-2009			ACCEPTABLE	JOHNSONE
07/2007 EI WAS NAI, ACCEPTABLE FOR CTL.				BASED ON FILE REVIEW	
OC RECOMMENDATION	24-APR-2009			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	
SUBMITTED TO OC	14-SEP-2012				BOUIET
OC RECOMMENDATION	14-SEP-2012			ACCEPTABLE	SAFAAIJAZIR
				BASED ON PROFILE	
REQUEST CANCELLED	26-SEP-2012				BOUIET
				HUMAN ERROR	
SUBMITTED TO OC	01-MAR-2013				BOUIET
SUBMITTED TO DO	04-MAR-2013	Product Specific and GMP Inspection			SAFAAIJAZIR
NME WITH NO PRIOR PS+GMP.PDUFA GOAL DATE: 11-AUG-2013					
DO RECOMMENDATION	13-MAR-2013			ACCEPTABLE	PHILPYE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	20-MAR-2013			ACCEPTABLE	STOCKM
				DISTRICT RECOMMENDATION	

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

Establishment Comment: PERFORMS THE PARTICLE SIZE DISTRIBUTION TEST FOR RELEASE OF THE DRUG SUBSTANCE ((b) (4)
(b) (4)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	10-APR-2009				HEIMANNM
SUBMITTED TO DO	13-APR-2009	Product Specific and GMP Inspection			STOCKM
DO RECOMMENDATION 8/2008 EI WAS NAI	23-APR-2009			ACCEPTABLE BASED ON FILE REVIEW	JOHNSONE
OC RECOMMENDATION	24-APR-2009			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM
SUBMITTED TO OC	14-SEP-2012				BOUIET
SUBMITTED TO DO WAS LAB COVERED IN 2011 INSPECTION?	14-SEP-2012	10-Day Letter			SAFAAIJAZIR
DO RECOMMENDATION	20-SEP-2012			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION	24-SEP-2012			ACCEPTABLE DISTRICT RECOMMENDATION	SAFAAIJAZIR
REQUEST CANCELLED	26-SEP-2012			HUMAN ERROR	BOUIET
SUBMITTED TO OC	01-MAR-2013				BOUIET
SUBMITTED TO DO NME WITH NO PRIOR PS+GMP.PDUFA GOAL DATE: 11-AUG-2013	04-MAR-2013	Product Specific and GMP Inspection			SAFAAIJAZIR
ASSIGNED INSPECTION TO IB	13-MAR-2013	Product Specific and GMP Inspection			PHILPYE
INSPECTION SCHEDULED	15-APR-2013		26-APR-2013		IRIVERA
DO RECOMMENDATION	30-JUL-2013			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION	30-JUL-2013			ACCEPTABLE DISTRICT RECOMMENDATION	SHARPT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities:
DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE STABILITY TESTER

Establishment Comment:
PERFORMS KARL FISHER TESTING FOR RELEASE OF DRUG SUBSTANCE ((b) (4)
MANUFACTURE OF (b) (4) ABLETS.
FINISHED PRODUCT PACKAGING (BOTTLES).
(b) (4) PRODUCT RELEASE TESTING (EXCEPT MICROBIOLOGICAL TESTING).FINISHED PRODUCT RELEASE (BOTTLES (VISUAL
INSPECTION AND APPEARANCE)) AND STABILITY TESTING (EXCEPT MICROBIOLOGICAL TESTING).
((b) (4)
THE SITE MANUFACTURES THE DRUG PRODUCT THROUGH FINAL PACKAGING ((b) (4)
(b) (4)
SITE PERORMS ALL RELEASE AND STABILITY TESTING OF THE DRUG PRODUCT, EXCEPT FOR MICROBIOLOGICAL TESTING. (b) (4)

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Milestone Name / Comment	Milestone Date	Request Type	Planned Completion	Decision / Reason	Creator
SUBMITTED TO OC	10-APR-2009				HEIMANNM
SUBMITTED TO DO	13-APR-2009	Product Specific and GMP Inspection			STOCKM
DO RECOMMENDATION (b) (4)				WITHHOLD PEND REG ACTION - WARNING LTR	JOHNSONE
OC RECOMMENDATION WL RECOMMENDATION	06-MAY-2009			WITHHOLD DISTRICT RECOMMENDATION	CRUZC
DO RECOMMENDATION CASE RE-CLASSIFIED TO VAI BASED ON ADEQUATE RESPONSE TO 483 ITEMS.	21-JUL-2009			ACCEPTABLE ADEQUATE FIRM RESPONSE	JOHNSONE
OC RECOMMENDATION	21-JUL-2009			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM
SUBMITTED TO OC	14-SEP-2012				BOUIET
SUBMITTED TO DO	14-SEP-2012	10-Day Letter			SAFAAIJAZIR
DO RECOMMENDATION	20-SEP-2012			ACCEPTABLE BASED ON FILE REVIEW	PHILPYE
OC RECOMMENDATION	21-SEP-2012			ACCEPTABLE DISTRICT RECOMMENDATION	STOCKM
REQUEST CANCELLED	26-SEP-2012				BOUIET

				HUMAN ERROR	
SUBMITTED TO OC	01-MAR-2013				BOUIET
SUBMITTED TO DO	04-MAR-2013	Product Specific and GMP Inspection			SAFAAIJAZIR
NME WITH NO PRIOR PS+GMP.PDUFA GOAL DATE: 11-AUG-2013					
ASSIGNED INSPECTION TO IB	13-MAR-2013	Product Specific and GMP Inspection			PHILPYE
INSPECTION SCHEDULED	16-MAY-2013		24-MAY-2013		IRIVERA
DO RECOMMENDATION	01-AUG-2013			ACCEPTABLE INSPECTION	TUNGL
OC RECOMMENDATION	01-AUG-2013			ACCEPTABLE DISTRICT RECOMMENDATION	SAFAAIJAZIR

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE PACKAGER

Establishment Comment: FINISHED PRODUCT PACKAGING (BLISTERS)
FINISHED PRODUCT RELEASE TESING (BLISTERS) ((b) (4)

Profile: TABLETS, PROMPT RELEASE **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	14-SEP-2012				BOUIET
OC RECOMMENDATION	14-SEP-2012			ACCEPTABLE BASED ON PROFILE	SAFAAIJAZIR
REQUEST CANCELLED	26-SEP-2012			HUMAN ERROR	BOUIET
SUBMITTED TO OC	01-MAR-2013				BOUIET
OC RECOMMENDATION	04-MAR-2013			ACCEPTABLE BASED ON PROFILE	SAFAAIJAZIR

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/s/

CHARLES F JEWELL
10/21/2013

OLEN M STEPHENS
10/21/2013
I concur; this NDA is recommended for approval from a CMC perspective.

NDA 22-416

Eslicarbazepine Acetate

Sunovion Pharmaceuticals, Inc.

Charles F. Jewell Jr.
Division of Neurology Products

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1. NDA 22416

2. REVIEW #: 4

3. REVIEW DATE: 29-Aug-2013

4. REVIEWER: Charles F. Jewell Jr.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
New NDA (Original Submission)	30-MAR-2009
Initial Quality Assessment (Martha Heimann)	23-APR-2009
CMC Information Request (Don Henry)	31-AUG-2009
SDN 16 (Quality Response to IR)	21-OCT-2009
CMC Review #1 (Charles Jewell)	26-OCT-2009
CMC Information Request on Score Line (Don Henry)	28-OCT-2009
SDN 17 (Quality Response to IR)	30-OCT-2009
SDN 23 (Quality Response to IR; Container Data)	10-DEC-2009
CMC Review #2 (Charles Jewell)	03-MAR-2010
CMC Review #3 (Christine Moore - Director's Memo)	16-APR-2010
Complete Response (Dorothy Demczar - No CMC issues)	30-APR-2010
SDN 56 Resubmission (Judged not to be complete by FDA, non-CMC related reasons)	04-SEP-2012
SDN 57 Quality Response to IR (Site Info)	10-SEP-2012
SDN 64 Quality Response to IR (DS Batch with DP Batch alignment data)	20-DEC-2012
SDN 65 Resubmission of NDA	11-FEB-2013
Mid-cycle CMC IR request (Teshara Bouie, some CMC, some Biopharmaceutics)	13-JUN-2013
SDN 105 Quality Response to IR	28-JUN-2013

Reference ID: 3365056

IR request for dissolution information relating to the 200 mg strength (Teshara Bouie)	11-JUL-2013
SDN 108 Multiple Categories including CMC, Field Copy Certification in response to question from Teshara Bouie.	12-JUL-2013
SDN 109 Includes proposed labeling text	24-JUL-2013
SDN 112 Quality Response to IR (Dissolution information on 200 mg strength)	01-AUG-2013
SDN 115 Quality Response to IR (This is not a CMC or biopharmaceutical related amendment)	16-AUG-2013

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
SDN 56 Resubmission (contains new strength in addition to original strengths, some new biopharm data)	04-SEP-2012
SDN 64 Quality Response to IR (batch information, what DS lots used in what DP lots)	20-DEC-2012
SDN 105 Quality Response to IR (Mid-cycle IR questions, CMC and biopharmaceutics)	28-JUN-2013
SDN 112 Quality Response to IR (Dissolution information on 200 mg strength)	01-AUG-2013

7. NAME & ADDRESS OF APPLICANT:

Name:	Sunovion Pharmaceuticals, Inc.
Address:	84 Waterford Drive Marlborough, MA 01752
Representative:	Karen Joyce, Director, Regulatory Affairs
Telephone:	508-357-7856

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: To Be Determined
b) Non-Proprietary Name (USAN): eslicarbazepine acetate
c) Code Name/# (ONDC only): SEP-0002093
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1

- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment for Epilepsy

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 200 mg, 400 mg, 600 mg, 800 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

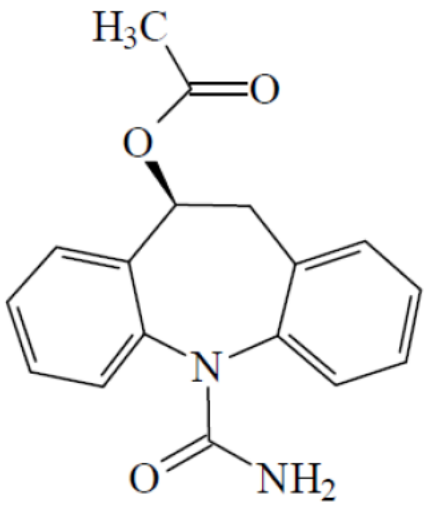
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

__X__Not a SPOTS product

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

Chemical Name: (S)-10-Acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide

Chemistry Review Data Sheet

	**Molecular Formula:** $C_{17}H_{16}N_2O_3$ **Molecular Weight**: 296.32

17. RELATED/SUPPORTING DOCUMENTS:

Reference ID: 3365056

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
22026	II	Bial	Eslicarbazepine acetate	1	Adequate	09-Jul-2013	LOA 28-JAN-2011
(b) (4)	III	(b) (4)		4	N/A		LOA 23-FEB-2012
	III			4	N/A		LOA 28-FEB-2012
	III			4	N/A		LOA 19-MAR-2012 and 24-JAN-2012
	III			4	N/A		LOA 20-JAN-2012
	III			4	N/A		LOA 09-NOV-2011
	III			4	N/A		LOA 18-JAN-2012
	III			4	N/A		LOA 07-OCT-2008
	III			4	N/A		LOA 26-SEP-2008
	III			4	N/A		LOA 19-SEP-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	(b) (4)	Initial IND for this drug

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			Xiang Ling
EES	Overall acceptable	01-AUG-2013	Report from EES
Pharm/Tox			Christopher Toscano
ONDQA Biopharm	Biowaiver for 200 mg strength is not granted, other strengths are adequate	27-Aug-2013	Elsbeth Chikhale
DMEPA			Julie Neshiewat
DDMAC			Olga, Salis
Methods Validation			Not assigned
EA	adequate	28-AUG-2013	Charles Jewell
Microbiology			Not assigned

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			

Reference ID: 3365056

Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 22416

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is adequate from the chemistry, manufacturing and controls (CMC) perspective, and the manufacturing sites have received an overall acceptable rating from the CDER Office of Compliance (CDER-OC) as reported in the Establishment Evaluation System (EES). However, the 200 mg strength tablet (a new strength in this resubmitted application due to a request from Division of Neurology Products (DNP) to satisfy the need for a lower starting dose for up-titration in patients with renal impairment) does not meet the comparative dissolution similarity criteria with drug product used in pivotal clinical trials, so the requested biowaiver is not acceptable (See review from the Office of New Drugs and Quality Assessment (ONDQA) Biopharmaceutical Reviewer: Elsbeth Chikhale; 27-AUG-2013 in DARRTS). This indicates that the 200 mg strength may not be bioequivalent to the 400, 600 and 800 mg strengths. For this reason, ONDQA does not recommend approval.

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

II. Summary of Chemistry Assessments

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

Eslicarbazepine acetate [(S)-10-acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide, ESL, BIA 2-093, SEP-0002093] is a novel voltage-gated sodium channel blocker. It can be considered a member of a third generation in an established family of dibenz[b,f]azepine antiepileptic drugs represented by carbamazepine (first-generation) and oxcarbazepine (second-generation). Unlike carbamazepine it is not metabolized to carbamazepine-10-11 epoxide and is not susceptible to auto-induction of its own metabolism. Unlike oxcarbazepine, it is not as readily metabolized into a racemic mixture of both eslicarbazepine and R-licarbazepine. The acetate is hydrolyzed to give mainly eslicarbazepine, the moiety responsible for the pharmacological effect.

The finished drug product, (eslicarbazepine acetate) Tablets are immediate release tablets of four different strengths, 200 mg, 400 mg, 600 mg and 800 mg. For the initial submission of this NDA, only three strengths were provided the applicant has introduced a new 200 mg strength tablet in this resubmission. Previously the other three strengths were found adequate for marketing based on the review from the CMC perspective. All tablets are (b) (4) The proposed marketing configuration consists of tablets in bottles

(HDPE with [redacted] (b) (4) caps and an aluminum induction seal; oblong bottles are the preferred configuration but round bottles in cartons are an alternative configuration), or tablets in [redacted] (b) (4)/ALU blisters. Blisters come in capacity of seven cards that are further packaged in cardboard wallets. The blisters are used for physician's samples and starter kits. The 200 mg, 600 mg and 800 mg strengths are white oblong tablets with a functional score on one side, and identifying engraving for substance and strength on the other side (ESL 200, ESL 400 or ESL 800). The score is demonstrated functional from the CMC and biopharmaceutics perspective. The 400 mg tablet is white round bi-convex with no score and engraved ESL 400 on one side.

The drug substance is a white to off-white, odorless crystalline solid, [redacted] (b) (4) with a melting point of 184°C to 187°C (melts with decomposition). It is manufactured by [redacted] (b) (4) under DMF 22026 for BIAL-Portela & C S.A. (Portugal) (BIAL is the DMF holder). It is only very slightly soluble in aqueous solvents. It is not ionizable under physiological conditions (pH = 1.2 to 7.4). It is not hygroscopic. Permeability studies indicate it is highly permeable, therefore it is expected to be easily absorbed by passive transport. The absorption rate will be directly proportional to its rate of dissolution. The drug substance is [redacted] (b) (4) The drug substance has a demonstrated [redacted] (b) (4) retest date supported by adequate stability studies at long term storage conditions (25°C / 60% RH).

Eslicarbazepine acetate is a single stereo-isomer, carbon-10 has the S-configuration. This assignment is experimentally supported from a single-crystal x-ray diffraction study of a derivative. A chiral chromatographic method was developed and used to verify the stereochemical purity of the drug substance. [redacted] (b) (4)

The tablet manufacturing process was explored and developed by Bial and transferred to [redacted] (b) (4) for scale-up to commercial scale. Early clinical studies were done with lower strength tablets. To obtain larger strengths, [redacted] (b) (4) Once desired strengths were determined in clinical studies, [redacted] (b) (4) was developed to produce all required strengths. The commercial formulation is designated formulation FP, to differentiate it from formulations FN (400 mg), FK (600 mg) and FC (800 mg) used in pivotal clinical studies. [redacted] (b) (4)

Reference ID: 3365056

(b) (4)

Batches of tablets using the different formulations were found to be equivalent when compared by human bioavailability studies. *In vitro* dissolution profiles across three pH ranges demonstrated adequate similarity based on similarity factor f2. Overall, tablets from the commercial formulation demonstrate a better dissolution profile (b) (4) The dissolution assay used a two-point specification (dissolution reported at 15 minutes and 45 minutes) in order to differentiate dissolution profiles.

Bioequivalence of the 200 mg strength tablets was not demonstrated relative to the 400 mg, 600 mg and 800 mg strength tablets used in pivotal clinical studies. The applicant requested a biowaiver, but the dissolution similarity is not adequate to support a biowaiver. See the review from the ONDQA Biopharmaceutical Reviewer, Elsbeth Chikhale, 27-AUG-2013 in DARRTS.

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

Eslicarbazepine acetate tablets are intended for use as an adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy. Treatment should be initiated with a once daily dose of 400 mg, for one week. Daily dosing may be increased at increments of 400 mg at approximately weekly intervals to a maximum recommended daily dose of 1200 mg once daily. The usual maintenance dose is 800 mg once daily. The 200 mg tablets are designed to be used in patients that required a lower starting dose than 400 mg per day.

Eslicarbazepine acetate tablets will be available in the following commercial configurations:

- 200 mg strength
  - 30-count bottles (oblong, 45 cc bottle / 28 mm cap)
  - 60-count bottles (round, 30 cc bottle / 28 mm cap)
- 400 mg strength
  - 30-count bottles (oblong, 45 cc bottle / 28 mm cap)
  - 30-count bottles (round, 30 cc bottle / 28 mm cap)
  - 7-count blisters in wallet (sample presentation)
  - 7-count blisters with 7-count 800 mg strength blisters in wallet (starter pack)
- 600 mg strength
  - 60-count bottles (oblong, 75 cc bottle / 33 mm cap)
  - 90-count bottles (oblong, 160 cc bottle / 38 mm cap)
  - 60-count bottles (round, 85 cc bottle / 33 mm cap)
  - 90-count bottles (round, 120 cc bottle / 38 mm cap)
  - 7-count blisters in wallet (sample presentation)
- 800 mg strength

- 30-count bottles (oblong, 75 cc bottle / 33 mm cap)
- 90-count bottles (oblong, 160 cc bottle / 38 mm cap)
- 30-count bottles (round, 50 cc bottle / 33 mm cap)
- 90-count bottles (round, 150 cc bottle / 38 mm cap)
- 7-count blisters in wallet (sample presentation)
- 7-count blisters with 7-count 400 mg strength blisters in wallet (starter pack)

Based on stability data, 24-months expiration dating is assigned to the 200 mg strength tablets and 48-months expiration dating is assigned to all configurations of the other three strengths. Drug product should be stored at 25°C (77°F); with temperature excursions in the range of 15°C to 30°C (59°F to 86°F) permitted.

The drug substance is designed to be rapidly metabolized to eslicarbazepine, the pharmacologically active moiety, and (R)-licarbazepine in (b) (4). Systemic exposure to eslicarbazepine acetate (the parent drug) is negligible in humans.

C. Basis for Approvability or Not-Approval Recommendation

The drug substance as manufactured was adequately characterized with respect to chemical purity, stereo-chemical purity, stability, impurity profile, physical properties and consistency in manufacture. The manufacturing process for the drug product was adequately studied and optimized to produce a controlled and consistent product. The drug product has adequate stability in the to-be-marketed packaging configurations as demonstrated by stability studies. This supports an approvability recommendation from the chemistry, manufacturing and controls perspective.

However, the overall ONDQA recommendation is to not approve because of the lack of bioequivalence data or an acceptable biowaiver for the 200 mg strength tablet in comparison with the 400 mg, 600 mg and 800 mg tablets used in pivotal clinical trials.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Charles F. Jewell Jr./ 28-Aug-2013
ONDQA Biopharmaceutics Reviewer: Elsbeth Chikhale / 28-Aug-2013
ChemistryTeamLeaderName/Date: Martha Heimann / 28-Aug-2013
ONDQA BiopharmaceuticsTeamLeader: Angelica Dorantes / 28-Aug-2013
ProjectManagerName/Date: Su-Lin Sun / 28-Aug-2013
ONDQA Project Manager/ Date: Teshara Bouie / 28-Aug-2013

C. CC Block

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/s/

CHARLES F JEWELL
08/29/2013

RAMESH K SOOD
08/29/2013

STEDESA™
(eslicarbazepine acetate) Tablets
NDA 22-416

Summary Basis for Recommended Action
From Chemistry, Manufacturing, and Controls

Applicant: Sepracor, Inc.
84 Waterford Drive
Marlborough, MA 01752-7010

Indication: Eslicarbazepine acetate is a novel voltage-gated sodium channel blocker. As a third-generation member of the first-line dibenz[b,f]azepine antiepileptic drugs represented by carbamazepine (first-generation) and oxcarbazepine (second-generation) it is intended for use as an adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy.

Presentation: Eslicarbazepine acetate tablets will be available as immediate release in 400 mg, 600 mg and 800 mg strengths. All tablets are white, the 400 mg is round with no groove or score line, the 600 mg and 800 mg are oblong with a groove on one side. The 400 mg tablet is embossed ESL 400 on one side, the 600 mg is embossed ESL 600 on one side and the 800 mg is embossed ESL 800 on one side. The tablets come in white opaque HDPE bottles with [redacted] (b) (4) caps and induction seal (400 mg: 30-count/30 cc; 600 mg: 60-count/85 cc and 90-count/120 cc; 800 mg: 30-count/50 cc and 90-count/150 cc) or aluminum/aluminum blister packaging (400 mg: 7-count; 600 mg and 800 mg: [redacted] (b) (4), or [redacted] (b) (4) aluminum blister packaging (400 mg: 7-count; 600 mg and 800 mg: [redacted] (b) (4)).

EER Status: Acceptable, 30-Sep-2009 – E. Johnson

Consults: Methods Validation – Revalidation by Agency was not requested.
EA – Categorical exclusion granted under 21 CFR §25.31(c).
Pharm Tox – Acceptable, 25-Aug-2009 – C. Toscano

Post-Approval Agreements: None

Drug Substance:

Eslicarbazepine acetate drug substance is a white to off-white, odorless, crystalline solid, manufactured by [redacted] (b) (4) for Bial of Portugal. CMC information on the drug substance was provided in this NDA in summary form and in detail in type II DMF No. 22026 (Bial-Portela & C[a] S.A., Portugal). All CMC information provided in the DMF and an amendment to the DMF for the drug substance was adequate to support its approval for use in the drug product.

The drug substance is a pure enantiomer. [redacted] (b) (4) melting at 184-187°C. It is only very slightly soluble in aqueous solvents. It is not ionizable in the gastro-intestinal pH range of 1.2 to 7.4. It is not hygroscopic. Through *in-vitro* permeability studies it is determined to be highly permeable. Stereochemical assignment was verified by solving the x-ray diffraction pattern from a single crystal of a derivative.

Eslicarbazepine acetate drug substance meets specifications for description (visual), particle size distribution (a laser diffraction method), identification (IR, HPLC retention time), water content (Karl Fischer method), melting point, residue on ignition, heavy metals, residual solvents [redacted] (b) (4) bacteria count, fungi count, absence of specific bacteria, purity (HPLC), specific impurities, enantiomeric purity (HPLC), and assay (HPLC). Long term stability studies support a retest date of [redacted] (b) (4).

Conclusion: The drug substance is satisfactory.

Drug product:

The drug product is a conventional immediate release tablet of three strengths: 400, 600 and 800 mg. Dosing of the drug product requires titration. Proposed dosing is approximately one week at 400 mg per day, then approximately one week at [redacted] (b) (4) 800 mg day. The normal dose is anticipated to be 800 mg per day, but can go up to 1200 mg day. Adequate data was provided to support divisibility of the 600 mg and 800 mg strength tablets but not for the 400 mg strength. Consequently, the 400 mg tablet has no score line.

The drug product is manufactured using [redacted] (b) (4) eslicarbazepine acetate drug substance. The drug product formulation includes eslicarbazepine acetate drug substance, povidone [redacted] (b) (4) croscarmellose sodium [redacted] (b) (4), and magnesium stearate [redacted] (b) (4) The tablets are manufactured using [redacted] (b) (4)

The drug product specification includes analysis for appearance, average weight, uniformity of dosage, thickness, hardness, friability, (b) (4) dissolution, identification (HPLC retention time and UV spectrum by HPLC with a diode-array detector), assay (HPLC), analysis for degradation products (HPLC), and total viable aerobic count (bacteria and fungi) and the absence of *E. coli*.

An expiration dating period of 24 months is supported by stability data and assigned for all of the drug product packaging configurations.

It is recommended that the applicant change the labeling on the carton and container labels to show the established name as *eslicarbazepine acetate* in parentheses so that the tradename will be clearly linked to this as opposed to (b) (4)

Conclusion: Drug product is satisfactory, pending resolution of labeling.

Additional Items:

All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

The analytical methods used in the testing procedures (release, stability and in-process) are well known and widely used by the pharmaceutical industry, and the validation reports contained in the application were reviewed to verify this, so further validation by Agency laboratories is not requested.

Overall Conclusion: Approval from the CMC perspective is recommended. However, the applicant should be requested to modify labeling to include the established name in parentheses.

Christine M. V. Moore, Ph.D.
Acting Director, DPA I/ONDQA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22416	ORIG-1	SEPRACOR INC	SEP-0002093 ESLICARBAZEPINE ACETATE

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/s/

CHRISTINE M MOORE
04/16/2010

NDA 22-416

STEDESA™ (eslicarbazepine acetate) Tablets

Sepracor Inc.

Charles Jewell, Ph.D.
Office of New Drug Quality Assessment
For Division of Neurology Products

Review of Chemistry, Manufacturing, and Controls

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C. CC Block 15

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S DRUG SUBSTANCE [Eslicarbazepine acetate, Bial] 16

P DRUG PRODUCT [Eslicarbazepine acetate, Tablets] 17

In an information request dated October 28, 2009, the following CMC comment was made to the applicant. 17

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APPEARS THIS WAY ON ORIGINAL

Chemistry Review Data Sheet

1. NDA: 22-416

2. REVIEW#: 2

3. REVIEW DATE: March 3, 2010

4. REVIEWER: Charles Jewell, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
REV-QUALITY-03 Number 1	26-Oct-2009
COR-NDAIR-01 (Information Request Submitted by Don Henry)	28-Oct-2009

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
SDN 17 (eCTD 0015), Data on the sub-division of the 400 mg tablet	30-Oct-2009
SDN 23 (eCTD 0021), USP<661> and USP<671> data supporting proposed HDPE bottles and caps, data on blister configurations to come later (early Jan 2010)	10-Dec-2009
SDN 28 (eCTD 0026), USP<661> and USP<671> Data on 800 mg blisters in response to IR, additional info on change in type of (b) (4) used in blisters.	04-Feb-2010
SDN 31 (eCTD 0029), amendment to change application to (b) (4) Draft labeling was submitted reflecting this change and to reflect a revision in the pregnancy registry information and to reflect the Medication Guide and new branding elements.	12-Feb-2010

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name:	Sepracor Inc.
Address:	84 Waterford Drive Marlborough, MA 01752-7010
Representative:	Karen Joyce Associate Director, Regulatory Affairs
Telephone:	(508) 357-7856

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Stedesa™
b) Non-Proprietary Name (USAN): eslicarbazepine acetate
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment for epilepsy

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 400mg, 600mg, 800mg

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

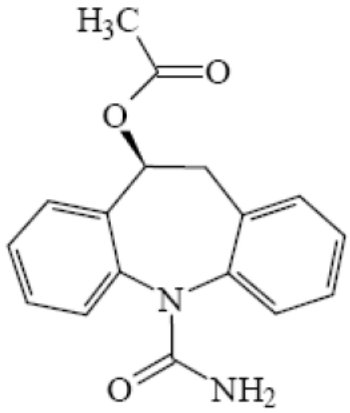
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

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

Chemical Name: (S)-10-acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide



Molecular Formula: $C_{17}H_{16}N_2O_3$
Molecular Weight: 296.32

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
22026	II	Bial, Coronado, Portugal	Drug Substance: eslicarbazepine acetate	1	adequate	07/02/2009 (original) 09/16/2009 (amendment SDN 4)	LOA date: 10/15/08, updated LOA: 7/31/09 (for amendment SDN 4)
(b) (4)	III	(b) (4)		4	N/A		LOA date: 9/18/08 sufficient info in application Schematics provided
	III			4	N/A		LOA date: 10/6/08 sufficient info in application

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4	N/A		LOA date: 11/26/08 GRAS, schematic/detailed technical info provided
	III			4	N/A		LOA date: 10/3/08 sufficient info in application, schematic/detailed technical info provided
	III			4	N/A		LOA date: 10/6/07 sufficient info in application, schematic/detailed technical info provided
	III			4	N/A		LOA date: 10/3/08 sufficient info in application, schematic/detailed technical info provided
	III			4	N/A		LOA date: 9/26/08 sufficient info in application, schematic/detailed technical info provided
	III			4	N/A		LOA date: 10/7/08 sufficient info in application, schematic/detailed technical info provided

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)		4	N/A		LOA date: 9/19/08 sufficient info in application, schematic/detailed technical info provided

[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	67,466	BIA 2-093, SEP-0002093, (synonyms of eslicarbazepine acetate), 400mg, 600mg and 800mg tablets

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	no consultation required		
EES	acceptable (overall)	30-Sep-2009	E. Johnson (HFD-320)
Pharm/Tox	concurrence that (b) (4)	25-Aug-2009	C. Toscano (Pharm/Tox Reviewer)
Biopharm	no consultation required		
LNC	no consultation required		
Methods Validation	no lab validation indicated		

Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
DMEPA	Proposed proprietary name Stedesa is acceptable (pending re-review 90 days before approval)	2-Jul-2009	L. Toombs (DMEPA)
EA	categorical exclusion request reviewed adequate	26-Oct-2009	C. Jewell (CMC reviewer), as part of submitted review #1
Microbiology	no consultation required		

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The Chemistry Review for NDA 22-416

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval from the CMC perspective is recommended pending resolution of the labeling recommendation mentioned at the end of this review.

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

Not applicable for this application.

II. Summary of Chemistry Assessments

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

Eslicarbazepine acetate [(S)-10-acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide, ESL, BIA 2-093, SEP-0002093] is a novel voltage-gated sodium chanel blocker.

Eslicarbazepine acetate was designed as a third-generation, single-enantiomer member of the established family of first-line dibenz[b,f]azepine antiepileptic drugs represented by carbamazepine (first-generation) and oxcarbazepine (second-generation). Eslicarbazepine acetate shares with both carbamazepine and oxcarbazepine the dibenzazepine nucleus bearing the 5-carboxamide substitutent but is structurally different at the 10,11-positions. This molecular difference results in differences in metabolism. Unlike carbamazepine, eslicarbazepine acetate is not metabolized to carbamazepine-10,11-epoxide and is not susceptible to auto-induction of its own metabolism. Unlike oxcarbazepine that is metabolized into both eslicarbazepine and R-licarbazepine, eslicarbazepine acetate is a prodrug of eslicarbazepine, which is the drug entity responsible for the pharmacological effect.

The finished product, SEP-0002093 (eslicarbazepine acetate) Tablets, is a conventional immediate-release tablet of three strengths, 400, 600 and 800 mg. The composition is (b) (4) between the strengths. Three different packages are used. Tablets are packaged in high-density polyethylene bottles with (b) (4) closures and in (b) (4) blisters with aluminum foil lidding (b) (4)

Eslicarbazepine acetate 400 mg tablets are white circular bi-convex tablets engraved ESL 400 on one side and plain on the other side. Eslicarbazepine acetate 600 mg tablets are white oblong tablets engraved ESL 600 on one side and with a groove on the other side. Eslicarbazepine acetate 800 mg tablets are white oblong tablets engraved ESL 800 on one side and with a groove on the other side.

Eslicarbazepine acetate drug substance is a white to off-white, odorless, crystalline solid. It is manufactured by (b) (4) It melts at 184°C to 187°C with decomposition. It is only very slightly soluble in aqueous solvents. It is not ionizable under physiological pH (1.2 to 7.4 gastro-intestinal pH range) conditions. It is not hygroscopic. Through a permeability study it is indicated to be a highly permeable compound ($P_{app} > 1x10^{-5}$ cm/s). Therefore it is expected to be easily absorbed by passive transport. The absorption rate will be directly proportional to the dissolution rate. (b) (4) The drug substance has a retest date of (b) (4), demonstrated by long term stability studies. Supporting stability studies suggest it is likely that this date will be extended, as further long term study results are received.

The compound is a single stereo-isomer, defined by having a single chiral center, carbon-10, in the S-configuration. This was experimentally demonstrated by solving the structure from a single-crystal x-ray diffraction pattern of a derivative of the compound. A chiral chromatographic method was developed and used to characterize the sterochemical purity of the drug substance. (b) (4)

The tablet manufacturing was explored and developed by Bial of Portugal and transferred to (b) (4) for scale-up to commercial scale. Standard tabletting techniques are used for the un-coated, immediate-release tablets. Throughout the development process, a significant amount of effort was extended in optimizing the immediate release tablet formulation. Early clinical studies were done with lower strength tablets. To obtain larger strengths, (b) (4) Once the desired strengths were determined in clinical studies, the development studies led in the direction (b) (4) of making

tablets for the three different strengths. (b) (4)

Optimization was also studied for the amount of (b) (4) (Povidone) and (b) (4) (magnesium stearate, (b) (4)).

Tablets manufactured by the final formulation (FP used for 400, 600, and 800 mg tablets) were different from the tablets used in the pivotal phase III studies (FN used for 400 mg tablets, FK used for 600 mg tablets, and FC used for 800 mg tablets). (b) (4) Batches of tablets prepared with formulation FP were compared in human bioavailability studies with tablets prepared from formulations FN, FK and FC, and they were found to be equivalent. Dissolution profile studies were done *in vitro* to compare the different formulations and their profiles were found to be comparable based on the similarity factor (f2). Overall, the tablets from formulation FP had a slightly better dissolution profile than the formulations containing (b) (4) The dissolution assay uses a two-point specification (dissolution reported at 15 and 45 minutes) in order to better differentiate the dissolution profiles.

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

Eslicarbazepine acetate tablets are intended for use as an adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy. Treatment should be

initiated with a once daily dose of 400 mg, for one week. Daily dosing may be increased at increments of 400 mg at approximately weekly intervals to a maximum recommended daily dose of 1200 mg once daily. The usual maintenance dose is 800 mg once daily.

Eslicarbazepine acetate tablets will be available in 400 mg, 600 mg and 800 mg strengths. The 400 mg strength will be available in a 30-count 30-cc bottle, the 600 mg strength will be available in either a 60-count 85-cc bottle or a 90-count 120 cc bottle and the 800 mg strength will be available in either a 30-count 50-cc bottle or a 90 count 150-cc bottle. These tablets will also be available in (b) (4) Aluminum blister packages and also Aluminum/Aluminum blister packages to be used as physician-targeted samples. These blister packages will be 7-count for the 400 mg strength and (b) (4) for the 600 mg and 800 mg strengths. An expiration dating period of 24 months was requested by the applicant and is supported by stability data for the drug product for all of these bottle configurations and all of the blister packaging configurations. . The drug product should be stored at 25°C (77°F); with temperature excursions in the range of 15°C to 30°C (59°F to 86°F) permitted. The currently assigned expiration dating and storage conditions are supported with available stability data, and may be extended as further stability data becomes available.

The drug substance is designed to be rapidly metabolized to eslicarbazepine, the pharmacologically active moiety, and (R)-licarbazepine (the stereo-isomer of eslicarbazepine) in (b) (4). Systemic exposure to eslicarbazepine acetate (the parent drug) is negligible in humans.

C. Basis for Approvability or Not-Approval Recommendation

The drug substance was adequately characterized with respect to chemical purity, stereo-chemical purity, stability, physical properties and consistency in manufacture. The manufacturing process for the drug product was adequately studied and it produces a controlled and consistent product. The product has adequate quality and stability. This supports the recommendation that this application is approved from the chemistry, manufacturing and controls perspective. .

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date:
ChemistryTeamLeaderName/Date

ProjectManagerName/Date

C. CC Block

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22416	ORIG-1	SEPRACOR INC	SEP-0002093 ESLICARBAZEPINE ACETATE

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

/s/

CHARLES F JEWELL
03/03/2010

RAMESH K SOOD
03/03/2010

NDA 22-416

STEDESA™ (eslicarbazepine acetate) Tablets

Sepracor Inc.

Charles Jewell, Ph.D.
Office of New Drug Quality Assessment
For Division of Neurology Products

Review of Chemistry, Manufacturing, and Controls

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Chemistry Review Data Sheet

1. NDA: 22-416

2. REVIEW#: 1

3. REVIEW DATE: October 23, 2009

4. REVIEWER: Charles Jewell, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
none	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	29-Mar-2009
SDN 7, Legacy Amendment Amendment - Multi Discipline (Partial Response to NDA Filing Review Letter, answers to CMC questions)	13-July-2009
SDN 16, Amendment (Response to CMC Information Request and Updates based on amendment to DMF 22026	20-Oct-2009

7. NAME & ADDRESS OF APPLICANT:

Name:	Sepracor Inc.
Address:	84 Waterford Drive Marlborough, MA 01752-7010
Representative:	Karen Joyce Associate Director, Regulatory Affairs
Telephone:	(508) 357-7856

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Stedesa™
b) Non-Proprietary Name (USAN): eslicarbazepine acetate
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Treatment for epilepsy

11. DOSAGE FORM: Tablet

12. STRENGTH/POTENCY: 400mg, 600mg, 800mg

13. ROUTE OF ADMINISTRATION: oral

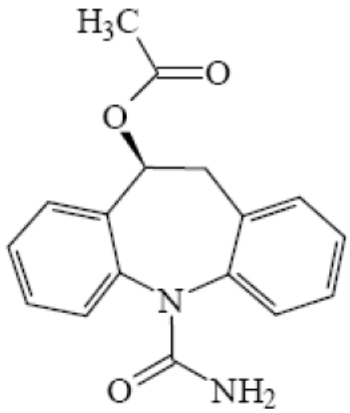
14. Rx/OTC DISPENSED: _X_Rx ___OTC

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: (S)-10-acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide



Molecular Formula: $C_{17}H_{16}N_2O_3$
Molecular Weight: 296.32

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
22026	II	Bial, Coronado, Portugal	Drug Substance: eslicarbazepine acetate	1	adequate	07/02/2009 (original) 09/16/2009 (amendment SDN 4)	LOA date: 10/15/08, updated LOA: 7/31/09 (for amendment SDN 4)
(b) (4)	III	(b) (4)		4	N/A		LOA date: 9/18/08 sufficient info in application Schematics provided
	III			4	N/A		LOA date: 10/6/08 sufficient info in application
	III			4	N/A		LOA date: 11/26/08 GRAS, schematic/detailed technical info provided

Chemistry Review Data Sheet

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III		(b) (4)	4	N/A		LOA date: 10/3/08 sufficient info in application, schematic/detailed technical info provided
	III			4	N/A		LOA date: 10/6/07 sufficient info in application, schematic/detailed technical info provided
	III			4	N/A		LOA date: 10/3/08 sufficient info in application, schematic/detailed technical info provided
	III			4	N/A		LOA date: 9/26/08 sufficient info in application, schematic/detailed technical info provided
	III			4	N/A		LOA date: 10/7/08 sufficient info in application, schematic/detailed technical info provided
	III			4	N/A		LOA date: 9/19/08 sufficient info in application, schematic/detailed technical info provided

[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	67,466	BIA 2-093, SEP-0002093, (synonyms of eslicarbazepine acetate), 400mg, 600mg and 800mg tablets

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	no consultation required		
EES	acceptable (overall)	30-Sep-2009	E. Johnson (HFD-320)
Pharm/Tox	concurrence that (b) (4) [redacted]	25-Aug-2009	C. Toscano (Pharm/Tox Reviewer)
Biopharm	no consultation required		
LNC	no consultation required		
Methods Validation	no lab validation indicated		
DMEPA	Proposed proprietary name Stedesa is acceptable (pending re-review 90 days before approval)	2-Jul-2009	L. Toombs (DMEPA)
EA	categorical exclusion request reviewed adequate	date of this review	C. Jewell (CMC reviewer)
Microbiology	no consultation required		

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The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approval from the CMC perspective.

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

Not applicable for this application.

II. Summary of Chemistry Assessments

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

Eslicarbazepine acetate [(S)-10-acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide, ESL, BIA 2-093, SEP-0002093] is a novel voltage-gated sodium chanel blocker.

Eslicarbazepine acetate was designed as a third-generation, single-enantiomer member of the established family of first-line dibenz[b,f]azepine antiepileptic drugs represented by carbamazepine (first-generation) and oxcarbazepine (second-generation). Eslicarbazepine acetate shares with both carbamazepine and oxcarbazepine the dibenzazepine nucleus bearing the 5-carboxamide substitutent but is structurally different at the 10,11-positions. This molecular difference results in differences in metabolism. Unlike carbamazepine, eslicarbazepine acetate is not metabolized to carbamazepine-10,11-epoxide and is not susceptible to auto-induction of its own metabolism. Unlike oxcarbazepine that is metabolized into both eslicarbazepine and R-licarbazepine, eslicarbazepine acetate is a prodrug of eslicarbazepine, which is the drug entity responsible for the pharmacological effect.

The finished product, SEP-0002093 (eslicarbazepine acetate) Tablets, is a conventional immediate-release tablet of three strengths, 400, 600 and 800 mg. The composition is [redacted] (b) (4) between the strengths. Three different packages are used. Tablets are packaged in high-density polyethylene bottles with [redacted] (b) (4) closures and in [redacted] (b) (4) blisters with aluminum foil lidding [redacted] (b) (4)

Eslicarbazepine acetate 400 mg tablets are white circular bi-convex tablets engraved ESL 400 on one side and scored on the other side. Eslicarbazepine acetate 600 mg tablets are white oblong tablets engraved ESL 600 on one side and scored on the other side. Eslicarbazepine acetate 800 mg tablets are white oblong tablets engraved ESL 800 on one side and scored on the other side.

Eslicarbazepine acetate drug substance is a white to off-white, odorless, crystalline solid. It is manufactured by (b) (4) It melts at 184°C to 187°C with decomposition. It is only very slightly soluble in aqueous solvents. It is not ionizable under physiological pH (1.2 to 7.4 gastro-intestinal pH range) conditions. It is not hygroscopic. Through a permeability study it is indicated to be a highly permeable compound ($P_{app} > 1x10^{-5}$ cm/s). Therefore it is expected to be easily absorbed by passive transport. The absorption rate will be directly proportional to the dissolution rate. (b) (4) The drug substance has a retest date of (b) (4), demonstrated by long term stability studies. Supporting stability studies suggest it is likely that this date will be extended, as further long term study results are received.

The compound is a single stereo-isomer, defined by having a single chiral center, carbon-10, in the S-configuration. This was experimentally demonstrated by solving the structure from a single-crystal x-ray diffraction pattern of a derivative of the compound. A chiral chromatographic method was developed and used to characterize the sterochemical purity of the drug substance. (b) (4)

The tablet manufacturing was explored and developed by Bial of Portugal and transferred to (b) (4) for scale-up to commercial scale. Standard tabletting techniques are used for the un-coated, immediate-release tablets. Throughout the development process, a significant amount of effort was extended in optimizing the immediate release tablet formulation. Early clinical studies were done with lower strength tablets. To obtain larger strengths, (b) (4) Once the desired strengths were determined in clinical studies, the development studies led in the direction (b) (4) of making

tablets for the three different strengths. (b) (4) [redacted]

Optimization was also studied for the amount of [redacted] (b) (4) (Povidone) and [redacted] (b) (4) (magnesium stearate, [redacted] (b) (4)).

Tablets manufactured by the final formulation (FP used for 400, 600, and 800 mg tablets) were different from the tablets used in the pivotal phase III studies (FN used for 400 mg tablets, FK used for 600 mg tablets, and FC used for 800 mg tablets). (b) (4) [redacted] Batches of tablets prepared with formulation FP were compared in human bioavailability studies with tablets prepared from formulations FN, FK and FC, and they were found to be equivalent. Dissolution profile studies were done *in vitro* to compare the different formulations and their profiles were found to be comparable based on the similarity factor (f2). Overall, the tablets from formulation FP had a slightly better dissolution profile than the formulations containing (b) (4) [redacted] The dissolution assay uses a two-point specification (dissolution reported at 15 and 45 minutes) in order to better differentiate the dissolution profiles.

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

Eslicarbazepine acetate tablets are intended for use as an adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy. Treatment should be

initiated with a once daily dose of 400 mg, for one week. Daily dosing may be increased at increments of 400 mg at approximately weekly intervals to a maximum recommended daily dose of 1200 mg once daily. The usual maintenance dose is 800 mg once daily.

Eslicarbazepine acetate tablets will be available in 400 mg, 600 mg and 800 mg strengths. The 400 mg strength will be available in a 30-count 30-cc bottle, the 600 mg strength will be available in either a 60-count 85-cc bottle or a 90-count 120 cc bottle and the 800 mg strength will be available in either a 30-count 50-cc bottle or a 90 count 150-cc bottle. These tablets will also be available in (b) (4) Aluminum blister packages and also Aluminum/Aluminum blister packages to be used as physician-targeted samples. These blister packages will be 7-count for the 400 mg strength and (b) (4) for the 600 mg and 800 mg strengths. An expiration dating period of 24 months was requested by the applicant and is supported by stability data for the drug product for all of these bottle configurations and all of the blister packaging configurations. . The drug product should be stored at 25°C(77°F); with temperature excursions in the range of 15°C to 30°C (59°F to 86°F) permitted. The currently assigned expiration dating and storage conditions are supported with available stability data, and may be extended as further stability data becomes available.

The drug substance is designed to be rapidly metabolized to eslicarbazepine, the pharmacologically active moiety, and (R)-licarbazepine (the stereo-isomer of eslicarbazepine) in (b) (4). Systemic exposure to eslicarbazepine acetate (the parent drug) is negligible in humans.

C. Basis for Approvability or Not-Approval Recommendation

The drug substance was adequately characterized with respect to chemical purity, stereo-chemical purity, stability, physical properties and consistency in manufacture. The manufacturing process for the drug product was adequately studied and it produces a controlled and consistent product. The product has adequate quality and stability. This supports the recommendation that this application is approved from the chemistry, manufacturing and controls perspective. .

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date

ProjectManagerName/Date

C. CC Block

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22416	ORIG-1	SEPRACOR INC	SEP-0002093 ESLICARBAZEPINE ACETATE

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

/s/

CHARLES F JEWELL
10/23/2009

RAMESH K SOOD
10/26/2009

Initial Quality Assessment
Branch I
Pre-Marketing Assessment Division I

OND Division:	Division of Neurology Products
NDA:	22-416
Applicant:	Sepracor, Inc
Stamp Date:	30-Mar-2009
PDUFA Date:	30-Jan-2010
Trademark:	Stedesa (proposed)
Established Name:	eslicarbazepine acetate (Eslicarbazepine is INN.)
Dosage Form:	Tablets
Route of Administration:	Oral
Indication:	Epilepsy
PAL:	Martha R. Heimann, Ph.D.

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

Summary and Critical Issues:

Summary

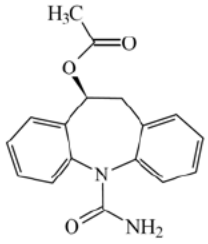
Eslicarbazepine acetate (SEP-0002093 or Bia 2-093) is a new molecular entity originally developed by a Portuguese firm, Bial Portela & Ca S.A. (Bial) for treatment of epilepsy. Sepracor acquired the rights to eslicarbazepine acetate in 2008. In the current NDA, the applicant proposes marketing of immediate release tablets containing 400 mg, 600 mg and 800 mg of eslicarbazepine acetate.

Eslicarbazepine acetate is a prodrug that is rapidly and extensively metabolized to the pharmacologically active moiety, eslicarbazepine, and its enantiomer, (R)-licarbazepine, (b) (4) Eslicarbazepine is a third-generation, single-enantiomer member of the family of dibenz[b,f]azepine antiepileptic drugs (AEDs) represented by carbamazepine (first-generation) and oxcarbazepine (second-generation). It behaves as a voltage-gated sodium channel (VGSC) blocker that competitively interacts with site 2 of the inactivated state of the channel, preventing its return to the active state and inhibiting repetitive neuronal firing.

Drug Substance

The active ingredient, eslicarbazepine acetate, is a small molecule with molecular formula $C_{17}H_{16}N_2O_3$ and molecular weight 296.32. The chemical name is (S)-10-acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide. There is a single chiral center at the C-10 position with *S*-configuration.

The structural formula of eslicarbazepine acetate is:



The bulk drug substance is a white to off white crystalline solid with a melting point of 184-187°C. It is very slightly soluble in aqueous solvents and is not ionizable under physiological conditions. The applicant states that [redacted] (b) (4) have been observed.

Eslicarbazepine acetate is manufactured by [redacted] (b) (4) The NDA itself contains manufacturer information, drug substance specification (including methods and validation, batch analysis data, and justification for specification). No specific details regarding the manufacturing process are provided in the NDA. The synthesis route is, however, described as [redacted] (b) (4) from carbamazepine [Section 3.3.S.4.4]. DMF 22026, which is held by Bial Portela & Ca, is referenced for all other information regarding the manufacture, characterization and control of the drug substance.

The proposed drug substance specification is reproduced on the following page (Table 1). The proposed analytical procedures for eslicarbazepine acetate are straight-forward. Assay/identification and related substances are determined using an achiral reverse-phase HPLC method [redacted] (b) (4) Enantiomeric purity is determined by a chiral HPLC method [redacted] (b) (4) Analytical procedures and method validation data are included in the NDA.

Table 1: Specification for Eslicarbazepine Acetate

Test	Specification	Method
Physicochemical properties		
Description*	White to off-white solid	PT-PTDPE102 [1] (LDFPE048) [2]
(b) (4)		
Identification		
IR spectrum	conforms to reference	PT-PTDPE38 [1] (LDFPE058) [2]
HPLC retention time*	conforms to reference	PT-PTDPE6 [1] (LDFPE004) [2]
Purity		
(b) (4)		
Melting point*	184 – 187 °C	PT-QCPE26 [1] (SCQPE044) [2]
Residue on ignition	(b) (4)	
Heavy metals		
Residual solvents		
(b) (4)		

Test	Specification	Method
Microbiological attributes** Total viable aerobic count - Bacteria - Fungi - *E. coli* - *Salmonella* - *Pseudomonas aeruginosa* - *Staphylococcus aureus*	 $\leq 10^2$ CFU/g, $\leq 10^2$ CFU/g Absent Absent Absent Absent	 USP <61 > Ph. Eur. 2.6.12 USP <62> Ph. Eur. 2.6.13
Purity (HPLC)		
(b) (4)		
Impurities (HPLC)		
(b) (4)		
Assay		
Assay (HPLC)		
(b) (4)		

[1] - Current method numbers were assigned when the test methods were processed via Bial's electronic document system. Some documents (e.g. validation reports) which were completed prior to the implementation of Bial's electronic document system, may cite previous method numbers.
[2] - Bial's previous method number
**This test is only performed during stability evaluation, on an annual basis (for studies at 40 °C/ 75 % RH, the determinations are performed at the beginning and after 6 months).

Drug Product

The proposed dosage form for Stedesa (eslicarbazepine acetate tablets), is an immediate release tablet containing 400 mg, 600 mg or 800 mg eslicarbazepine acetate. The 400 mg tablet presentation is white circular bi-convex tablets, engraved ESL 400 on one side (b) (4) The quantitative formulation is summarized in Table 1. (b) (4) .

Table 1: Compositions of Eslicarbazepine Acetate 400, 600 and 800 mg Tablets

Strength	**400 mg**	**600 mg**	**800 mg**		
Component	**Quantity (mg/ tablet)**			**Function**	**Reference**
Eslicarbazepine acetate	400.0	600.0	800.0	Active substance	PT-QCMN1
Povidone (b) (4)	(b) (4)				USP
Croscarmellose sodium					NF
(b) (4)					USP
Magnesium stearate					NF
Tablet weight (target in mg)	467	700	933		

(b) (4)

Tablet excipients are typical ingredients for solid oral dosage forms and all excipients comply with compendial requirements. The proposed commercial tablet formulation is (b) (4) different from the tablet formulations used for Phase 3 clinical trials. The clinical formulations are summarized in Table 2. The primary differences between the clinical formulations and the proposed commercial products are (b) (4) Linkage between the clinical formulations and the proposed commercial formulation is based on a comparative BA/BE study.

Table 2: Compositions of Eslicarbazepine Acetate Clinical Formulations

Component	Function	Quantity (mg/tablet)		
		400 mg [1]	600 mg [2]	800 [3]
Eslicarbazepine acetate	Active substance	400.0	600.0	800.0
(b) (4)	(b) (4)			
Povidone				
Croscarmellose sodium				
(b) (4)				
Magnesium stearate				
Tablet Weight				

1. Formulation FN
2. Formulation FK
3. Formulation FC

(b) (4)

The commercial product will be manufactured by (b) (4) A summary of the process development studies is provided in the Pharmaceutical Development section.

The proposed regulatory specification for 400 mg Stedesa (eslicarbazepine acetate tablets) is shown on the following page. Acceptance criteria for the 600 mg and 800 mg strengths are the same. Assay and related substances are determined using the same achiral reverse phase HPLC methods as for the drug substance. The only specified degradant is (b) (4) which is limited to NMT (b) (4). All other degradants are controlled to NMT (b) (4) Dissolution is quantitated by UV assay. It is noted that the firm proposes two point dissolution acceptance criteria rather than a single time point.

Table 1: Drug Product Specification for SEP-0002093 (eslicarbazepine acetate) Tablets 400 mg

Attribute	Method	Specification
Appearance	PT-QCPE28	White circular biconvex tablets, engraved ESL 400 on one side (b) (4)
Average weight	PT-PTDPE44	467 mg ± 3 %
Uniformity of dosage	Ph. Eur. 2.9.40**	(b) (4)
Thickness*	PT-MFGPE10	
Hardness*	Ph. Eur. 2.9.8**	
Friability*	Ph. Eur. 2.9.7**	
(b) (4)		
Dissolution	PT-PTDPE9	(b) (4) (Q) after 15 minutes and (Q) after 45 minutes
Identification (HPLC)	PT-PTDPE6	(b) (4)

Attribute	Method	Specification
Identification (DAD HPLC)	PT-PTDPE42	(b) (4)
Assay (HPLC)	PT-PTDPE6	
Degradation Products (HPLC) Specified Degradation (b) (4) Unspecified Degradation Product - Each unknown degradation product Total Degradation Products	PT-PTDPE7	
Microbiological attributes - Total viable aerobic count Bacteria Fungi - *E. coli*	USP <61> Ph. Eur. 2.6.12 USP <62> Ph. Eur. 2.6.13	 $\leq 10^3$ CFU/g, $\leq 10^2$ CFU/g Absence

* Obtained from in-process samples

** A comparison of Ph. Eur. analytical procedures and the corresponding USP procedure is provided in Section 3.2.P.5.2.

The applicant proposes marketing of Stedesa in HDPE bottles, (b) (4) Al blisters, and Al/Al blisters; the blister presentations are intended as professional samples. The proposed bottle configurations are shown in Table 2 below. Blister cartons will contain 7 tablets (400 mg) (b) (4) (600 mg, 800 mg).

Table 2: Summary of Tablet Count, HDPE Bottle Size and (b) (4) Cap Dimensions

Tablet	400mg	600mg	800mg
30-count	30 cc bottle/28 mm cap		50 cc bottle /33 mm cap
60-count		85 cc bottle/ 33 mm cap	
90-count		120 cc bottle/ 38 mm cap	150 cc bottle/ 38 mm cap

The NDA stability package includes long-term and intermediate data through 12 months plus accelerated data through 6 months for three pilot-scale batches per strength manufactured at the (b) (4) and packaged in 90 count bottles, (b) (4) Al blisters and Al/Al blisters. Stability data through 6 months under long term, intermediate, and accelerated are provided for the all strengths packaged in 30-count bottles and for 600 mg and 800 mg tablets in 120-count bottles. The 30-count bottle will be used for 400 mg and 800 mg tablets and brackets the 60-count bottle proposed for 600 mg tablets. The 120-count bottle is not proposed for marketing at this time. Supportive stability data are provided for one batch per tablet strength manufactured at the Bial facility in Portugal and packaged in bottles and blisters.

Note: Although stability results are summarized in the NDA and statistical results are provided in graphical format, the stability data are provided in SAS transport (xpt) format only. The sponsor will be asked to provide the data in pdf format for the CMC reviewer.

Critical issues for review

Drug Substance

As information on manufacture of the drug substance has been submitted in Bial's DMF 22026, critical issues related to the drug substance are not included in this initial quality assessment.

Drug Product

The drug product is an immediate release tablet manufactured using (b) (4) No critical issues were identified during the initial assessment; however, the lack of detailed information on formulation and manufacturing process development is noted.

Additional issues

Administrative: A claim for categorical exclusion is included in Module 1 of the application.

Establishment Evaluation: An updated list of manufacturing sites and contract testing facilities was provided on 10-Apr-2009. [Refer to Attachment 1.] All sites have been entered into EES, and were submitted for facility evaluation on 10-Apr-2009.

Labeling/Established Name: The active ingredient, eslicarbazepine acetate, is the acetate ester prodrug for eslicarbazepine. The potency statement is based on the content of the ester. Thus,

the name "eslicarbazepine acetate tablets" is consistent with labeled potency. The name "eslicarbazepine acetate", however, does not appear to have been adopted by the USAN Council. The applicant will be asked to address this issue.

Comments for 74-Day Letter

- With respect to product labeling and nomenclature, clarify whether the name eslicarbazepine acetate has been submitted to, and accepted by, the United Stated Adopted Names (USAN) Council. If not, you will need to apply for designation of eslicarbazepine acetate as the USAN.

- To assist in our review, please provide copies of the drug product stability data tables in Adobe (pdf) or Microsoft Excel (xls) format.

Review, Comments and Recommendation:

The NDA is fileable from a CMC perspective. The drug substance is a new molecular entity. The dosage form, however, is a conventional immediate release tablet and there are no QbD aspects to the application. Assignment of the NDA to a single reviewer is recommended.

Martha R. Heimann, Ph.D.

Pharmaceutical Assessment Lead, DPA 1, ONDQA Date

Ramesh Sood, Ph.D.

Branch Chief, DPA 1, ONDQA Date

CHEMICAL MANUFACTURING CONTROLS
FILING CHECKLIST FOR A NEW NDA/BLA

NDA Numbers: 22-416 **Applicant: Sepracor, Inc.** **Stamp Date: 30-Mar-2009**

Drug Name: eslicarbazepine acetate tablets **NDA Type: Standard**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?	X		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	X		Updated facility information provided 10-Apr-2009.
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?	X		
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	X		A claim for categorical exclusion was submitted.
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	X		LoA to cross-reference DMF 22026 is provided in NDA.
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	X		Drug product stability data tables are provided in SAS xpt format only.
7	If applicable, has all information requested during the IND phases, and at the pre-NDA meetings been included?	NA		
8	Have draft container labels and package insert been provided?	X		
9	Have all DMF References been identified?	X		
10	Is information on the investigational formulations included?	X		
11	Is information on the Methods Validation included?	X		
12	If applicable, is documentation on the sterilization process validation included?	NA		

IS THE CMC SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant. **NA**

Martha R. Heimann, Ph.D.

Pharmaceutical Assessment Lead, DPA 1, ONDQA Date

Ramesh Sood, Ph.D.

Branch Chief, DPA 1, ONDQA Date

Manufacturing Facilities for Stedesa (eslicarbazepine acetate) Tablets

Drug Substance

Establishment	Address	Contact Information	Establishment Registration No.	Responsibility
(b) (4)				

Manufacturing Facilities for Stedesa (eslicarbazepine acetate) Tablets

Drug Substance

Establishment	Address	Contact Information	Establishment Registration No.	Responsibility
(b) (4)				
Bial – Portela & Cª, S.A.	À Av. da Siderurgia Nacional 4745-457 S. Mamede do Coronado Portugal	Luis Sintra Telephone +351 22 986 6100 Email: luis.sintra @bial.com	Requested	Stability testing

Drug Product

Establishment	Address	Contact Information	Establishment Registration No.	Responsibility
(b) (4)				

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

/s/

Martha Heimann
4/10/2009 01:39:43 PM
CHEMIST

Ramesh Sood
4/16/2009 11:09:08 AM
CHEMIST