CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-253 & 22-254

CHEMISTRY REVIEW(S)

MEMORANDUM

TO: NDA 22-254

FROM: Wendy I. Wilson, Review Chemist

SUBJECT: CMC Review of Revised Labeling

DATE: 10/23/2008

CC: Jacqueline Ware, HFD 120 RPM; Scott Goldie, ONDQA PM; Martha Heimann, ONDQA PAL; Ramesh Sood, ONDQA Branch Chief; Blair Fraser, ONDQA Division Director

Revised Labeling

Schwarz incorporated all of the CMC recommendations concerning the carton container labels during the initial CMC review cycle. As part of that review, we recommended that the sponsor

b(4)

Overall Recommendation

We recommend that Schwarz revise the labeling

b(4)

Wendy I. Wilson

Wendy I. Wilson, Ph.D.
Review Chemist
ONDQA DPA-I

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/s/

Wendy I. Wilson
10/23/2008 04:09:43 PM
CHEMIST

Ramesh Sood
10/24/2008 09:38:16 AM
CHEMIST

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 16, 2008

FROM: Prafull Shiromani, Ph.D.
Reviewing Chemist
Division of Neurology Products, HFD-120

b(4)

TO: File NDA 22-253 ———

SUBJECT: Approval recommendation for Vimpat® (Lacosamide) Tablets, (NDA 22-253 ——— , Schwarz Biosciences, Inc.)

b(4)

This memo recommends the approval of Vimpat® (Lacosamide) Tablets from CMC perspective based on the overall acceptable establishment report from the Office of Compliance, the summary of which is attached. All other CMC related issues had been resolved as per earlier CMC reviews.

Prafull Shiromani
Chemist

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 22253/000
Org Code : 120
Priority : 1S

Sponsor: SCHWARZ BIOSCIENCES
NO CITY, , XX

Brand Name : LACOSAMIDE (SPN807) TABLETS

Stamp Date : 28-SEP-2007
PDUFA Date : 28-JUL-2008
Action Goal :
District Goal: 29-MAY-2008

Estab. Name:
Generic Name: LACOSAMIDE
Dosage Form: (TABLET)
Strength : 50,100,150,200,250,300

FDA Contacts:	S. GOLOIP	Project Manager	301-796-2055
	S. SHIROMANI	Review Chemist	301-796-2133
	M. HEIMANN	Team Leader	301-796-1678

Overall Recommendation: ACCEPTABLE on 15-JUL-2008by S. ADAMS (HFD-325) 301-796-3

Establishment : CFN : FEI : b(4)

b(4)

OSE No: AADA:

Responsibilities: b(4)

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 15-APR-08

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9610732 FEI : 3002808160

SCHWARZ PHARMA LTD

SHANNON INDUSTRIAL ESTATE

SHANNON, , EI

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

DRUG SUBSTANCE STABILITY TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 14-JUL-06

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 1919171 FEI : 1819171

SCHWARZ PHARMA MANUFACTURING

1101 C AVE W

SEYMOUR, IN 472743342

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Profile :	TCM	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	06-FEB-08		
Decision :	ACCEPTABLE		
Reason :	DISTRICT RECOMMENDATION		

Establishment : CFN : FEI : 3002948803

SCHWARZ PHARMA PRODUKTIONS GMBH

GALILEISTRABE 6

ZWICKAU, , GM

DME No: AADA:

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

DRUG SUBSTANCE STABILITY TESTER

FINISHED DOSAGE MANUFACTURER

Profile :	CTL	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	15-JUL-08		
Decision :	ACCEPTABLE		
Reason :	DISTRICT RECOMMENDATION		
Profile :	TCM	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	15-JUL-08		
Decision :	ACCEPTABLE		

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI : 3002943189

SCHWARZ PHARMA PRODUKTIONS GMBH

ALFRED NOBEL STRABE 10

MONHEIM, , GM

DMF No: AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 21-NOV-07

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : [redacted] FEI : [redacted] b(4)

[redacted] b(4)

DMF No: AADA:

Responsibilities: [redacted] b(4)

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Profile :	TCN	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	18-OCT-07		
Decision :	ACCEPTABLE		
Reason :	BASED ON PROFILE		

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/s/

Prafull Shiromani
7/16/2008 09:44:34 AM
CHEMIST

MEMORANDUM

TO: NDA 22-254 &

FROM: Wendy I. Wilson, Review Chemist

SUBJECT: Outcomes of Micro Consult and Facility Inspections

DATE: 7/16/2008

CC: Jacqueline Ware, HFD 120 RPM; Scott Goldie, ONDQA PM; Martha Heimann, ONDQA PAL; Ramesh Sood, ONDQA Branch Chief; Blair Fraser, ONDQA Division Director

Microbiology Consults

The microbiology reviewer recommended approval of lacosamide injection (NDA 22-254) on 04-JUN-2008 b(4)

Facility Inspections

OC provided an overall recommendation of acceptable for all facilities listed for lacosamide injection (NDA 22-254) on 15-JUL-2008. b(4)

NDA 22-254 – b(4)

Overall Recommendation

Based on the outcomes of the microbiology consult and facility inspections , we recommend lacosamide injection (NDA 22-254) for approval pending labeling, from a CMC perspective. b(4)

Wendy I. Wilson

Wendy I. Wilson, Ph.D.
Review Chemist
ONDQA DPA-I

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/s/

Wendy I. Wilson
7/16/2008 10:40:12 AM
CHEMIST

Ramesh Sood
7/16/2008 10:42:25 AM
CHEMIST

Vimpat™
(lacosamide)
Injection

NDA 22-254

Division Director Review
Chemistry, Manufacturing, and Controls

Applicant: Schwarz Biosciences, Inc.
8010 Arco Corporate Drive, Suite 100
Raleigh, NC 27617

Indication: adjunctive treatment of partial-onset seizures in patients with epilepsy, aged 16 years and older

Presentation: Vimpat (lacosamide) Injection is supplied as a single strength, sterile — 10 mg/mL solution of lacosamide. Each single-use, 20 mL vial contains 200 mg of lacosamide in an — saline solution in a —, colorless glass vial with a grey rubber stopper — and aluminum overseal. b(4)

EER Status:		Acceptable	15-JUL-2008
Consults:	Microbiology -	Acceptable	1-JUN-2008
	EA – OPS	No significant impact	15-MAY-2008
	Methods Validation –	Revalidation by Agency not requested.	

Original Submission: 27-SEP-2007

Post-Approval Agreements: None

Drug Substance:

The applicant referenced NDA 22-253 for all information concerning the chemistry, manufacturing, and control of the lacosamide drug substance.

Lacosamide is a member of a series of functionalized amino acids that were specifically synthesized as anticonvulsive drug candidates. The drug substance, lacosamide, is a small, synthetic, New Molecular Entity (NME) with an empirical formula of $C_{13}H_{18}N_2O_3$ and a molecular weight of 250.30. Known chemically as (R)-2-acetamido-N-benzyl-3-methoxypropionamide, it is a white to light yellow powder with a melting range of — Lacosamide is sparingly soluble in water (—) — and slightly soluble in ethanol. Lacosamide, a chiral drug substance, — b(4)

b(4)

The bulk drug substance is synthesized from [redacted] *Comprehensive information for all the impurities at the starting material level, at the intermediate level and at the final synthesis level was presented. Noteworthy were controls over* [redacted] *starting materials and intermediates.* b(4)

The structure of lacosamide was elucidated using several analytical techniques, [redacted] b(4)

The proposed release specification for lacosamide includes [redacted] b(4

[redacted] *The proposed regulatory methods are either compendial or were developed and validated for their intended purpose. The primary reference standard for drug substance, manufactured by commercial process, has been characterized by the proposed regulatory methods as well as additional methods. The impurity and degradation profiles have been investigated. Reference standards for known impurities and in-process intermediates have been synthesized and fully characterized.*

The stability data for three commercial batches support a [redacted] *retest period for the bulk drug substance stored inside* [redacted] *at controlled room temperature, 25 °C /60%RH, protected from light.* b(4)

Conclusion: Drug substance is acceptable.

Drug Product:

Vimpat (lacosamide) Injection is supplied as a single strength, sterile, [redacted] 10 mg/mL solution of lacosamide. Each single-use, 20 mL vial contains 200 mg of lacosamide in an [redacted] saline solution in a [redacted] colorless glass vial with a grey rubber stopper [redacted] and aluminum overseal. b(4)

Each 20 mL vial of Vimpat contains 10 mg/mL lacosamide, [redacted], sodium chloride USP, adjusted to pH 4.0 with hydrochloric acid USP, in Water for Injection. The manufacturing process is [redacted] b(4)

b(4)

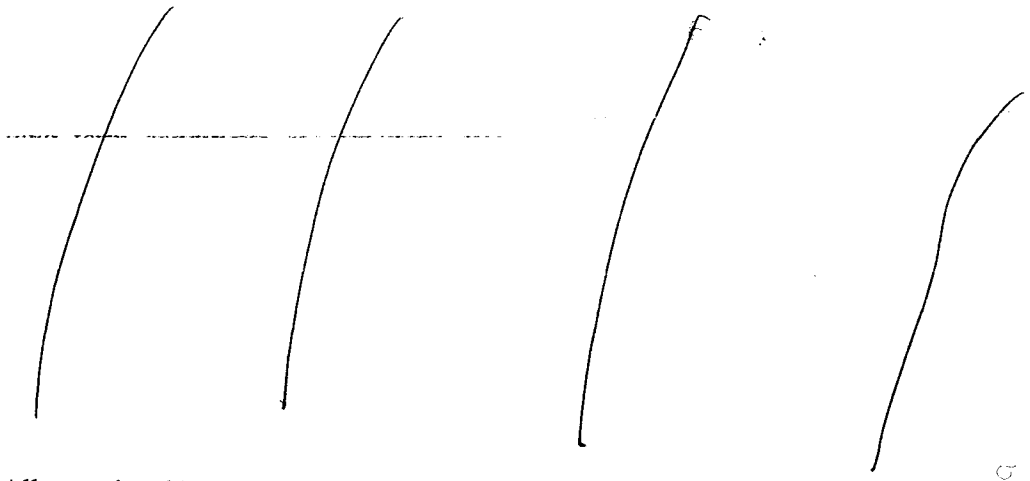
Specification of the drug product includes: [redacted]

[redacted] ne lacosamide reference standard for drug product is the same as that for drug substance. All test methods are compendial or have been appropriately validated for their intended purpose.

The drug product stability data supports the proposed 36 month expiry for drug product stored at controlled room temperature [25° C (77° F); excursion permitted to 15-30° C (59-86° F)], and packaged in 20 mL [redacted] colorless glass vials with a grey rubber stopper [redacted] and aluminum overseal. b(4)

Conclusion: Drug product is acceptable.

Additional Items:



b(4)

- All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.
- The applicant submitted a methods validation package containing all relevant documentation (tests, methods, and acceptance criteria) for the control of the drug substance and the drug product.

Overall Conclusion:

From a CMC perspective, the application is recommended for **Approval,** pending agreement on product labeling.

Blair A. Fraser, Ph.D.
Director
DPA I/ONDQA

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/s/

Blair Fraser
7/16/2008 11:03:04 AM
CHEMIST

Initial Quality Assessment
Branch I
Pre-Marketing Assessment Division I

OND Division:	Division of Neurology Products/Division of Anesthesia, Analgesia, and Rheumatology Products
NDA:	22-253. —
Applicant:	Schwarz Biosciences b(4)
Stamp Date:	28-Sep-2007
PDUFA Date:	28-Jul-2008
Trademark:	TBD.
Established Name:	Lacosamide
Dosage Form:	Tablets
Route of Administration:	Oral
Indication:	Epilepsy/Neuropathic pain
PAL:	Martha R. Heimann, Ph.D.

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

Summary and Critical Issues:

Summary

Lacosamide (previously known as harkoseride or erlosamide) has been developed by Schwarz for two indications, adjunctive treatment of partial onset seizures and management of diabetic neuropathic pain — dosage forms have been developed including immediate release tablets that are the subject of NDAs 22-253 (epilepsy) and — (neuropathic pain). NDAs 22-254 — were submitted —, and provide for use of lacosamide injection — — for treatment of epilepsy. b(4)

The applicant proposes marketing of Lacosamide Tablets in 6 strengths, 50 mg 100 mg, 150 mg, 200 mg, 250 mg and 300 mg. All tablet strengths are compositionally proportional but differ with respect to film-coat color. Recommended doses — b(4)
for management of neuropathic pain, and 200 mg to 400 mg for treatment of partial onset seizures. The maximum dose should not exceed — mg/day.

Drug Substance

The active ingredient, lacosamide [(*R*)-2-acetamido-N-benzyl-3-methoxypropionamide], is a well characterized small molecule with molecular formula $C_{13}H_{18}NO_3$ and molecular weight 250.30. The drug substance is sparingly soluble in water (~30 mg/mL at 25°C) — — The applicant classifies lacosamide as a high solubility drug according to the Biopharmaceutics Classification System (BCS). The calculated dose solubility volume for the highest tablet

[redacted]

strength (— mg) is — mL.

b(4)

The proposed regulatory specifications for lacosamide involve straight-forward analytical procedures. A HPLC method is used for assay and determination of related substances. The principal impurity, , and the are controlled with limits of NMT and NMT %, respectively. The remaining specified impurities are controlled at the ICH qualification threshold, NMT b(4)

The drug substance stability package includes between 3 and 48 months of long-term data for drug substance batches that were manufactured by . or Schwarz Pharma, County Clare, Ireland, and are characterized by the applicant as primary stability batches. The batches include b(4)

Drug Product

Lacosamide 50 mg, 100 mg, 150 mg, 200 mg, 250 mg and 300 mg film-coated tablets are conventional, immediate-release, oval tablets. The tablet formulations are compositionally proportional; however, the film-coat colors are different. All tablet excipients are commonly used for manufacture of immediate-release solid oral dosage forms. All ingredients except microcrystalline cellulose) and the film-coat formulations are compendial. and the film-coat formulations are manufactured using compendial ingredients. It is noted that the proposed commercial tablet formulations are qualitatively and quantitatively different from the 50 mg and 100 mg tablets that were used for Phase 3 clinical trials. The quantitative compositions for the proposed commercial tablets and a comparison of the 100 mg clinical tablet formulation are presented on the following pages. Information on the composition of the 50 mg clinical tablet formulation was not provided and will be requested. These composition differences are characterized by the applicant as minor; and a waiver of *in vivo* bioequivalence studies for the commercial formulation is requested. b(4)

Lacosamide Tablets will be manufactured by Schwarz Pharma at two sites located in Zwickau, Germany and Seymour, Indiana. [Note: Although the electronic submission is formatted with separate P sections for each facility, all subsections for each site except P.3.2 (Batch Formula) and P.3 (Description of Manufacturing Process) are linked to common PDF files.] The tablets are manufactured from b(4)

Composition of Proposed Commercial Lacosamide Tablets

Quantitative composition per film-coated tablet

Component	Reference to standard	Function	50 mg pinkish [mg]	100 mg dark yellow [mg]	150 mg salmon [mg]	200 mg blue [mg]	250 mg [mg]	300 mg [mg]
Lacosamide	In-house	Active ingredient	50.00	100.00	150.00	200.00	250.00	300.00
Cellulose, microcrystalline	USP-NF							
Crospovidone	USP-NF							
Magnesium stearate	USP-NF							
Hydroxy-propylcellulose	USP/NF							
Total (film-coated tablet)			126.00	252.00	378.00	504.00		

b(4)

Comparison of Clinical and Commercial 100 mg Lacosamide Tablets

Tablet formulations (exemplary for a 100 mg dosage strength)

Ingredient	Function	Clinical trial formulation [mg]	Commercial formulation (proportional) [mg]
Lacosamide	Active substance	100.00	100.00
Cellulose, microcrystalline			
Hypromellose			
Hydroxypropyl cellulose			
Cellulose, microcrystalline			
Crospovidone			
Magnesium stearate			
Titanium dioxide			

b(4)

The proposed regulatory specifications for Lacosamide Tablets involve straight-forward analytical procedures. A HPLC method is used for assay and determination of related substances. This method is similar to the drug substance assay/related substance method; the primary differences are b(4)

Tablet dissolution results are quantitated by HPLC, however, the method is different from that used for assay and related substances. It is noted that the specification does

b(4)

not include a [redacted]. The applicant does not include a justification for omitting of these tests. b(4)

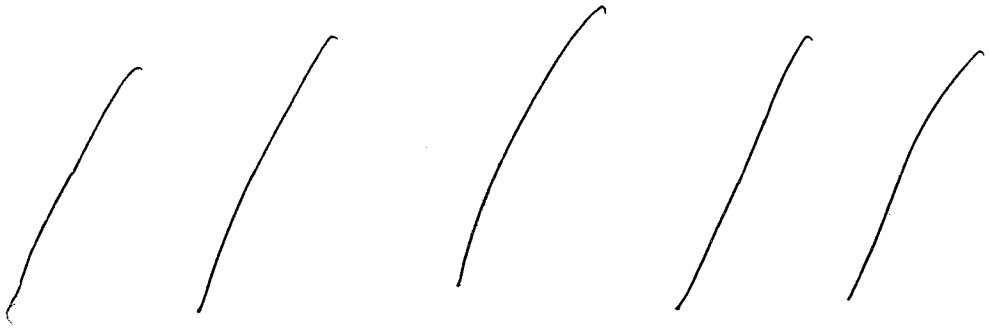
Lacosamide Tablets will be packaged in [redacted] bottles (60-, 180-, [redacted] count) [redacted] CMC documentation for [redacted] packaging configurations is provided in the submission. Draft bottle labels are provided; [redacted]

The NDA stability package includes data through at least 18 months for 12 primary stability batches of [redacted] film-coated 50 mg, 200 mg and 300 mg Lacosamide Tablets, plus 6 batches of colored, film-coated 50 mg tablets. The three strengths of [redacted] film-coated were chosen to bracket the range of commercial strengths; the 50 mg colored tablet batches include all proposed commercial film–coat colors. The 50 mg colored tablet batches were added to the protocol to address concerns raised during End of Phase 2 discussions. b(4)

Critical issues for review

Drug Substance

The drug substance manufacturing process involves [redacted] b(4)



Drug Product

The drug product is an immediate-release tablet manufactured using conventional manufacturing processes. No critical issues were identified during the initial assessment; however the following points are noted:

- A biowaiver is requested for the commercial tablet formulations.
- Although the active ingredient is the (*R*)-isomer, the tablet specification [redacted] est. The application should include a justification for omission of any [redacted] in the product. b(4)

Additional issues

Administrative: An environmental assessment for all proposed lacosamide dosage forms is included in Module 1 of the application. It is requested that the ONDQA Project Manager arrange for a consult review.

Establishment Evaluation: A full list of manufacturing sites and contract testing facilities is appended to the Form 356h. The sites that have been entered into EES for facility evaluation are listed in Attachment 1

Labeling/Established Name: The active ingredient, lacosamide, is ~~~~ There are no issues related to consistency between the established name and labeled potency. b(4)

Comments for 74-Day Letter

The formulation of the 50 mg lacosamide clinical tablets is not provided in the original NDA. Provide the quantitative unit composition for all strengths of each formulation that was used in clinical studies to support this application.

Container closure documentation for ~~~~ bottles is provided in the application. ~~~~ b(4)

Review, Comments and Recommendation:

The NDA is fileable from a CMC perspective. The drug substance is a well-characterized small molecule and the dosage form is relatively simple. As the applicant has submitted concurrent NDAs for an intravenous formulation (22-254 ~~~~ it is recommended that a team review of the ~~applications be performed. At least one reviewer should have appropriate biopharmaceutics experience and qualifications to review the biowaiver request for the commercial tablets. No novel manufacturing processes are involved and the submission does not appear to require a review by the Manufacturing Sciences Branch. b(4)

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

Ramesh Sood, Ph.D. _____
Branch Chief Date

ATTACHMENT 1

Manufacturing Sites for Lacosamide Tablets

Facility Information	Function
[redacted]	[redacted]
SCHWARZ PHARMA Limited Shannon Industrial Estate Shannon, Co. Clare Ireland Registration No.: 3002808160 Site Contact: Daniel J. Dooley Tel. No.: +353 61 714234 US Agent: Ruth Hill Phone: 919 767 2634	Drug substance release and stability testing
SCHWARZ PHARMA Produktions GmbH Galileistrasse 6 08056 Zwickau Germany Registration No.: 3002948883 Site Contact: Wilhelm Lehr Tel. No.: +49 375 322 300 US Agent: Ruth Hill Phone: 919 767 2634	Drug substance release testing Drug product manufacture
SCHWARZ PHARMA Manufacturing 1101 C Avenue West Seymour, IN 47274 Registration No.: 1819171 Site Contact: Chad Kurdziel Tel. No.: 812 523 5396	Drug substance retest Drug product manufacture, packaging, release and stability testing

b(4)

b(4)

ATTACHMENT 1

Manufacturing Sites for Lacosamide Tablets

Facility Information	Function
[redacted]	[redacted]
SCHWARZ PHARMA Produktions GmbH Alfred-Nobel-Straße 10 40789 Monheim am Rhein Germany Registration No.: 3002943189 Site Contact: Werner Schick Tel. No.: +49 2173 48 1178 US Agent: Ruth Hill Phone: 919 767 2634	Drug product stability testing

b(4)

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/s/

Blair Fraser
7/16/2008 11:07:39 AM
CHEMIST

Vimpat™
(lacosamide)
Tablets

NDA 22-253

Division Director Review
Chemistry, Manufacturing, and Controls

Applicant: Schwarz Biosciences, Inc.
8010 Arco Corporate Drive, Suite 100
Raleigh, NC 27617

Indication: adjunctive treatment of partial-onset seizures in patients with epilepsy, aged 16 years and older

b(4)

Presentation: Film-coated, colored, oval, ——— , immediate release, tablets are available in six strengths (50 mg – pinkish; 100 mg – dark yellow; 150 mg – salmon; 200 mg – blue; 250 mg – ——, and 300 mg – ——— debossed with "SP" on one side and tablet strength on the other side.

Tablets of all strengths are packaged in ——————— bottles, at 60, 180, ——— count. b(4)

EER Status: **Pending**

Consults: EA – OPS No significant impact 15-MAY-2008
Methods Validation – Revalidation by Agency not requested.

Original Submission: 27-SEP-2007

Post-Approval Agreements: None

Background:

This application was chosen by the Division of Neurology Products to serve as the pilot for the *Good Review Management Principles and Practices (GRMPs) for PDUFA Products (April 2005).*

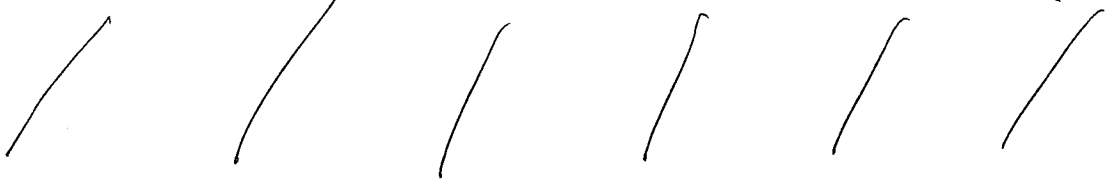
Drug Substance:

Lacosamide is a member of a series of functionalized amino acids that were specifically synthesized as anticonvulsive drug candidates. The drug substance, lacosamide, is a small, synthetic, New Molecular Entity (NME) with an empirical formula of $C_{13}H_{18}N_2O_3$ and a molecular weight of 250.30 . Known chemically as (R)-2-acetamido-N-benzyl-3- b(4)

methoxypropionamide, it is a white to light yellow powder with a melting range of [redacted] b(4)
Lacosamide is sparingly soluble in water [redacted] and slightly soluble in ethanol.
Lacosamide, a chiral drug substance, [redacted]

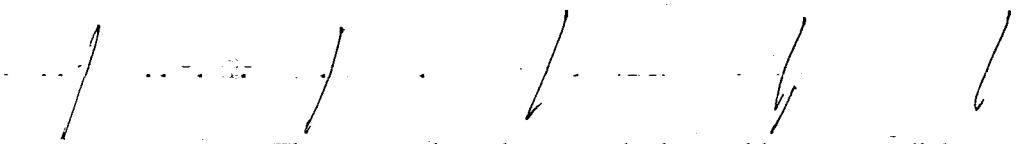
The bulk drug substance is synthesized from [redacted] b(4)
[redacted]. Comprehensive information for all the impurities at the starting material level, at the intermediate level and at the final synthesis level was presented. Noteworthy were controls over [redacted] of starting materials and intermediates.

The structure of lacosamide was elucidated using several analytical and [redacted]
techniques [redacted]



b(4)

The proposed release specification for lacosamide includes [redacted]



b(4)

[redacted] The proposed regulatory methods are either compendial or were developed and validated for their intended purpose. The primary reference standard for drug substance, manufactured by commercial process, has been characterized by the proposed regulatory methods as well as additional methods. The impurity and degradation profiles have been investigated. Reference standards for known impurities and in-process intermediates have been synthesized and fully characterized.

The stability data for three commercial batches support a [redacted] retest period for the bulk drug substance stored inside [redacted] b(4)
[redacted] at controlled room temperature, 25°C /60%RH, protected from light.

Conclusion: Drug substance is acceptable.

Drug Product:

Vimpat (lacosamide) tablets are film-coated, colored, oval, [redacted] immediate release, tablets available in six strengths (50 mg – pinkish; 100 mg – dark yellow; 150 mg – salmon; 200 mg – blue; 250 mg – [redacted] and 300 mg – [redacted] debossed with "SP" on one side and tablet strength on the other side. Tablets of all strengths are packaged in [redacted] bottles, [redacted] sizes, at 60, 180, [redacted] count. b(4)

b(4)

The drug product is manufactured [redacted] and final packaging. Adequate information on the drug product manufacture has been provided.

The composition of the 50 mg strength, oval tablet is lacosamide (50.00 mg), microcrystalline cellulose NF [redacted], crospovidone NF [redacted], magnesium stearate NF [redacted] hypromellose USP [redacted]. Folowing [redacted] film-coating, the total film-coated tablet weight was 126.00 mg. The higher strength tablets are sequential weight multiples of the lowest strength giving rise to compositionally proportional formulations.

b(4)

The sponsor has submitted adequate information to support classification of lacosamide tablets as a BCS class 1 drug, *i.e.* the drug substance is highly soluble, highly permeable. Accordingly, Dr. A. Selen, Associate Director, Biopharmaceutics, ONDQA, concluded in her review, dated 04-Apr-2008, that the sponsor's dissolution method and their biowaiver requests are acceptable.

b(4)

The release specification for drug product includes: [redacted] The lacosamide reference standard for drug product is the same as that for drug substance. The proposed regulatory methods are either compendial or were developed and validated for their intended purpose.

The stability data support expiration dating of 36 months for all strengths of drug product stored at controlled room temperature conditions [25° C (77° F); excursion permitted to 15-30° C (59-86° F)], and packaged in HDPE bottles.

Conclusion: Drug product is acceptable.

Additional Items:

b(4)

[redacted]

b(4)

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

- The applicant submitted a methods validation package containing all relevant documentation (tests, methods, and acceptance criteria) for the control of the drug substance and the drug product.

Overall Conclusion:

From a CMC perspective, the application is recommended for **Approval,** Pending a satisfactory recommendation from the Office of Compliance.

Blair A. Fraser, Ph.D.
Director
DPA I/ONDQA

APPEARS THIS WAY
ON ORIGINAL

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/s/

Blair Fraser
5/27/2008 01:16:22 PM
CHEMIST

NDA 22-254

Lacosamide Injection

Schwarz Biosciences, Inc.

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

Table of Contents

b(4)

Chemistry Review Data Sheet

1. NDA: 22-254

2. REVIEW #: 01

3. REVIEW DATE: 19-MAY-2008

4. REVIEWER: Wendy I. Wilson, Ph. D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	28-SEP-2007
Amendment	22-APR-2008
Amendment	14-MAY-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Schwarz Biosciences, Inc.
Address:	8010 Arco Corporate Drive, Suite 100, Raleigh, NC 27617
Representative:	Alan L. Blumberg Sr. Director, US Regulatory Affairs
Telephone:	919-767-2513

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:
b) Non-Proprietary Name (USAN): Lacosamide
c) Code Name/# (ONDQA only): SPM 927
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Anticonvulsant

11. DOSAGE FORM: Injection, Solution

12. STRENGTH/POTENCY: 200 mg

13. ROUTE OF ADMINISTRATION: Intravenous

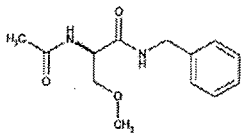
14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

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: (*R*)-2-acetamido-N-benzyl-3-methoxypropionamide
Mol. Formula: $C_{13}H_{18}NO_3$
Mol. Weight: 250.30



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	III			3	Adequate.	26-MAR-2007	
	III			4	N/A	N/A	
	V			3	Adequate.	16-AUG-2007	

b(4)

[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	57,939	ADD 234037 for Treatment of Epilepsy
IND		SPM 927 (formerly Harkoseride) for Treatment of Neuropathic Pain
IND	68,407	SPM 927 (formerly ADD 234037) for Treatment of Epilepsy
IND	73,809	Lacosamide (formerly SPM 927) for Treatment of Epilepsy

b(4)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Pending		S. Adams
Pharm/Tox	Pending		J Edward Fisher
Biopharm	Pending		V. Tandon
LNC	N/A	N/A	N/A
Methods Validation	Validation by FDA not needed	05-MAR-2008	W. Wilson
DMETS	No objection to use of Vipmat as proprietary name	13-MAY-2008	J. Park
EA	Finding of no significant impact	15-MAY-2008	R. Bloom
Microbiology	Pending		V. Pawar

List of Tables

b(4)

b(4)

APPEARS THIS WAY
ON ORIGINAL

List of Figures

b(4)

APPEARS THIS WAY
ON ORIGINAL

Chemistry Review for NDA 22-254

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a CMC perspective, lacosamide injection (10 mg/mL) is approvable (AE) pending labeling, completion of the manufacturing site inspections, and completion of the microbiology consult review. We will add a subsequent memo to the file once we receive acceptable recommendations from OC and microbiology.

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

There are no CMC-related Phase 4 recommendations.

II. Summary of Chemistry Assessments

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

b(4)

Schwarz referenced NDA 22-253 for all information concerning the chemistry, manufacturing, and control of the lacosamide drug substance. Lacosamide is a white to light yellow powder with a [redacted] for the (*R*)-enantiomer. Lacosamide is soluble in [redacted] and sparingly soluble in water. The drug substance [redacted] Lacosamide does not exhibit a pK_a in the pH range of [redacted] The drug substance manufacturer identified [redacted] Lacosamide is a Biopharmaceutics Classification System (BCS) Class I drug substance.

b(4)

Lacosamide 10 mg/mL injection is a clear, colorless, [redacted] liquid. The drug product is a solution for infusion, packaged in clear glass vials with rubber stoppers and aluminum crimping caps. This container closure system, together with a cardboard carton, represents the packaging system for shipment and storage of the drug product. The vial contains 20 mL of the 10 mg/mL lacosamide solution. The total drug substance content in the drug product is 200 mg. The proposed doses are 100 mg, 200 mg, 400 mg, [redacted] daily depending on the indication or stage of therapy. The FDA recommended maximum daily dose is 400 mg/day. The drug product excipients are compendial and are common in parenteral drug products. There are no issues with agreement between the established name and drug product strength because lacosamide [redacted] The target amount of drug substance per mL of solution [redacted]. Lacosamide injection is an [redacted] aqueous solution with a drug concentration of 10 mg/mL and a slightly acidic pH. The manufacturing process is [redacted]

b(4)

The proposed specification controls the appearance, identity, purity, strength, quality, and microbial contamination of the drug product. The manufacturer controls [redacted] in-process. Schwarz does not propose criteria for extractables or leachables based on the lack of evidence of extractables and leachables in tests conducted in accordance with USP <381>, USP <87>, and USP <88>. The results of these compendial tests, as well as the provided stability data, support not including criteria for extractables and leachables. Schwarz bases the proposed limits for extractable volume, osmolality, sodium, chloride, pH, particulate matter, sterility, and bacterial endotoxins on the current USP requirements. The sponsor bases the proposed limits for appearance, identity, assay, and chromatographic purity on the results observed at release and during stability. The proposed lacosamide 10 mg/mL injection container closure system is clear, colorless glass vials closed with a rubber stopper

and sealed with an aluminum crimping cap with grey flip-off seal. The secondary packaging material for the vial is a cardboard carton, used to protect the glass vial from damage. The secondary packaging material does not provide additional protection to the drug product.

Schwarz tested the primary and supportive stability batches according to the relevant ICH Q1A guidelines (25°C/60% RH for long-term, 30°C/65% RH (30°C/70% RH for WE 12690) for intermediate, and 40°C/75% RH for accelerated testing). The sponsor stored vials from Batch 0512130002 upright as well as inverted, with a reduced stability program for the inverted vials. Schwarz also tested additional storage conditions, including samples from Batch WE 12690 stored at 5°C and vials from Batch 0411110001 stored at -20°C and 5°C. In additional, the sponsor provided 36 months of data for Batch WE 12690 stored at 5°C, 6 months of data for Batch 0411110001 stored at -20°C, and 24 months of data for Batch 0411110001 stored at 5°C. Data from one supportive stability batch covers up to 36 months. Data from one primary stability batch, manufactured at [redacted] instead of the commercial scale, covers up to 36 months. The remaining primary stability batches cover storage up to 24 months. The statistical evaluation via regression analysis performed on pH, chromatographic purity and assay support the proposed 36 month drug product shelf -life. b(4)

Based on our current analysis of the drug product stability data, the sponsor's statistical evaluation, the drug substance stability, and the guidelines set forth in ICH Q1E, we grant the proposed 36 month drug product expiry, when stored at controlled room temperature, for lacosamide 10 mg/mL injection packaged in 20 mL [redacted] colorless glass vials with a grey rubber stopper [redacted] and aluminum overseal. b(4)

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

The sponsor applied for two indications for lacosamide, use in the treatment of neuropathic pain and use in the treatment of partial-onset seizures in patients, 16 years or older, with epilepsy. The sponsor indicates the solution for injection drug product as adjunctive therapy in the treatment of partial-onset seizures as an alternative for patients for whom oral administration is temporarily not feasible. Schwarz intends to market the lacosamide 10 mg/mL injection as Vipmat. Vipmat (lacosamide) injection may be given without further dilution or mixed in a compatible diluent for intravenously administration over at least [redacted] minutes. b(4)

The recommended dosing regimen includes a starting dose of 100 mg/day given twice daily with weekly incremental increases of 100 mg/day to reach the maintenance dose of 200 – 400 mg/day. The FDA recommended maximum daily dose is 400 mg/day. If necessary, the practitioner may switch the patient to intravenous administration of a dose equivalent to the oral dose. When switching patients from oral lacosamide formulations, the initial total daily intravenous dosage of lacosamide should be equivalent to the total daily dosage and frequency of oral lacosamide. At the end of the intravenous treatment period, the patient may be switched to Vipmat oral administration at the equivalent daily dosage and frequency of the intravenous administration.

The proposed commercial container closures for lacosamide 10 mg/mL injection is 20 mL [redacted] colorless glass vials with a grey rubber stopper [redacted] and aluminum overseal. The recommended Vipmat expiry is 36 months when stored at 25°C/60% RH in the commercial packaging. b(4)

C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, lacosamide injection (10 mg/mL) is approvable (AE) pending labeling, completion of the manufacturing site inspections, and completion of the microbiology consult review. We will add a subsequent memo to the file once we receive acceptable recommendations from OC and microbiology. All manufacturing facilities, except Schwarz Pharma Producktions GmBH in Germany (FEI 3002948883) and Schwarz Pharma Limited in Ireland (FEI 3002808160), are acceptable based on the OC recommendations. OC scheduled an inspection for the Ireland site and assigned the inspection to the IB for the Germany site. The manufacturing process and the associated process controls are adequate from a CMC perspective. As the microbiology CMC

review is still pending, the manufacturing process and associated controls are adequate from a CMC perspective, pending a satisfactory recommendation from the microbiology CMC review.

b(4)

Data provided by Schwarz to support

III. Administrative

A. Reviewer's Signature

Wendy I. Wilson

B. Endorsement Block

WWilson:	19-MAY-2008
MHeimann:	19-MAY-2008
RSood:	20-MAY-2008

C. CC Block

SGoldie:
JWare:
NDA22-254:

45 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Wendy I. Wilson
6/4/2008 03:59:01 PM
CHEMIST

Ramesh Sood
6/5/2008 12:30:05 PM
CHEMIST

NDA 22-253 and [redacted] b(4)

Vimpat (Lacosamide) Tablets
(50, 100, 150, 200, 250, & 300 mg)

Schwarz Biosciences, Inc.

Prafull Shiromani Ph.D.

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

Table of Contents

APPEARS THIS WAY ON ORIGINAL

Chemistry Review Data Sheet

1. NDA 22-253 & ——— b(4)

2. REVIEW #: 2

3. REVIEW DATE: 20-May-2008

4. REVIEWER: Prafull Shiromani, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

Previous Documents	b(4)	Document Date
NDAs 22-253/———		28-Sep-2007

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Sponsor's Responses to IR Letter.	E-mail attachments of 11-Apr-2008, (M. DOttavio to M. Sullivan). E-mail attachments of 29-Apr-2008 (M. DOttavio to M. Sullivan).

7. NAME & ADDRESS OF APPLICANT:

Name:	Schwarz Biosciences, In.
Address:	P. O. Box 110167, Research Triangle Park, NC 27709
Representative:	Alan Blumberg, Sr. Director, US Regulatory Affairs
Telephone:	919—767-2555

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Lacosamide
c) Code Name/# (ONDC only): SPM 927
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Epilepsy (16 years and older) - NDA 22-253 and neuropathic pain associated with diabetic peripheral neuropathy – NDA [redacted]

b(4)

11. DOSAGE FORM: Tablets – Immediate Release

12. STRENGTH/POTENCY: 50, 100, 150, 200, 250 & 300 mg

13. ROUTE OF ADMINISTRATION: Oral

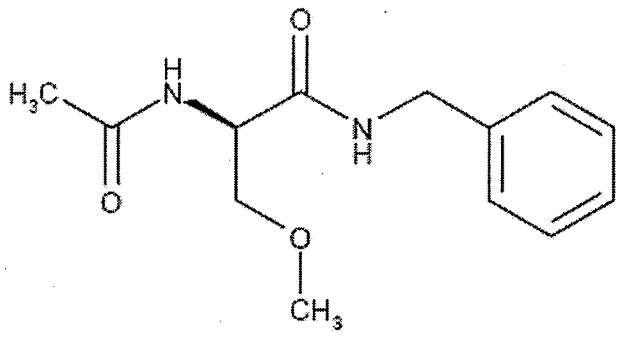
14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
SPOTS product – Form Completed
Not a SPOTS product

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

APPEARS THIS WAY
ON ORIGINAL

Structural formula



Molecular formula

$C_{13}H_{18}N_2O_3$

Relative molecular mass

250.30

17. RELATED/SUPPORTING DOCUMENTS:

I. A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
—	IV	/	/	3	Adequate	21-Sep-2003	None
—	IV	/	/	4			

b(4)

[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)

II. B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	None
EES	pending		
Pharm/Tox	N/A	N/A	None
Biopharm	N/A	N/A	None
LNC	N/A	N/A	None
Methods Validation	Samples not sent to Lab. since conventional methods	N/A	None
DMETS			
EA	Acceptable	15-May-2008	Ruth Ganunis
Microbiology	N/A	N/A	None

Labeling			
Bioequivalence			None
Radiopharmaceutical			None

The Chemistry Review for NDA 22-253 ——— b(4)
The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended as "Approvable" from a CMC perspective pending satisfactory recommendation from the Office of Compliance for facilities. A separate memorandum will be entered into the DFS regarding recommendation from the Office of Compliance, when received.

The applicant has provided adequate responses to the FDA IR letter sent to the applicant on 20-Mar-2008.

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

N/A

I. Summary of Chemistry Assessments

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

There are — related NDA submissions under review: as an adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 16 years and older (NDA 022-253, 022-254 ——— for — dosage forms: tablet, solution, for iv infusion, ———) and for the management of neuropathic pain associated with diabetic peripheral neuropathy (NDA —). The NDA 022-253 (immediate release film-coated tablets) serves as the primary NDA to which other NDAs refer to, as applicable. b(4)

Drug Substance

Lacosamide is a member of a series of functionalized amino acids that were specifically synthesized as anticonvulsive drug candidates. In clinical trials it has been shown to be effective in the treatment of partial-onset seizures in patients with epilepsy ——— b(4)

Lacosamide is a new chemical entity. The drug substance is the ——— ——— The chemical name is (R)-2-acetamido-N-benzyl-3-methoxypropionamide. b(4)

Executive Summary Section

The drug substance for the commercial product is synthesized by

b(4)

Lacosamide drug substance is very stable. Stability data at long-term, intermediate and accelerated storage conditions did not result in any degradation. The drug substance does not require any special storage conditions. Based on the stability data presented in the NDA a re-test date of for the drug substance is justified, conforming To ICH Q 1 E

The sponsor has provided adequate responses to deficiencies conveyed to them through an IR letter. These deficiencies related to: a) Description of Manufacturing Process and Process Controls and b) Control of Materials, including b(4)

The updated drug substance specification is presented in this review. This update reflects the sponsor's lowering of the acceptance criterion of the impurity by the sponsor from NMT to NMT and so conforming to the ICH qualification threshold. Their action was prompted by a request from the FDA reviewer. b(4)

Drug Product

The solid oral drug product developed for the treatment of epilepsy and neuropathic pain is an immediate release, oval, film-coated tablet containing 50 mg, 100 mg, 150 mg, 200 mg, 250 mg or 300 mg lacosamide, respectively. The tablets are compositionally proportionally (The different strength tablets are differentiated by employing different colored film-coats. b(4)

In clinical trials, capsules were used for some phase 1 and early phase 2 trials. Thereafter a tablet formulation with 50 mg or 100 mg lacosamide, with a matching placebo has been used. Due to the commercial tablets with dosages up to 300 mg have been developed. Although differences are noted in the composition of the proposed commercial tablets and the clinical trial tablet, the excipients included in the former are well characterized and can not further increase the lacosamide bioavailability (i.e. lead to unexpected lacosamide exposure) as the absolute lacosamide bioavailability from the clinical tablet is 100%. The manufacturing process for both the clinical tablets and the commercial product, includes The commercial table is manufactured by either SCHWARZ PHARMA Produktions-GmbH, b(4)

Zwickau, Germany or by SCHWARZ PHARMA Manufacturing Inc., Seymour, Indiana, USA.

The proposed commercial tablets have not been studied *in vivo* and hence, the Sponsor is requesting a biowaiver for the proposed commercial tablets. The sponsor has submitted adequate information to support classification of lacosamide tablets according to the Biopharmaceutics Classification System (BCS) as a BCS class 1 drug, i.e. the drug substance is highly soluble, highly permeable. Furthermore, the tablets are rapidly dissolving. Accordingly, Dr. A. Selen, Associate Director, Biopharmaceutics, ONDQA, concludes in her review, dated 04-Apr-2008 (resides in the DFS), that the sponsor's dissolution method and their biowaiver requests are acceptable.

Stability data for the clinical trial formulation and the commercial tablet formulation did not show any degradation of the drug substance in tablets. The sponsor has provided additional stability data in their response to the IR letter. Based on the 24-month satisfactory bottle —— stability data presented for the primary stability batches in the NDA a proposed shelf-life of 36 months for the drug product is justified, conforming to ICH Q1E. b(4)

The sponsor has provided adequate responses to deficiencies conveyed to them through an IR letter. These deficiencies related to: a) Process Controls for —— b) Drug Product Specification, c) Updated Stability Data, d) Dissolution Method Paddle Speed, and e) Labeling and Package Insert. b(4)

The updated drug product specification is presented in this review. This update reflects the decrease in the dissolution paddle speed from — to 50 rpm. b(4)

The sponsor's Environmental Assessment was reviewed to be acceptable (Finding of No Significant Impact) by Dr. Ruth Ganunis of OPS.

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

The following tablet strengths will be available:

50 mg (pink), 100 mg (dark yellow), 150 mg (salmon), 200 mg (blue), —— —— film-coated tablets b(4)

Partial onset seizures: Initially, 100 mg/day given as twice-daily dosing. The dose may be increased, based on clinical response and tolerability, at weekly intervals by 100 mg/day to a daily dose of 200 mg/day to 400 mg/day. The maximum dose should not exceed — mg/day. b(4)

The above doses are covered by the tablet strengths developed.

C. Basis for Approvability or Not-Approval Recommendation

Approval will be based on a positive outcome of pending, a) FDA Review of Environmental Assessment and b) recommendation from the Office of Compliance.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Prafull Shiromani, Ph.D.
ChemistryTeamLeaderName/Date: Ramesh Sood, Ph.D.
ProjectManagerName/Date: Jacqueline Ware, Pharm.D.

C. CC Block

20 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Prafull Shiromani
5/20/2008 02:17:40 PM
CHEMIST

Ramesh Sood
5/21/2008 04:46:53 PM
CHEMIST

b(4)

NDA 22-253 and ——

Vimpat (Lacosamide) Tablets (50, 100, 150, 200, 250, & 300 mg)

Schwarz Biosciences, Inc.

Prafull Shiromani Ph.D.

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

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-253 & ——— b(4)

2. REVIEW #: 1

3. REVIEW DATE: 11-Apr-2008

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 22-253 / ———	b(4)	28-Sep-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Schwarz Biosciences, In.
Address:	P. O. Box 110167, Research Triangle Park, NC 27709
Representative:	Alan Blumberg, Sr. Director, US Regulatory Affairs
Telephone:	919—767-2555

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Lacosamide

Chemistry Review Data Sheet

c) Code Name/# (ONDC only): SPM 927
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOL. CATEGORY: Epilepsy (16 years and older) - NDA 22-253 and neuropathic pain associated with diabetic peripheral neuropathy – NDA [redacted] b(4)

11. DOSAGE FORM: Tablets – Immediate Release

12. STRENGTH/POTENCY: 50, 100, 150, 200, 250 & 300 mg

13. ROUTE OF ADMINISTRATION: Oral

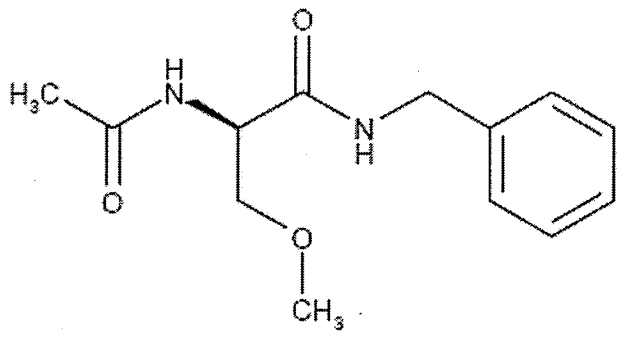
14. Rx/OTC DISPENSED: __X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
SPOTS product – Form Completed
Not a SPOTS product

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

(R)-2-Acetamido-N-benzyl-3-methoxypropionamide (IUPAC)

Structural formula



Molecular formula

$C_{13}H_{18}N_2O_3$

Relative molecular mass

250.30

17. RELATED/SUPPORTING DOCUMENTS:

I. A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	IV	[redacted]		3	Adequate	21-Sep-2003	None
[redacted]	IV	[redacted]		4			

b(4)

[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)

II. B. Other Documents: N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	None
EES	pending		
Pharm/Tox	N/A	N/A	None
Biopharm	N/A	N/A	None
LNC	N/A	N/A	None
Methods Validation	Samples not sent to Lab. since conventional methods	N/A	None
DMETS			
EA	pending		Raanan Bloom
Microbiology	N/A	N/A	None

Labeling			
Bioequivalence			None
Radiopharmaceutical			None

The Chemistry Review for NDA 22-253 b(4)

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA is recommended as "Approvable" from a CMC perspective. The approvability of this application, from a CMC perspective, depends on the applicants response to the FDA IR letter sent to the applicant on 20-Mar-2008.
Additionally, the overall Compliance and EA recommendations have not been received at this time.

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)

There are related NDA submissions under review: as an adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 16 years and older (NDA 022-253, 022-254 for dosage forms: tablet, solution for iv infusion,) and for the management of neuropathic pain associated with diabetic peripheral neuropathy (NDA . The NDA 022-253 (immediate release film-coated tablets) serves as the primary NDA to which other NDAs refer to, as applicable. b(4)

Drug Substance

Lacosamide is a member of a series of functionalized amino acids that were specifically synthesized as anticonvulsive drug candidates. In clinical trials it has been studied in the treatment of partial-onset seizures in patients with epilepsy and the management of neuropathic pain associated with diabetic peripheral neuropathy.

Lacosamide is a new chemical entity. The drug substance is the The chemical name is (R)-2-acetamido-N-benzyl-3-methoxypropionamide. b(4)

The drug substance for the commercial product is synthesized by [redacted] b(4)

Adequate justification of the drug substance specification is provided based on results of batch analyses for more than [redacted] batches.

The drug substance is packaged in [redacted] b(4)

Lacosamide drug substance is very stable. Stability data at long-term, intermediate and accelerated storage conditions did not result in any degradation. The drug substance does not require any special storage conditions. Based on the stability data presented in the NDA a re-test date of [redacted] for the drug substance is justified. b(4)

Drug Product

The solid oral drug product developed for the treatment of epilepsy and neuropathic pain is an immediate release, oval [redacted], film-coated tablet containing 50 mg, 100 mg, 150 mg, 200 mg, 250 mg or 300 mg lacosamide. The tablets are compositionally proportionally [redacted] b(4)

[redacted]). The different strength tablets are differentiated by employing different colored film-coats.

In clinical trials, capsules were used for some phase 1 and early phase 2 trials. Thereafter a tablet formulation with 50 mg or 100 mg lacosamide, with a matching placebo has been used. Due to [redacted], the commercial tablets with dosages up to 300 mg has been developed. Although minor differences are noted in the composition of the proposed commercial tablets and the clinical trial tablet, the excipients included in the former are well characterized and can not further increase the lacosamide bioavailability (i.e. lead to unexpected lacosamide exposure) as the absolute lacosamide bioavailability from the clinical tablet is 100%. The manufacturing process for both the clinical tablets and the commercial product, includes [redacted] b(4)

[redacted] The commercial tablet is manufactured by either SCHWARZ PHARMA Produktions-GmbH, Zwickau, Germany or by SCHWARZ PHARMA Manufacturing Inc., Seymour, Indiana, USA.

The proposed commercial tablets have not been studied *in vivo* and hence, the Sponsor is requesting a biowaiver for the proposed commercial tablets. The sponsor has submitted adequate information to support classification of lacosamide tablets according to the Biopharmaceutics Classification System (BCS) as a BCS class 1 drug, i.e. the drug substance is highly soluble,

highly permeable. Furthermore, the tablets are rapidly dissolving. Accordingly, Dr. A. Selen, Associate Director, Biopharmaceutics, ONDQA, concludes in her review, dated 04-Apr-2008 (resides in the DFS), that the sponsor's dissolution method and their biowaiver requests are acceptable.

The current package insert states that the product will be supplied in bottles with tablet counts of 60, 180, , though the primary stability batches were stored in bottles b(4)

Stability data for the clinical trial formulation and the commercial tablet formulation did not show any degradation of the drug substance in tablets. Based on the 18 months stability data presented for the primary stability batches in the NDA a shelf-life of — months for the drug product is justified, conforming to ICH Q1E. b(4)

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

The following tablet strengths will be available: b(4)

50 mg (pink), 100 mg (dark yellow), 150 mg (salmon), 200 mg (blue), 250 mg , and 300 mg film-coated tablets

b(4)

Partial onset seizures: Initially, 100 mg/day given as twice-daily dosing. The dose may be increased, based on clinical response and tolerability, at weekly intervals by 100 mg/day to a daily dose of 200 mg/day to 400 mg/day. The maximum dose should not exceed mg/day. b(4)

All proposed doses can be achieved using the proposed commercial strengths.

C. Basis for Approvability or Not-Approval Recommendation

Approvability will be based on the sponsor's response to FDA review comments Submitted through an IR-letter dated 20-Mar-2008. These comments are the following:

DRUG SUBSTANCE

1. S.2.2: Description of Manufacturing Process and Process Controls

b(4)

b(4)

2. S.2.3: Control of Materials

b(4)

DRUG PRODUCT (Applicable to NDAs 22-253 and , tablet formulation)

4. P.8.1 Stability Summary and Conclusions

The stability data provided for the primary stability batches (2 batches-18 months at Zwickau, one batch each at 18 & 24 months at Seymour, one batch-18 months for each 50 mg colored tablets) does not support your proposed 36 month expiration. Please provide justification for your proposed 36 months expiration period as per ICH Q1E.

5. **P.8.3 Stability Data** b(4)

Since stability data indicate only a slight enhancement of dissolution at a paddle speed of — n (mean @ 100%) over 50 rpm (mean @ 95%) for all strength tablets, use a paddle speed of 50 rpm for all strength tablets. This recommendation is supported by your statistical analysis of the stability data and is in alignment with the paddle speed employed in your BA/BE studies.

6. **Review of Common Technical Document – Quality (Ctd-Q) Module 1 – A. Labeling and Package Insert**

a. Description Section:

Delete the inactive ingredient hypromellose from Section 11.1 'Tradename Tablets' as it is not included in the tablet formulation.

b. How Supplied Section:

Provide data to show equivalency (e.g. ———————) between the bottle sizes studied in the stability program and those bottle sizes which will be used additionally for commerce, i.e. for the 60, 180, — tablet counts. b(4)

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Prafull Shiromani, Ph.D.
ChemistryTeamLeaderName/Date: Ramesh Sood, Ph.D.
ProjectManagerName/Date: Jacqueline Ware, Pharm.D.

C. CC Block

172 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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

/s/

Prafull Shiromani
4/15/2008 04:16:14 PM
CHEMIST

Ramesh Sood
4/16/2008 07:36:29 AM
CHEMIST

Initial Quality Assessment
Branch I
Pre-Marketing Assessment Division I

OND Division:	Division of Neurology Products
NDA:	22-254
Applicant:	Schwarz Biosciences
Stamp Date:	28-Sep-2007
PDUFA Date:	28-Jul-2008
Trademark:	TBD
Established Name:	Lacosamide
Dosage Form:	Injection
Route of Administration:	Intravenous
Indication:	Epilepsy

PAL: Martha R. Heimann, Ph.D.

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

Summary and Critical Issues:

Summary

Lacosamide (previously known as harkoseride or erlosamide) has been developed by Schwarz for two indications, adjunctive treatment of partial onset seizures and management of diabetic neuropathic pain. [redacted] dosage forms have been developed including immediate release tablets that are the subject of NDAs 22-253 (epilepsy) and [redacted] (neuropathic pain). NDAs 22-254 [redacted] were submitted [redacted] and provide for use of lacosamide injection [redacted], for treatment of epilepsy. b(4)

The applicant proposes marketing of Lacosamide Injection under NDA 22-254 as s 10 mg/mL solution in aqueous saline. Each vial will contain 20 mL (200 mg).

Drug Substance

The active ingredient, lacosamide [(*R*)-2-acetamido-N-benzyl-3-methoxypropionamide], is a well characterized small molecule with molecular formula $C_{13}H_{18}NO_3$ and molecular weight 250.30. The drug substance is sparingly soluble in water ([redacted]). CMC b(4)
information for the bulk drug substance will be reviewed under NDA 22-253. The only change in controls for the parenteral formulation is the addition of Microbial Limits and Bacterial Endotoxins tests to the specification.

Drug Product

Lacosamide Injection is a 10 mg/mL solution of lacosamide in a saline vehicle adjusted to pH 4.0 with hydrochloric acid. The solution is packaged in 20 mL clear glass vials with rubber stoppers. Each vial contains 20 mL (200 mg) of Lacosamide Injection. The quantitative composition is shown below. b(4)

Quantitative composition per mL of solution for infusion

Name of ingredients	Reference to standard	Function	Amount per mL
Lacosamide	In-house	Active ingredient	10.00 mg
Sodium chloride	USP		
Diluted hydrochloric acid	USP-NF	pH-adjustment	
Water for injection	USP		

b(4)

The drug product will be manufactured by The product is b(4)

The proposed regulatory specifications for Lacosamide Injection involve straight-forward analytical procedures. A single, HPLC method is used for assay and determination of related substances. The HPLC procedure is the same as proposed under NDA 22-253 for control of Lacosamide Tablets. As for Lacosamide tablets, the specification does not include a b(4)
The applicant does not include a justification for omitting of these tests.

The NDA stability package includes data for four production scale, primary stability batches of Lacosamide Injection infusion manufactured at a. The first batch placed on stability was a clinical batch with long-term data through 24 months provided in the NDA. The remaining three batches are process validation batches for which 18 month of long-term data are provided. The principal degradation product observed under stability conditions is b(4)
is also a drug substance process impurity, and is controlled in the drug product to NMT

Critical issues for review

Drug Substance

Refer to the Initial Quality Assessment for NDAs 22-253 and No critical issues specific to the parenteral formulation are identified. b(4)

Drug Product

The drug product is an aqueous solution that is
The primary critical issue for this dosage form is assurance of sterility. This issue will be addressed by the Microbiology reviewer. b(4)

Additional issues

Administrative: An environmental assessment for all proposed lacosamide dosage forms is included in Module 1 of NDA 22-253. It is requested that the ONDQA Project Manager arrange for a consult review.

Microbiology: The product is required to be sterile, thus a microbiology review is required. It is requested that the Project Manager arrange for a consult review.

Establishment Evaluation: A full list of manufacturing sites and contract testing facilities is appended to the Form 356h. The sites that have been entered into EES for facility evaluation are listed in Attachment 1

Labeling/Established Name: The active ingredient, lacosamide, is the [redacted] There are no issues related to consistency between the established name and labeled potency. [redacted] b(4)

Comments for 74-Day Letter

With respect to product labeling, we recommend that [redacted] b(4)

Review, Comments and Recommendation:

The NDA is fileable from a CMC perspective. The drug substance is a well-characterized small molecule and the dosage form is relatively simple. No novel manufacturing processes are involved and the submission does not appear to require a review by the Manufacturing Sciences Branch.

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

Date

Ramesh Sood, Ph.D.
Branch Chief

Date

ATTACHMENT 1

Manufacturing Sites for Lacosamide Injection

Facility Information	Function
[redacted]	[redacted]
SCHWARZ PHARMA Limited Shannon Industrial Estate Shannon, Co. Clare Ireland Registration No.: 3002808160 Site Contact: Daniel J. Dooley Tel. No.: +353 61 714234 US Agent: Ruth Hill Phone: 919 767 2634	Drug substance release and stability testing
SCHWARZ PHARMA Produktions GmbH Galileistrasse 6 08056 Zwickau Germany Registration No.: 3002948883 Site Contact: Wilhelm Lehr Tel. No.: +49 375 322 300 US Agent: Ruth Hill Phone: 919 767 2634	Drug substance release testing
SCHWARZ PHARMA Manufacturing 1101 C Avenue West Seymour, IN 47274 Registration No.: 1819171 Site Contact: Chad Kurdziel Tel. No.: 812 523 5396	Drug substance retest Drug product release and stability testing, labeling

b(4)

ATTACHMENT 1

Manufacturing Sites for Lacosamide Injection

Facility Information	Function
	b(4)
	b(4)
SCHWARZ PHARMA Produktions GmbH Alfred-Nobel-Straße 10 40789 Monheim am Rhein Germany Registration No.: 3002943189 Site Contact: Werner Schick Tel. No.: +49 2173 48 1178 US Agent: Ruth Hill Phone: 919 767 2634	Drug product release and stability testing
	b(4)

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/s/

Martha Heimann
10/30/2007 02:53:04 PM
CHEMIST

Ramesh--Corrections are made. Vial total content statement (200 mg/20 mL) in 74-day comment is correct.

Ramesh Sood
10/30/2007 03:04:34 PM
CHEMIST