

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**022255Orig1s000**

**CHEMISTRY REVIEW(S)**

**Vimpat® (lacosamide) Oral Solution**  
**NDA 22-255**  
**Branch Chief 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 17 years and older

**Presentation:** Immediate-release oral solution containing 10 mg/mL of lacosamide and the following excipients: glycerin, carboxymethylcellulose sodium, sorbitol solution, polyethylene glycol, sodium chloride, anhydrous citric acid, acesulfame potassium, methylparaben (b) (4) strawberry flavor, masking flavor, and water. The drug product is packaged in (b) (4) (b) (4) polyethylene terephthalate bottles sealed with white, child-proof, tamper-evident (u) (4) caps.

**EER Status:** Acceptable 15-JUL-2008

**Consults:** Microbiology – Approval 30-MAR-2010  
EA – OPS No significant impact 15-MAY-2008  
Methods Validation – Revalidation by Agency not requested.

**Resubmission:** 16-OCT-2009

**Post-Approval Agreements:** None

**Drug Substance:** The applicant referenced NDA 22-253 for all information concerning the chemistry, manufacturing, and control of lacosamide drug substance. We approved NDA 22-253 on 28-OCT-2008.

**Conclusion:** Drug substance is acceptable.

**Drug Product:** This resubmission is in response to the DMEPA request for the sponsor to reformulate the oral solution so that standard dosing measurements and devices could be used for administration. The original oral solution concentration was (b) (4). Based on DMEPA's request, Schwarz proposed a 10 mg/mL formulation. The 10 mg/mL formulation is similar to the original (b) (4) formulation with slight modifications in excipient amounts. Schwarz removed the (b) (4) based on comments received from the European Union. Schwarz confirms that this reformulation does not require any changes in the drug product manufacturers, manufacturing process, analytical methods, or impurity profile. All analytical methods remain appropriate for use and validated with respect to the new 10 mg/mL formulation. (b) (4)

Each bottle of drug product contains lacosamide (10.0 mg/mL), glycerin USP (b) (4) carboxymethylcellulose sodium USP (b) (4) sorbitol solution USP (b) (4) polyethylene glycol (b) (4) USP (b) (4) sodium chloride USP (b) (4) anhydrous citric acid USP (b) (4) (b) (4), acesulfame potassium NF (b) (4) methylparaben (b) (4) USP (b) (4) strawberry

flavor (b) (4), masking flavor (b) (4), and purified water USP (b) (4)

(b) (4)

Specification of the drug product includes: appearance, contents, odor, color, clarity, identification by RP-HPLC and UV spectrophotometry, methylparaben content by RP-HPLC, pH, purity by RP-HPLC, impurities and related substances by RP-HPLC, assay by RP-HPLC, assay of methylparaben by RP-HPLC, and microbial limits. The 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 18 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 the proposed commercial bottles, sealed with caps.

In accordance with 21 CFR 320.22, the data provided adequately support granting the biowaiver request. Based on these results and the fact that the drug substance in the oral solution formulation is in the dissolved state, a request for waiver of an *in vivo* bioequivalence study for the 10 mg/mL lacosamide oral solution is justified. The conclusions of the ONDQA Biopharmaceutics reviewer (23-FEB-2010) indicate that the data provided support granting the biowaiver request. The CMC microbiology team recommended approval (30-MAR-2010).

**Conclusion:** Drug product is acceptable.

**Additional Items:**

- The applicant agreed to conduct primary stability studies on the first three consecutive drug product batches, in all packaging configurations, to firmly establish the proposed drug product expiry.
- The applicant agreed to place one batch of drug product per year for each of the largest and smallest packaging configuration, stored upright, on stability at 25°C/60% RH (long term conditions) with testing throughout the commercial life of the drug product and submission of the stability results in the annual report.
- All associated Drug Master Files (DMFs) are acceptable or the pertinent information was 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**.

Ramesh Sood, Ph.D.  
Branch Chief  
DPA I/ONDQA

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22255	ORIG-1	SCHWARZ BIOSCIENCES INC	VIMPAT

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/s/

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WENDY I WILSON

04/19/2010

Branch Chief Memo entered on behalf of Ramesh K. Sood, Branch Chief, DPA I, ONDQA

MARTHA R HEIMANN

04/19/2010

for Ramesh Sood



**NDA 22-255**  
**Quality Review #2**

**Vimpat® (lacosamide) Oral Solution**  
**10 mg/mL**

**Schwarz Biosciences, Inc.**

**Wendy I. Wilson-Lee, Ph. D.**  
**Office of New Drug Quality Assessment**  
**For**  
**Office of Neurology Drug Products**

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**Chemistry Review Data Sheet**

- 1. NDA: 22-255
- 2. REVIEW: 02
- 3. REVIEW DATE: 22-MAR-2010
- 4. REVIEWER: Wendy I. Wilson-Lee, Ph.D.
- 5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Memo to File	16-JUL-2008
Quality Review #1	05-JUN-2008

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment	31-MAR-2010
Amendment	16-OCT-2009

7. NAME & ADDRESS OF APPLICANT:

<b>Name:</b>	Schwarz Biosciences, Inc
<b>Address:</b>	8010 Arco Corporate Drive Suite 100 Raleigh, NC 27617
<b>Representative:</b>	Susan Tegtmeyer Senior Manager, Regulatory Affairs UCB, Inc (U S Agent) 1950 Lake Park Drive Building 2100 Smyrna, GA 30080
<b>Telephone:</b>	770-970-8654

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Vimpat®
- b) Non-Proprietary Name (USAN): Lacosamide
- c) Code Name/# (ONDQA only):
- d) Chem. Type/Submission Priority (ONDQA only):
  - Chem. Type: 3
  - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Anti-convulsant

11. DOSAGE FORM: Oral Solution

## Chemistry Review Data Sheet

12. STRENGTH/POTENCY: 10 mg/mL

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  Rx  OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

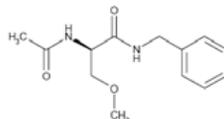
Not a SPOTS product

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

Chemical Name: (R)-2-acetamide-N-benzyl-3-methoxypropionamide

Mol. Formula: C<sub>13</sub>H<sub>18</sub>NO<sub>3</sub>

Mol. Weight: 250.30



17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV	(b) (4)	(b) (4)	1	Adequate	17-MAR-2008	
	III			4	N/A	04-JAN-2010	
	III			4	N/A	04-JAN-2010	
	III			4	N/A	04-JAN-2010	
	III			4	N/A	04-JAN-2010	
	III			4	N/A	04-JAN-2010	
	III			4	N/A	04-JAN-2010	
	III			4	N/A	04-JAN-2010	
	III			4	N/A	04-JAN-2010	
	III			4	N/A	04-JAN-2010	
	III			4	N/A	04-JAN-2010	
	III			4	N/A	04-JAN-2010	
	III			4	N/A	04-JAN-2010	
	III			4	N/A	04-JAN-2010	
	III			4	N/A	04-JAN-2010	
	III			4	N/A	04-JAN-2010	

<sup>1</sup> 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")

## Chemistry Review Data Sheet

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	22-253	Vimpat® (lacosamide) Tablets

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Acceptable.	15-JUL-2008	OC
Pharm/Tox	Acceptable.	10-JUN-2008	J. Fisher
Biopharm	Acceptable.	10-JUN-2008	V. Tandon
LNC	N/A	N/A	N/A
Methods Validation	Validation by FDA labs not needed.	08-JAN-2010	W. Wilson-Lee
DMEPA	Pending.		J. Park
EA	Finding of no significant impact.	15-MAY-2008	R. Bloom
Microbiology	Acceptable.	30-MAR-2010	V. Pawar

**List of Tables**

(b) (4)



**List of Figures**

(b) (4)



## Chemistry Review for NDA 22-255

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

We recommend approval of the 10 mg/mL strength of Vimpat® (lacosamide) Oral Solution, from a CMC perspective, pending final labeling. Include the following three comments in the approval letter:

1. Based on our analysis of the stability data and in accordance with ICH Q1E, we grant the proposed 18 month expiry for Vimpat® 10 mg/mL Oral Solution packaged in (b) (4) (b) (4) PET bottles (b) (4), stored at controlled room temperature [25°C (77°F); excursions 15-30°C (59-86°F)].
2. Based on our analysis of the in-use stability data, we grant an in-use expiry of seven (7) weeks after first opening of the bottle for Vimpat® (lacosamide) Oral Solution.
3. Based on our review, we grant the request for a biowaiver for the in vivo bioequivalence study for Vimpat® (lacosamide) Oral Solution 10 mg/mL.

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

There are no CMC Phase 4 commitments.

**II. Summary of Chemistry Assessments****A. Description of the Drug Product(s) and Drug Substance(s)**

Lacosamide is intended for use as drug for adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy 17 years and older. 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 chiral purity of (b) (4) for the (R)-enantiomer. Lacosamide is soluble in 2-propanol and sparingly soluble in water. The drug substance is not hygroscopic and does not form any hydrates. Lacosamide does not exhibit a pKa in the pH range of 1.5 – 12. The manufacturer identified four crystalline and one amorphous form of lacosamide. Form 1 and Form 2 are the most thermodynamically stable crystal forms. Lacosamide is a BCS Class I drug substance.

Schwarz developed the Vimpat® 10 mg/mL oral solution as an alternative oral formulation for those patients who find swallowing tablets difficult. The proposed doses are 200 mg and 400 mg. There are no strength equivalency issues because the drug substance is a free base. The major solvent in the formulation is purified water. The oral solution contains sweeteners, (b) (4) and flavoring agents to improve the palatability of the bitter drug substance. (b) (4)

The formulation contains a (b) (4) (b) (4) to ensure the drug substance remains in solution over the drug product shelf-life. With the exception of the flavoring agents, the excipients are compendial. (b) (4)

The manufacturing process for Vimpat® 10 mg/mL Oral Solution is conventional (b) (4)

(b) (4). The typical Vimpat® 10 mg/mL oral solution batch sizes (b) (4)

## Executive Summary Section

(b) (4). The drug product specification ensures the identity of the drug substance (b) (4) (b) (4) as well as ensures the chemical purity, microbiological purity, drug substance potency, (b) (4), and quality of the drug product.

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

Vimpat® Oral Solution is intended for use as an adjunctive therapy in the treatment of partial-onset seizures in patients 17 years or older, with epilepsy. The oral solution may be taken with or without food. 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 maximum dose is 400 mg/day. If necessary, the practitioner may switch the patient to intravenous administration of a dose equivalent to the oral dose. The Vimpat® Oral Solution will be supplied commercially with fill volumes of (b) (4) 465 mL in (b) (4) polyethylene terephthalate (PET) bottles with a child-resistant induction sealed closure (b) (4)

round amber glass bottles with a child-resistant closure. The recommended Vimpat® Oral Solution expiry is 18 months when stored at 25°C/60% RH in the commercial container closures. Based on in-use stability results, the recommended in-use expiry is seven (7) weeks after first opening the bottle.

**C. Basis for Approvability or Not-Approval Recommendation**

From a CMC perspective, we recommend approval of Vimpat® Oral Solution, pending final labeling. Based on our analysis of the stability data and in accordance with ICH Q1E, we grant the proposed 18 month expiry for Vimpat® 10 mg/mL Oral Solution packaged in (b) (4) (b) (4) PET bottles (b) (4), stored at controlled room temperature [25°C (77°F); excursions 15-30°C (59-86°F)]. We concur with the proposed in-use expiry of seven (7) weeks after first opening of the bottle. Based on our review, we grant the request for a biowaiver for the in vivo bioequivalence study. The manufacturing process and the associated process controls are adequate. The CMC microbiology review recommends approval as well. The drug product specification ensures the identity of the drug substance (b) (4) as well as ensures the chemical purity, microbiological purity, drug substance potency, (b) (4) and quality of the drug product. The stability data supports the proposed expiry. The carton and container labels along with the prescribing information contain all of the required information, from a CMC perspective. The recommendation from the Office of Compliance was acceptable for all facilities.

**III. Administrative****A. Reviewer's Signature**

*Wendy I. Wilson-Lee, Ph.D.*

**B. Endorsement Block**

WWilson-Lee: 31-MAR-2010  
MHeimann: 31-MAR-2010  
RSood: 31-MAR-2010

**C. CC Block**

DHenry  
SDaugherty

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22255	ORIG-1	SCHWARZ BIOSCIENCES INC	VIMPAT

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/s/

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WENDY I WILSON  
04/05/2010

MARTHA R HEIMANN  
04/05/2010  
Signed for Ramesh Sood

# **NDA 22-255**

**Lacosamide Oral Solution**

**Schwarz Biosciences, Inc.**

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

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**Chemistry Review Data Sheet**

- 1. NDA: 22-255
- 2. REVIEW #: 01
- 3. REVIEW DATE: 21-MAY-2008
- 4. REVIEWER: Wendy I. Wilson, Ph. D.
- 5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
None.	N/A

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
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: Solution

12. STRENGTH/POTENCY: (b) (4)

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:   X   Rx      OTC

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

\_\_\_\_\_ SPOTS product – Form Completed

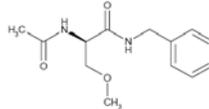
X  Not a SPOTS product

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

Chemical Name: (R)-2-acetamido-N-benzyl-3-methoxypropionamide

Mol. Formula: C<sub>13</sub>H<sub>18</sub>NO<sub>3</sub>

Mol. Weight: 250.30



17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

DMF	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	REVIEW COMPLETED	COMMENT
(b) (4)	IV	(b) (4)	(b) (4)	1	Adequate	17-MAR-2008	
	III	(b) (4)	(b) (4)	4			
	III	(b) (4)	(b) (4)	4			
	III	(b) (4)	(b) (4)	4			
	III	(b) (4)	(b) (4)	7	Adequate.	06-FEB-2008	(b) (4)
	III	(b) (4)	(b) (4)	4			

<sup>1</sup> 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")

<sup>2</sup> 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	(b) (4)	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

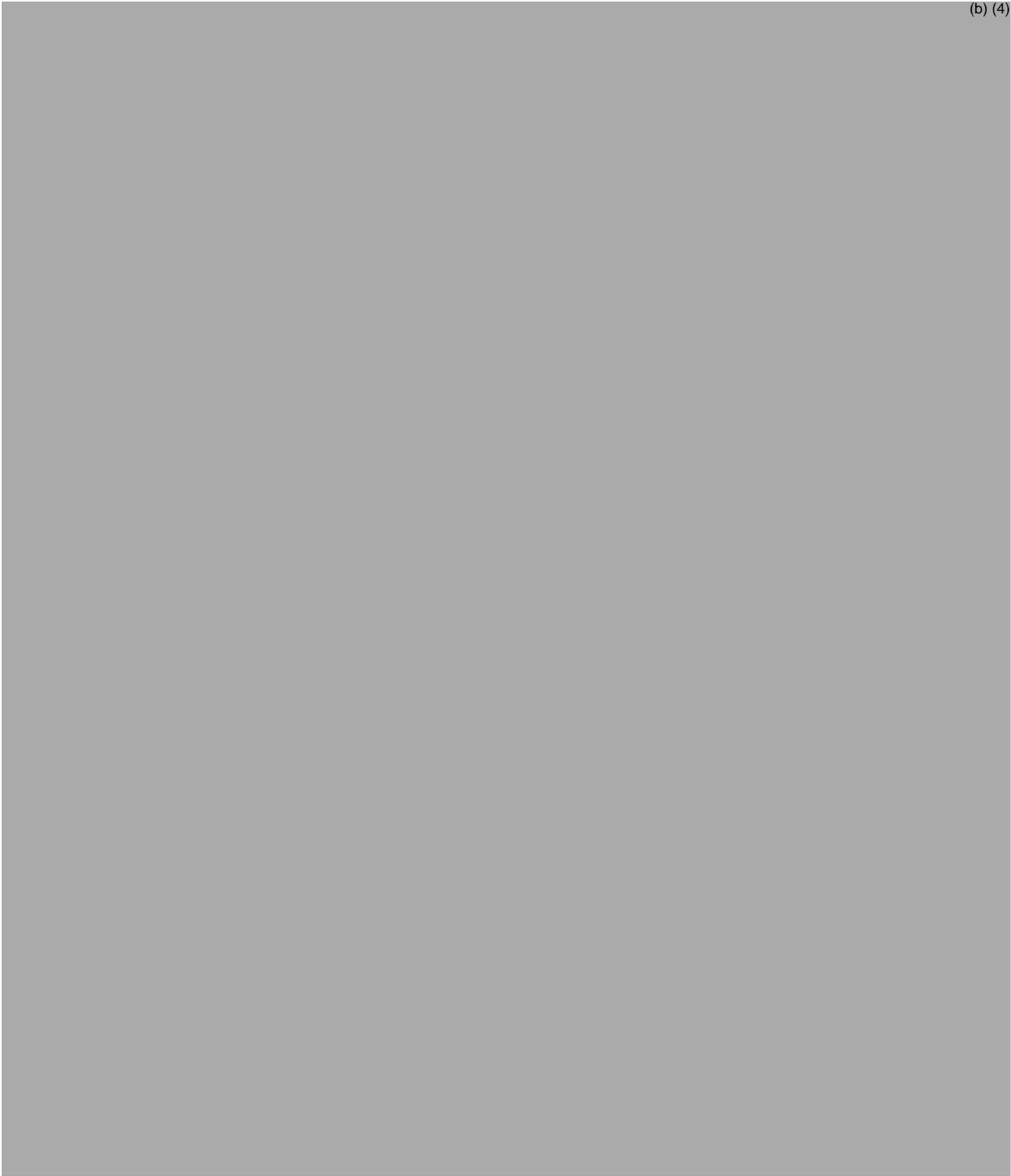
(b) (4)

18. STATUS:

CONSULTS	RECOMMENDATION	DATE	REVIEWER
<b>Biometrics</b>	N/A	N/A	N/A
<b>EES</b>	Pending		S. Adams
<b>Pharm/Tox</b>	Pending		J Edward Fisher
<b>Biopharm</b>	Pending		V. Tandon
<b>LNC</b>	N/A	N/A	N/A
<b>Methods Validation</b>	No validation by FDA needed.	17-APR-2008	W. Wilson
<b>DMETS</b>	Use of Vipmat as tradename is acceptable Recommend alternate dosing device and reformulation to allow for standard unit of measure	13-MAY-2008	J. Park
<b>EA</b>	Finding of no significant impact	15-MAY-2008	R. Bloom
<b>Microbiology</b>	Pending		V. Pawar

**List of Tables**

(b) (4)



(b) (4)



**List of Figures**

(b) (4)

## Chemistry Review for NDA 22-255

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

From a CMC perspective, lacosamide oral solution (b) (4) is approvable (AE) pending labeling, completion of manufacturing site inspections, and completion of the microbiology 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 Phase IV recommendations.

**II. Summary of Chemistry Assessments****A. Description of the Drug Product(s) and Drug Substance(s)**

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 chiral purity (b) (4) for the (R)-enantiomer. Lacosamide is soluble in isopropanol and sparingly soluble in water. The drug substance is not hygroscopic and does not form any hydrates. Lacosamide does not exhibit a pK<sub>a</sub> in the pH range of 1.5 – 12. The drug substance manufacturer identified four crystalline and one amorphous form of lacosamide. Form 1 and Form 2 are the most thermodynamically stable crystal forms. Lacosamide is a BCS Class I drug substance.

Schwarz developed the lacosamide (b) (4) oral solution as an alternative oral formulation for those patients who find swallowing tablets difficult. The proposed doses are 200 mg, 400 mg, (b) (4). The clinical division recommends a maximum daily dose of 400 mg. Therefore, for our review, the maximum daily dose is 400 mg.

The typical drug product use period is four weeks. There are no strength equivalency issues because the drug substance is a free base. The major solvent in the formulation is purified water. The formulation does not contain co-solvents. The oral solution contains sweeteners, (b) (4) and flavoring agents to improve the palatability of the bitter drug substance. The sorbitol sweetener in the formulation is (b) (4) of sorbitol. The formulation also (b) (4) of the drug substance through the oral solution to the taste buds. The oral solution also contains (b) (4). The formulation contains a (b) (4).

With the exception of the flavoring agents, the excipients are compendial. All of the excipients are commonly used in this type of drug product.

The manufacturing process for lacosamide (b) (4) oral solution is conventional (b) (4) (b) (4)

The typical lacosamide (b) (4) oral solution batch sizes (b) (4) (b) (4). The proposed drug product specification ensures the identity of the drug substance (b) (4) (b) (4) as well as ensures the chemical purity, microbiological purity, drug substance potency, (b) (4)

(b) (4) and quality of the drug product. The specification establishes release and shelf-life criteria for color, related substances, lacosamide assay (b) (4).

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

The sponsor applied for (b) (4) lacosamide, (b) (4) use in the treatment of partial-onset seizures in patients, (b) (4) years or older, with epilepsy. The sponsor indicates the oral solution drug product as adjunctive therapy in the treatment of partial-onset seizures. The proposed drug product tradename is Vipmat. The oral solution may be taken with or without food. 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 maximum dose recommended by FDA is 400 mg/day. If necessary, the practitioner may switch the patient to intravenous administration of a dose equivalent to the oral dose. Based on DMET comments communicated to the sponsor, Schwarz committed to evaluate an alternative oral solution concentration that would permit the use of a standard, commercially available dosing device.

The proposed commercial container closures for lacosamide (b) (4) oral solution are (b) (4) (b) (4) PET bottles filled with (b) (4) 465 mL of oral solution sealed with a white, child-proof, tamper-evident, (b) (4) cap. The bottles, inside a cardboard carton, represent the finished product packaging systems. The recommended Vipmat expiry is (b) (4) when stored at 25°C/60% RH in the commercial container closures. Based on in-use stability results, the recommended in-use expiry is (b) (4) weeks after first opening the bottle.

## C. Basis for Approvability or Not-Approval Recommendation

From a CMC perspective, lacosamide oral solution (b) (4) is approvable (AE) pending labeling, completion of manufacturing site inspections, and completion of the microbiology 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 Produktions 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, pending a satisfactory recommendation from the microbiology CMC review.

## III. Administrative

### A. Reviewer's Signature

*Wendy I. Wilson*

### B. Endorsement Block

WWilson: 20-MAY-2008  
MHeimann: 20-MAY-2008  
RSood: 28-MAY-2008

### C. CC Block

SGoldie:  
JWare:  
NDA22-255:

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Following this Page as B4 (CCI/TS)

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

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Wendy I. Wilson  
6/4/2008 04:03:56 PM  
CHEMIST

Ramesh Sood  
6/5/2008 12:28:11 PM  
CHEMIST