

Ware, Jacqueline H

From: Ware, Jacqueline H
Sent: Monday, May 19, 2008 5:10 PM
'Blumberg Alan'; 'Dottavio Misty'
Subject: Sullivan, Matthew; Ware, Jacqueline H
Question about LCM

Dear Alan,
Can you please assist with the following question? If Schwarz has already submitted this information, please just let me know where/when it was submitted.

- Has Schwarz submitted additional information on the nephropathy of subject #588/8061?

We believe this information was requested 2-3 weeks ago. However, I searched Misty's list of requests/responses to see if I could find it and was not successful.

Thanks,
Jackie

Jacqueline H. Ware, Pharm.D., RAC
Commander, United States Public Health Service
Regulatory Project Manager Team Leader

Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4348
Silver Spring, MD 20993-0002

Phone: 301-796-1160
Fax: 301-796-9842
email: jacqueline.ware@fda.hhs.gov

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Ware, Jacqueline H

From: Ware, Jacqueline H
Sent: Monday, May 19, 2008 2:10 PM
'Blumberg Alan'; 'DOttavio Misty'
Cc: Sullivan, Matthew; Ware, Jacqueline H
Subject: RE: Clarification request RE: FDA Request for Information - NDA 22-253, 22-254, _____ May 12, 2008

b(4)

Dear Alan,
The clinical team has considered your proposals and had determined that they would like Option 2.

On a separate note, I believe that I sent a request about the exposure to placebo in the epilepsy population, (including those pts exposed to placebo while randomized to LCM) a couple of weeks ago. Do you recall such a request and, if so, have you sent a response?

Thanks,
Jackie

Jacqueline H. Ware, Pharm.D., RAC
Commander, United States Public Health Service
Regulatory Project Manager Team Leader

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Center for Drug Evaluation and Research, FDA
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From: Blumberg Alan [mailto:Alan.Blumberg@ucb-group.com]
Sent: Friday, May 16, 2008 5:34 PM
To: Ware, Jacqueline H; Sullivan, Matthew
Cc: DOttavio Misty; Moe Kirsten
Subject: Clarification request RE: FDA Request for Information - NDA 22-253, 22-254, _____ May 12, 2008

This message contains an encrypted email which can be read by opening the attachment

SCHWARZ BIOSCIENCES, Inc.
A Member of the UCB Group
Mail P.O. Box 110167 - Research Triangle Park - NC 27709 - USA
Via Courier 8010 Arco Corporate Drive - Suite 100 - Raleigh - NC 27617 - USA
Phone +1 919 767 2555 - Fax +1 919 767 2570 - E-mail info@schwarzpharma.com

5/27/2008

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5/27/2008

Ware, Jacqueline H

From: Ware, Jacqueline H
Sent: Monday, May 19, 2008 1:38 PM
'Blumberg Alan'; 'Dottavio Misty'
Cc: Sullivan, Matthew; Ware, Jacqueline H
Subject: FW: Partial Response to FDA Request for Information - NDA 22-253, 22-254 _____ May 12, 2008

b(4)

Dear Alan,
Thanks for clarifying. This response is clear.
Jackie

Jacqueline H. Ware, Pharm.D., RAC
Commander, United States Public Health Service
Regulatory Project Manager Team Leader

Division of Neurology Products
Center for Drug Evaluation and Research, FDA
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From: Blumberg Alan [mailto:Alan.Blumberg@ucb-group.com]
Sent: Monday, May 19, 2008 1:19 PM
To: Ware, Jacqueline H; Dottavio Misty
Cc: Sullivan, Matthew; Moe Kirsten
Subject: RE: Partial Response to FDA Request for Information - NDA 22-253, 22-254, _____ May 12, 2008
Importance: High

b(4)

Dear Jackie,
Please see if the attached clarifies the situation for the Clinical Reviewer. If not, perhaps we should set up a short telecom?
Best regards,
Alan

From: Ware, Jacqueline H [mailto:jacqueline.ware@fda.hhs.gov]
Sent: Friday, May 16, 2008 4:12 PM
To: Blumberg Alan; Dottavio Misty
Cc: Sullivan, Matthew
Subject: FW: Partial Response to FDA Request for Information - NDA 22-253, 22-254. _____ May 12, 2008

b(4)

Dear Alan,
The clinical reviewer has asked for clarification regarding your recent partial response to our May 12, 2008 requests. Please see below.

The original request refers to concomitant medications and diseases at baseline before entering the studies. The sponsor's table EP 5.1.1 is entitled: "medications taken during the baseline phase in population pool S1". It is unclear whether this

table refers to medications at entry or to medications taken during the placebo-controlled period ("baseline phase") which (would include baseline plus new medications taken during the placebo-controlled period). Similarly, EP 5.1.2 refers to concomitant diseases.

Please clarify that these tables refer to the baseline use of medications and diseases.

Thanks,
Jackie

Jacqueline H. Ware, Pharm.D., RAC
Commander, United States Public Health Service
Regulatory Project Manager Team Leader

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Center for Drug Evaluation and Research, FDA
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From: Blumberg Alan [mailto:Alan.Blumberg@ucb-group.com]

Sent: Friday, May 16, 2008 2:15 PM

To: Ware, Jacqueline H; Sullivan, Matthew

Cc: DOTTAVIO Misty; Moe Kirsten

Subject: Partial Response to FDA Request for Information - NDA 22-253, 22-254, _____

May 12, 2008

b(4)

Dear Jackie,

Please find attached a partial response to the request made on May 12 in a WORD document. Responses to questions 2, 3 and 4 with tables to support the responses 2 and 3 are included.

Best regards,
Alan

APPEARS THIS WAY
ON ORIGINAL

Ware, Jacqueline H

From: Ware, Jacqueline H
Sent: Friday, May 16, 2008 5:04 PM
'Blumberg Alan'; 'DOttavio Misty'
Sullivan, Matthew; Ware, Jacqueline H
subject: FDA Request for Information - NDA 22-253, 22-254

b(4)

Dear Alan,

Attached are several additional requests from DNP's clinical team for lacosamide. Like other requests, you may respond via email and follow up with an official submission.

- Please comment on the apparent dose response in the treatment emergent use of analgesics (including opiates), anesthetics, psycholeptics, systemic corticosteroids, muscle relaxants, cough and cold preparations, beta blocking agents, calcium channel blockers and agents acting on the renin-angioetensin system in EP S2 (as per Table EP 4.1.4).
- Please comment on whether PR prolongation or adverse cardiac events occurred with concomitant use of beta-blockers or calcium channel blockers with LCM.

We request that you submit this information by May 20, 2008, if possible.

Thanks,
Jackie

**APPEARS THIS WAY
ON ORIGINAL**

Ware, Jacqueline H

From: Blumberg Alan [Alan.Blumberg@ucb-group.com]

Sent: Friday, May 16, 2008 4:57 PM

Ware, Jacqueline H

Subject: RE: Partial Response to FDA Request for Information - NDA 22-253, 22-254, _____

ay 12, 2008

b(4)

I have sent this clarification back to the team for a response. Have a nice weekend, Jackie. I will be sending you a question for clarification in a few minutes, as it is only fair. ☺

-----Original Message-----

From: Ware, Jacqueline H [mailto:jacqueline.ware@fda.hhs.gov]

Sent: Friday, May 16, 2008 4:12 PM

To: Blumberg Alan; Dottavio Misty

Cc: Sullivan, Matthew

Subject: FW: Partial Response to FDA Request for Information - NDA 22-253, 22-254, _____
2008

ay 12,

b(4)

Dear Alan,

The clinical reviewer has asked for clarification regarding your recent partial response to our May 12, 2008 requests. Please see below.

- The original request refers to concomitant medications and diseases at baseline before entering the studies. The sponsor's table EP 5.1.1 is entitled: "medications taken during the baseline phase in population pool S1". It is unclear whether this table refers to medications at entry or to medications taken during the placebo-controlled period ("baseline phase") which (would include baseline plus new medications taken during the placebo-controlled period). Similarly, EP 5.1.2 refers to concomitant diseases. Please clarify that these tables refer to the baseline use of medications and diseases.

Thanks,
Jackie

Jacqueline H. Ware, Pharm.D., RAC
Commander, United States Public Health Service
Regulatory Project Manager Team Leader

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From: Blumberg Alan [mailto:Alan.Blumberg@ucb-group.com]

Sent: Friday, May 16, 2008 2:15 PM

To: Ware, Jacqueline H; Sullivan, Matthew

Cc: Dottavio Misty; Moe Kirsten

Subject: Partial Response to FDA Request for Information - NDA 22-253, 22-254, _____

ay 12, 2008

b(4)

Dear Jackie,

Please find attached a partial response to the request made on May 12 in a WORD document. Responses to questions 2, 3 and 4 with tables to support the responses 2 and 3 are included.

Best regards,
Alan

SCHWARZ BIOSCIENCES, Inc.

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5/27/2008

Ware, Jacqueline H

From: Gunther, Sheryl
Sent: Thursday, May 15, 2008 7:21 PM
Hershkowitz, Norman; Ware, Jacqueline H
Subject: Vimpat (lacosamide)

Hi Norman and Jackie:

We have received all of the domestic and foreign clinical inspection results, albeit in some cases we only have a summary of findings and are waiting to receive the full reports with exhibits. The sponsor inspection is starting on Monday. My supervisor would like to wait for the findings from the sponsor inspection before signing off on the Clinical Inspection Summary for this application. We should have the sponsor inspection results by late May, or at the very latest, the first week in June.

Is this all right?

Thanks,
Sheryl Gunther

Sheryl D. Gunther, R.Ph., Pharm.D.
LCDR, U.S. Public Health Service
Senior Regulatory Review Officer
Good Clinical Practice Branch 1
Division of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 51, Rm. 5330
Silver Spring, MD 20993
C Phone: 301-796-3386
E. sheryl.gunther@fda.hhs.gov

5/27/2008

Ware, Jacqueline H

From: Ware, Jacqueline H
Sent: Monday, May 12, 2008 10:59 AM
'Blumberg Alan'; 'Dottavio Misty'
Cc: Sullivan, Matthew; Ware, Jacqueline H
Subject: Additional Lacosamide Injection and Solution CMC IR Comments
Importance: High
Attachments: lacosamideCMCIR#3.doc

Dear Alan,

In the attached WORD document, please find several additional requests from the chemistry review team for lacosamide. Like other requests, you may respond via email and follow up with an official submission.

We request that you submit this information by May 16, 2008, if possible.

Thanks, Jackie

Jacqueline H. Ware, Pharm.D., RAC
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Regulatory Project Manager Team Leader

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NDA 22-254

b(4)

CMC IR #3

Comments for NDA 22-254 (solution for infusion)

1. The diluent compatibility data indicates an incompatibility between the drug product and the dextrose diluent. The impurity contents associated with RT ~~_____~~ and RT ~~_____~~ exceed the ICH qualification limit based on your proposed maximum daily dose. Provide justification for the use of the drug product with the dextrose diluent. Include in your justification the identity of the impurities identified by RT ~~_____~~ and RT ~~_____~~ as well as data demonstrating their safety for use in humans.

b(4)

~~_____~~
~~_____~~
~~_____~~
~~_____~~
~~_____~~
~~_____~~
~~_____~~
~~_____~~

b(4)

b(4)

Ware, Jacqueline H

From: Ware, Jacqueline H
Sent: Monday, May 12, 2008 10:38 AM
'Blumberg Alan'; 'DOttavio Misty'
Sullivan, Matthew
Subject: FDA Request for Information - NDA 22-253, 22-254,
Attachments: LCM.May 12.doc

b(4)

Dear Alan,
In the attached WORD document, please find several additional requests from DNP's clinical team for lacosamide. Like other requests, you may respond via email and follow up with an official submission.

We request that you submit this information by May 16, 2008, if possible.

Thanks,
Jackie

Jacqueline H. Ware, Pharm.D., RAC
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Regulatory Project Manager Team Leader

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LCM May 12.doc
(32 KB)

May 12, 2008. Request for information for LCM.

- 1) Please provide the total number of subjects screened and the total number of subjects who did not fulfill eligibility criteria for the placebo-controlled epilepsy studies. Provide the reasons for which these patients failed eligibility criteria. The following format is provided as an example.

	n	%
Screened		
Entered studies		
Did not fulfill eligibility criteria		
Concomitant disease		
Uncontrolled hypertension		
Elevated LFT		
Elevated creatinine		
Etc.		
Protocol exclusionary medication		
Antipsychotics		
Benzodiazepines		
Etc.		
Etc.		

- 2) Provide a summary table of all baseline concomitant medications in the EP S1, by treatment group (similar to Table 4.1.1, but including all medications, not only medications taken by 10% of patients).
- 3) Provide a summary table of all baseline concomitant diseases in the EP S1 pool, by treatment group (similar to Table 5.1.1, but including all diseases, not only those presented by 5% of patients).
- 4) The intravenous (IV) phase 2/3 epilepsy studies recruited patients from the open label oral tablet studies. Please clarify what were the criteria for selection of patients for the phase 2/3 IV LCM studies.
- 5) Provide a summary table of all baseline concomitant diseases and concomitant medications taken by patients in the IV phase 2/3 LCM studies.

Ware, Jacqueline H

From: Ware, Jacqueline H
Sent: Wednesday, May 07, 2008 7:38 PM
'Blumberg Alan'; 'DOttavio Misty'
Ware, Jacqueline H; Sullivan, Matthew
subject: FDA Request for Information - NDA 22-253, 22-254,

b(4)

Dear Alan,

Attached are several additional requests from DNP's clinical team for lacosamide. Like other requests, you may respond via email and follow up with an official submission.

- The following patients discontinued from the open label epilepsy studies due to either cardiac disorders or ECG investigations.

667010502
667016937
755122402
755108404

Please provide the narratives and CRFs for these patients. If this information has been submitted, direct the reviewer to the exact location in the application.

- Please also submit the ECGs for Subject 755122303.
- Please clarify why subject # 754/12512, who attempted suicide during the placebo controlled phase of study 754 while taking LCM 200 mg/day, was not included in your analysis of suicidality.

We request that you submit this information by May 19, 2008, if possible.

Thanks,
Jackie

Jacqueline H. Ware, Pharm.D., RAC
Commander, United States Public Health Service
Regulatory Project Manager Team Leader

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Ware, Jacqueline H

From: Sullivan, Matthew
Sent: Tuesday, April 29, 2008 11:02 AM
Dottavio Misty; Blumberg Alan
Ware, Jacqueline H
subject: Lacosamide IR 4/29/08

Alan and Misty –

Jackie is out of town this week, so I'm filling in for her. Please find below a request from the DNP team:

Please provide narratives of patients with the adverse event (MedDRA Preferred Term) "dyskinesia" in all Lacosamide studies. For the patients with epilepsy, include a description of the type and frequency of seizures the patient had at baseline and at the end of the studies. Please send the information no later than Monday, May 5.

Please note that the reviewer made a specific turnaround timeframe request. Please let me know if you aren't able to meet this request. (I believe that the request applies to our advance electronic version, rather than the official lifecycle submission.)

Thanks
Matt

①

 1 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Ware, Jacqueline H

From: Ware, Jacqueline H
Sent: Friday, April 25, 2008 6:28 PM
'Blumberg Alan'; 'DOttavio Misty'
Ware, Jacqueline H; Sullivan, Matthew
subject: FDA Request for Information - NDA 22-253, 22-254, _____

b(4)

Dear Alan,

Below are several requests from DNP's CMC review team related to their ongoing review of the lacosamide applications. Please submit your responses to these requests in electronic archival format as an amendment to the above NDAs. It is acceptable for you to email your responses to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

b(4)

Comment for All Formulations (NDA 22-253, 22-254 _____)

1. Provide updated specifications, for both the oral use and parenteral use drug substances, that reflect the revised limit for impurity _____ NMT _____. Update the relevant sections of the CTD submissions.

b(4)

Comments for Solution for Infusion _____ (NDA 22-254 _____)

b(4)

1. Provide justification for omitting _____ in _____ the solution for infusion _____ drug product specifications.
2. Provide all available updated stability data for both the solution for infusion _____ including results from inverted solution for infusion samples from the last time point tested _____
3. Revise the primary and secondary container labels _____

b(4)

b(4)

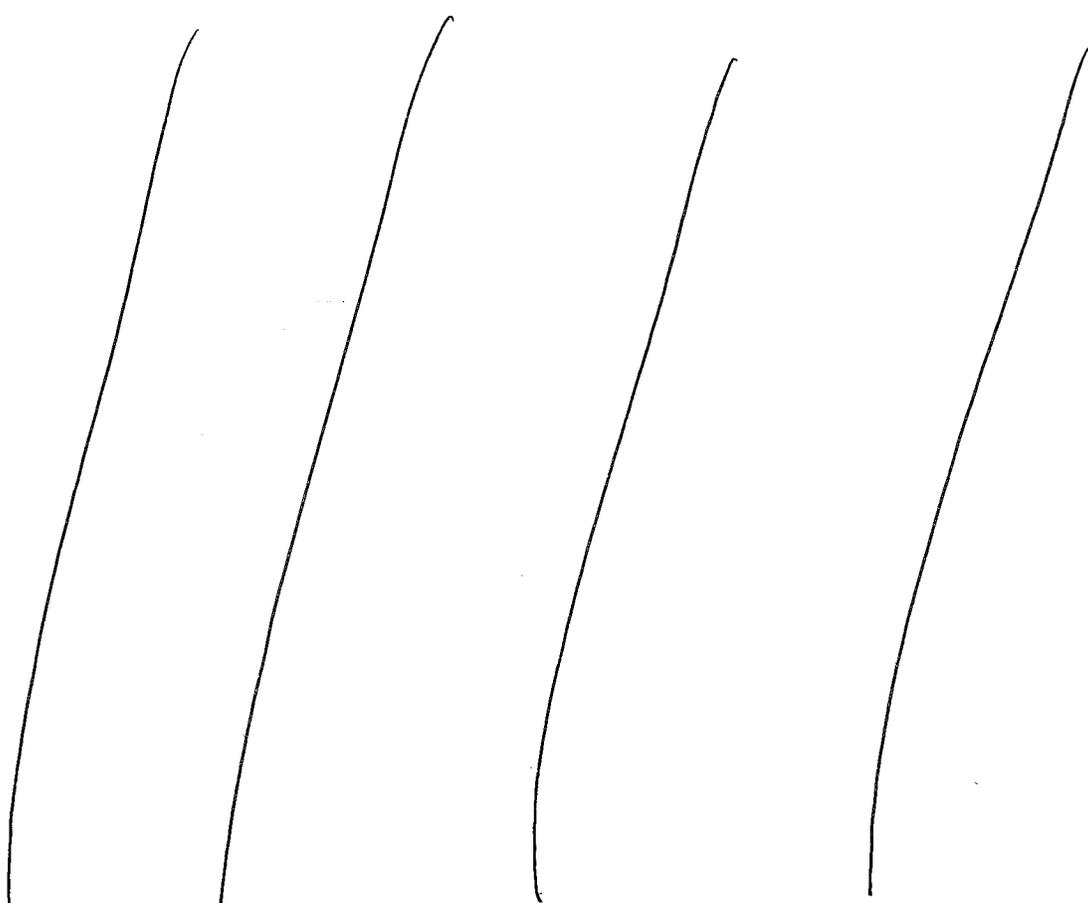
b(4)

Comment for Solution for Infusion Formulation (NDA 22-254)

1. Explain why the BPR does not document that the water for injection used in each batch meets the standards established for the drug product. Also explain why the in-process control _____ is not clearly recognized in the BPR.

b(4)

b(4)



b(4)

b(4)

b(4)

CMC & Nonclinical Review Comment (NDA 22-254)

b(4)

1. Provide the full report of the rabbit pharmacokinetics study (Study no. 1106) referred to in your recent submission (4/4/08), and demonstrate that the impurity _____ could have been present _____ in rabbits treated with lacosamide during the embryofetal development study at levels greater than or equal to those anticipated in humans receiving lacosamide formulations containing the impurity at the proposed specification limit.

b(4)

Thank you,
Jackie Ware

Jacqueline H. Ware, Pharm.D., RAC
Commander, United States Public Health Service
Regulatory Project Manager Team Leader

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**APPEARS THIS WAY
ON ORIGINAL**

Ware, Jacqueline H

From: Ware, Jacqueline H
Sent: Friday, April 18, 2008 7:25 PM
: 'Blumberg Alan'; 'DOttavio Misty'
: Ware, Jacqueline H
Subject: FW: Word version of Table

Alan,
Below is the reviewer's response to your clarification request.

"I would like to see the number of patients who were randomized to placebo plus those who were randomized to LCM but received placebo (only) during the initial weeks of the titration phase (before starting LCM)."

Hope this helps,
Jackie

Jacqueline H. Ware, Pharm.D., RAC
Commander, United States Public Health Service
Regulatory Project Manager Team Leader

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From: Blumberg Alan [mailto:Alan.Blumberg@ucb-group.com]
Sent: Thursday, April 17, 2008 6:29 PM
To: Ware, Jacqueline H
Cc: DOttavio Misty
Subject: RE: Word version of Table

Dear Jackie,

I am sorry but my statistician and the team need a clarification of the latest request. Kindly ask your Team to guide us on the following question.

"Regarding the request for the number of patients actually exposed to placebo, does the DIVISION want the count (and associated subject years of exposure) for subjects who were ever treated with placebo regardless of whether or not they also received LCM (ie, for EP pool oral formulation, this would include subjects who were randomized and received LCM, but also received placebo during the Titration Phase)? This would result in some subjects being counted in both the LCM and Placebo columns of the table requested (and thus would not represent unique exposures). Alternatively, is the DIVISION requesting the count of subjects randomized to receive placebo who actually received placebo? "

Thanks for your assistance.

Best regards,

Alan

-----Original Message-----

From: Ware, Jacqueline H [mailto:jacqueline.ware@fda.hhs.gov]
Sent: Wednesday, April 16, 2008 9:56 PM
To: Blumberg Alan
Subject: Word version of Table

Dear Alan,
Here you go...

Jackie

Jacqueline H. Ware, Pharm.D., RAC
Commander, United States Public Health Service
Regulatory Project Manager Team Leader

Division of Neurology Products
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<<Request 4 11 08.doc>>

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<mailto:info@schwarzpharma.com>

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**APPEARS THIS WAY
ON ORIGINAL**

Ware, Jacqueline H

From: Ware, Jacqueline H
Sent: Friday, April 18, 2008 7:18 PM
:
: 'Blumberg Alan'; 'Dottavio Misty'
: Ware, Jacqueline H; Sullivan, Matthew
Subject: FDA Request for Information - Lacosamide NDAs

Dear Alan,

Attached is an additional request from DNP's clinical team for lacosamide. Like other requests, you may respond via email and follow up with an official submission..

Patients #170106 and # 170111 discontinued from study SP757 (IV lacosamide) because of adverse events of "bradycardia" and "ECG QTc interval prolonged", respectively. Please provide copies of all 12-lead ECG and ECG reports (not just the ECG interpretations currently included in the CRFs) for these patients, from studies SP755, SP774 and SP757.

Thanks,
Jackie

Jacqueline H. Ware, Pharm.D., RAC
Commander, United States Public Health Service
Regulatory Project Manager Team Leader

Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4348
Silver Spring, MD 20993-0002

Phone: 301-796-1160
: 301-796-9842
Email: jacqueline.ware@fda.hhs.gov

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Ware, Jacqueline H

From: Taylor, Kellie
Sent: Friday, April 18, 2008 6:48 PM
Subject: Ware, Jacqueline H; Brounstein, Daniel; Park, Judy
RE: Updated lacosamide carton & container labels

Sounds good.
We'll shoot for the 27th
KT

-----Original Message-----

From: Ware, Jacqueline H
Sent: Friday, April 18, 2008 6:47 PM
To: Brounstein, Daniel; Taylor, Kellie; Park, Judy
Cc: Ware, Jacqueline H
Subject: RE: Updated lacosamide carton & container labels

Hi Folks,
How does a completion date of May 27th sound? That's 1 day before the 8 month mark, which (according to GRMP) is when primary reviews are supposed to be finished.

I'll send the new consult next week.

Thanks,
Jackie

-----Original Message-----

From: Brounstein, Daniel
Sent: Thursday, April 17, 2008 8:17 AM
To: Taylor, Kellie; Ware, Jacqueline H; Park, Judy
Subject: RE: Updated lacosamide carton & container labels

Hi all,

I'll create these into a new consult before I receive the request (since this is a GRMP process), and update the rest of the Record later (with the requested completion date - please note that DMEDP asks for at least 30 days for labeling reviews). That way, we'll be able to officially begin work on them sooner. So that gives you a little leeway, Jackie (but please don't forget to get the request form in so we can officially document our work!)

I just wanted to clarify that this is a new consult because these labels are very different from the previous product labels. If the sponsor had sent labels that were merely updated or incorporated minor changes and DMEDP's recommendations, then this could all fall under the same consult. Correct?

Dan

-----Original Message-----

From: Taylor, Kellie
Sent: Wednesday, April 16, 2008 5:50 PM
To: Ware, Jacqueline H; Brounstein, Daniel; Park, Judy
Subject: RE: Updated lacosamide carton & container labels

New consult please. These are radically different than the others. Let Dan know what sort of timeframe is appropriate.
Thanks for sending them on,
Kellie

-----Original Message-----

From: Ware, Jacqueline H
Sent: Wednesday, April 16, 2008 3:57 PM

To: Brounstein, Daniel; Taylor, Kellie; Park, Judy
Subject: Updated lacosamide carton & container labels

Dan, Kellie, and Judy,
Attached below is the electronic link to Schwarz's submission that contains updated carton & container labels for all lacosamide products. Although it arrived last week, we just received the EDR notice today. Sorry for the delay!

Please let me know if you need a new consult in order to review these or if they can be incorporated into your current review for the existing consult.

Thanks,
Jackie

-----Original Message-----

From: EDRAdmin@cdcr.fda.gov [mailto:EDRAdmin@cdcr.fda.gov]
Sent: Wednesday, April 16, 2008 8:50 AM
To: Ware, Jacqueline H; CDER-EDRADMIN; Thomas, Elmer *; Saunders, James; Prather, Mia; Nighswander, Robbin M; Chandra, Savithri*
Cc: Almoza, Damus *; Blumstein, Eyal*; Auguste, George*; Talastas, Hercules*; Emmons, Prentiss*; Auguste, Rodney *; Langhnoja, Urvi *
Subject: NDA022253 from SCHWARZ BIOSCIENCES drug name LACOSIMIDE (SPM927) TABLETS

Hi!

The EDR has received an Electronic Document on CD-ROM for division 120:

NDA# N22253
Incoming Document Type: N
Incoming Document Type Sequence Number: 000
Supplement Modification Type: BL
Letter Date: 09-APR-2008

It has section 1
The network location is : \\CDSESUB1\EVSPROD\NDA022253\0008
It is now available on the network. You can review this submission by entering EDR in your browser.

Please address any question concerning this electronic submission to :

EDRAdmin@cdcr.fda.gov

Thanks,
EDR Staff

Ware, Jacqueline H

From: Brounstein, Daniel
Sent: Thursday, April 17, 2008 8:32 AM
Subject: Taylor, Kellie; Ware, Jacqueline H; Park, Judy
RE: Updated lacosamide carton & container labels

Ok, guys, update: I've entered the record into the RCM system and linked the EDR submission in the synopsis. The new record number for the updated labeling for lacosamide is RCM # 2008-633.

Dan

-----Original Message-----

From: Taylor, Kellie
Sent: Wednesday, April 16, 2008 5:50 PM
To: Ware, Jacqueline H; Brounstein, Daniel; Park, Judy
Subject: RE: Updated lacosamide carton & container labels

New consult please. These are radically different than the others. Let Dan know what sort of timeframe is appropriate.
Thanks for sending them on,
Kellie

-----Original Message-----

From: Ware, Jacqueline H
Sent: Wednesday, April 16, 2008 3:57 PM
To: Brounstein, Daniel; Taylor, Kellie; Park, Judy
Subject: Updated lacosamide carton & container labels

Dan, Kellie, and Judy,

Attached below is the electronic link to Schwarz's submission that contains updated carton container labels for ~~the~~ lacosamide products. Although it arrived last week, we just received the EDR notice today. Sorry for the delay!

b(4)

Please let me know if you need a new consult in order to review these or if they can be incorporated into your current review for the existing consult.

Thanks,
Jackie

-----Original Message-----

From: EDRAAdmin@cderr.fda.gov [mailto:EDRAAdmin@cderr.fda.gov]
Sent: Wednesday, April 16, 2008 8:50 AM
To: Ware, Jacqueline H; CDER-EDRADADMIN; Thomas, Elmer *; Saunders, James; Prather, Mia; Nighswander, Robbin M; Chandra, Savithri*
Cc: Almoza, Damus *; Blumstein, Eyal*; Auguste, George*; Talastas, Hercules*; Emmons, Prentiss*; Auguste, Rodney *; Langhnoja, Urvi *
Subject: NDA022253 from SCHWARZ BIOSCIENCES drug name LACOSIMIDE (SPM927) TABLETS

Hi!

The EDR has received an Electronic Document on CD-ROM for division 120:

NDA# N22253
Incoming Document Type: N
Incoming Document Type Sequence Number: 000
Supplement Modification Type: BL
Letter Date: 09-APR-2008

It has section 1
The network location is : \\CDSESUB1\EVSPROD\NDA022253\0008
It is now available on the network. You can review this submission by entering EDR in

your browser.

Please address any question concerning this electronic submission to :

EDRAdmin@cdcr.fda.gov

Thanks,
EDR Staff

Ware, Jacqueline H

From: Ware, Jacqueline H
Sent: Wednesday, April 16, 2008 9:44 PM
:
:
subject: 'Blumberg Alan'; 'DOttavio Misty'
Sullivan, Matthew; Ware, Jacqueline H
FDA Request for Information - NDA 22-253, 22-254.

b(4)

Dear Alan,

Below is a request from DNP's clinical team related to their ongoing review of the lacosamide applications. Please submit your responses to these requests in electronic archival format as an amendment to the above NDAs. It is acceptable for you to email your responses to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

- As per the table in pg 46 of the Clinical Overview submitted with the original application, total exposure to LCM in ALL clinical studies was 3639 subjects. Please provide information to fill out the following table:

Table. Overall exposure to lacosamide and placebo in all studies

Formulation/population	Total number of unique exposures	
	LCM	Placebo
Oral formulation (tablet, capsule)		
Phase 1 – oral only	644	
Partial-onset seizures: EP Pool (tablet)	1327	781
Partial-onset seizures: SP586/SP598 (capsule)	13	
Diabetic Neuropathic Pain Pool	1566	291
Mixed neuropathic pain	25	
Post-herpetic neuralgia	37	
Total exposures to oral formulation (tablet, capsule)	3610	
Solution for infusion		
Phase 1 iv pool	86	
Partial-onset seizures: Phase 2/3 iv pool	199	
Total exposures to solution for infusion	285	
Total unique exposures	3639	
Person-years of exposure (as of 10/16/06)		

When providing number of patients exposed to placebo include the number of patients actually exposed to placebo during the titration periods as well as those receiving placebo during crossover phase 1 studies.

Thank you,
Jackie Ware

Jacqueline H. Ware, Pharm.D., RAC
Commander, United States Public Health Service
Regulatory Project Manager Team Leader

Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4348
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b(4)

Ware, Jacqueline H

From: Ware, Jacqueline H
Sent: Monday, April 07, 2008 3:25 PM
To: 'Blumberg Alan'; 'Dottavio Misty'
Cc: Sullivan, Matthew; Ware, Jacqueline H
Subject: RE: FDA Review Comments - NDA 22-253, 22-254

.acosamide Tabs, Injection,

b(4)

Dear Alan,

The team has reviewed your request for clarification and agree that the value should be /day. Apologies for the mistake!
Thanks for checking,
Jackie

b(4)

Jacqueline H. Ware, Pharm.D., RAC
Commander, United States Public Health Service
Regulatory Project Manager Team Leader

Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4348
Silver Spring, MD 20993-0002

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From: Blumberg Alan [mailto:Alan.Blumberg@ucb-group.com]
Sent: Monday, April 07, 2008 2:29 PM
To: Ware, Jacqueline H; Dottavio Misty
Cc: Sullivan, Matthew
Subject: RE: FDA Review Comments - NDA 22-253, 22-254,

.acosamide Tabs, Injection,

b(4)

Jackie,

Under Drug Substance, we believe that the , mg/day highlighted below, should be µg/day. Please confirm.

b(4)

Thanks,
Alan

From: Ware, Jacqueline H [mailto:jacqueline.ware@fda.hhs.gov]
Sent: Friday, April 04, 2008 8:14 AM
To: Blumberg Alan; Dottavio Misty
Cc: Ware, Jacqueline H; Sullivan, Matthew
Subject: FDA Review Comments - NDA 22-253, 22-254,

Lacosamide Tabs, Injection,

b(4)

Dear Alan,

At the request of the ONDQA and OND non-clinical review teams for the lacosamide applications, I am

5/27/2008

b(4)

providing the below comments related to your proposed impurity specifications for these NDAs. Please submit your responses to these comments in electronic archival format as an amendment to the above NDAs. It is acceptable for you to email your responses to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

Drug Substance: For drug substance impurity _____, you have proposed specification limit of NMT _____, which is above the ICH qualification limit of 0.15%. This impurity was adequately tested in the chronic oral toxicology (6-month rat, 12-month dog), reproductive toxicology, and genetic toxicology studies for lacosamide. However, _____ was not detectable in the drug batch used in the rodent carcinogenicity studies. Carcinogenicity testing of impurities is not generally required. However, there is concern regarding the genotoxic potential of _____ because of the positive results obtained in the in vitro mouse lymphoma tk assays, both in the absence and presence of metabolic activation. Therefore, you will need to either lower the drug substance specification to a level that would result in a daily dose of _____ day or conduct genetic toxicity testing (in vitro Ames and in vitro mouse lymphoma tk assays) of _____ directly in order to support the proposed specification limit.

b(4)

IV formulation drug product: For drug product degradant _____ you have proposed a specification limit of NMT _____, which is above the ICH qualification limit of 0.20%. While the _____ provides an acceptable means of qualification, your test _____ did not include _____ which we require for establishing the safety of an impurity for drugs of this category (chronic use, antiepileptic). Without information on the potential developmental toxicity of _____ we cannot approve an acceptance criterion greater than 0.20% at release or over the drug product shelf-life for _____. In order to support the proposed limit of _____, you will need to conduct an embryo-fetal development study in at least one species, either in the mouse or another species using a drug batch containing an appropriate level of _____.

b(4)

Thank you,
Jackie Ware

Jacqueline H. Ware, Pharm.D., RAC
Commander, United States Public Health Service
Regulatory Project Manager Team Leader

Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4348
Silver Spring, MD 20993-0002

phone: 301-796-1160
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b(4)

Ware, Jacqueline H

From: Ware, Jacqueline H
Sent: Friday, April 04, 2008 4:25 PM
'Dottavio Misty'
Cc: 'Blumberg Alan'; Ware, Jacqueline H; Sullivan, Matthew
Subject: RE: FDA Review Comments - NDA 22-253, 22-254. Lacosamide Tabs, Injection.

b(4)

Misty,
It is acceptable to submit revised carton & container labels by the end of next week. As for updates from our internal meeting this week, I'd like to call you on Monday to discuss. Are you free between 1pm and 3pm?

Thanks,
Jackie

Jacqueline H. Ware, Pharm.D., RAC
Commander, United States Public Health Service
Regulatory Project Manager Team Leader

Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4348
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From: Dottavio Misty [mailto:Misty.Dottavio@ucb-group.com]
Sent: Friday, April 04, 2008 3:31 PM
To: Ware, Jacqueline H
Cc: Blumberg Alan
Subject: RE: FDA Review Comments - NDA 22-253, 22-254 Lacosamide Tabs, Injection.

b(4)

Dear Jackie,

I will inform the team of this information.

Do you have any update from your internal meeting this week regarding CSS and the tradename? I also wanted to let you know that we will have the revised label/container cartons to you by the end of next week. Can you confirm this is acceptable for review?

Best regards,

Misty

From: Ware, Jacqueline H [mailto:jacqueline.ware@fda.hhs.gov]
Sent: Friday, April 04, 2008 3:15 PM
To: DOTTAVIO Misty
Cc: Blumberg Alan; Ware, Jacqueline H; Sullivan, Matthew
Subject: RE: FDA Review Comments - NDA 22-253, 22-254, _____

_____, Lacosamide Tabs, Injection, _____

Dear Misty,
Thanks for confirming receipt of this morning's message. Since sending it, however, I have been asked to share one additional comment. I was asked by the team to inform you that comment #2 below about the IV formulation specification

b(4)

Hope you have a nice weekend too!

Best regards,
Jackie

Jacqueline H. Ware, Pharm.D., RAC
Commander, United States Public Health Service
Regulatory Project Manager Team Leader

Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4348
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From: DOTTAVIO Misty [mailto:Misty.DOTTAVIO@ucb-group.com]
Sent: Friday, April 04, 2008 2:27 PM
To: Ware, Jacqueline H
Subject: RE: FDA Review Comments - NDA 22-253, 22-254, _____

_____, Lacosamide Tabs, Injection, _____

b(4)

Dear Jackie,

We have received your request and will respond as soon as possible.

Have a great weekend,

Misty

From: Ware, Jacqueline H [mailto:jacqueline.ware@fda.hhs.gov]
Sent: Friday, April 04, 2008 8:14 AM
To: Blumberg Alan; DOTTAVIO Misty
Cc: Ware, Jacqueline H; Sullivan, Matthew
Subject: FDA Review Comments - NDA 22-253, 22-254, _____

_____, Lacosamide Tabs, Injection, _____

b(4)

Dear Alan,

b(4)

At the request of the ONDQA and OND non-clinical review teams for the lacosamide applications, I am providing the below comments related to your proposed impurity specifications for these NDAs. Please submit your responses to these comments in electronic archival format as an amendment to the above NDAs. It is acceptable for you to email your responses to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

Drug Substance: For drug substance impurity _____ you have proposed a specification limit of NMT _____, which is above the ICH qualification limit of 0.15%. This impurity was adequately tested in the chronic oral toxicology (6-month rat, 12-month dog), reproductive toxicology, and genetic toxicology studies for lacosamide. However, _____ was not detectable in the drug batch used in the rodent carcinogenicity studies. Carcinogenicity testing of impurities is not generally required. However, there is concern regarding the genotoxic potential of _____ because of the positive results obtained in the in vitro mouse lymphoma tk assays, both in the absence and presence of metabolic activation. Therefore, you will need to either lower the drug substance specification to a level that would result in a daily dose of <= _____ day or conduct genetic toxicity testing (in vitro Ames and in vitro mouse lymphoma tk assays) of _____ directly in order to support the proposed specification limit.

b(4)

IV formulation drug product: For drug product degradant _____, you have proposed a specification limit of NMT _____, which is above the ICH qualification limit of 0.20%. While the _____ provides an acceptable means of qualification, your _____ did not include an _____ which we require for establishing the safety of an impurity for drugs of this category (chronic use, antiepileptic). Without information on the potential developmental toxicity of _____ we cannot approve an acceptance criterion greater than 0.20% at release or over the drug product shelf-life for _____. In order to support the proposed limit of _____ you will need to conduct an embryo-fetal development study in at least one species, either in the mouse or another species using a drug batch containing an appropriate level of _____.

b(4)

Thank you,
Jackie Ware

Jacqueline H. Ware, Pharm.D., RAC
Commander, United States Public Health Service
Regulatory Project Manager Team Leader

Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4348
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e-mail the sender immediately at jacqueline.ware@fda.hhs.gov.

b(4)

**APPEARS THIS WAY
ON ORIGINAL**

Ware, Jacqueline H

From: Ware, Jacqueline H
Sent: Wednesday, April 02, 2008 10:51 PM
'Blumberg Alan'; 'DOttavio Misty'
Ware, Jacqueline H; Sullivan, Matthew
Subject: FDA Request for Information - NDA 22-253, 22-25 [redacted] Lacosamide Tabs, Injection [redacted]

b(4)

Dear Alan,

Below are several requests from DNP's statistical team related to their ongoing review of the lacosamide applications. Please submit your responses to these requests in electronic archival format as an amendment to the above NDAs. It is acceptable for you to email your responses to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

1. In study 667 protocol amendment 3, it was stated that the number of subjects to be enrolled was re-estimated and that the number needed for the primary analysis remained unchanged. Please indicate the date that this re-estimation was done as well as whether it involved any unblinding of the internal study data. Please provide any relevant documentation.
2. The protocols of study 754 and study 755 were also amended after the studies were underway to increase the sample size for the primary analysis.
 - A) Were there any unblinded interim looks at the data? Please provide any relevant documentation.
 - B) Was any unblinded sample size re-estimation done using internal trial data?
 - C) Who had access to the data during the trials and were there any limits on their access?

I would appreciate receiving your responses to these requests as soon as possible.

Thank you,
Jackie Ware

Jacqueline H. Ware, Pharm.D., RAC
Commander, United States Public Health Service
Regulatory Project Manager Team Leader

Division of Neurology Products
Center for Drug Evaluation and Research, FDA
10903 New Hampshire Avenue; WO22 Rm. 4348
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Ware, Jacqueline H

From: Sullivan, Matthew
Sent: Monday, March 31, 2008 5:17 PM
Dottavio Misty; Blumberg Alan
Cc: Ware, Jacqueline H
Subject: RE: N — (lacosamide) - information request

b(4)

Misty –

I think that adding the extra variable is fine.

The urinalysis file isn't so large that it has to be broken down into smaller pieces, but it is unwieldy (341k records, I think), so you might as well send us that too, just in case. Thanks for checking.

matt

From: Dottavio Misty [mailto:Misty.Dottavio@ucb-group.com]
Sent: Monday, March 31, 2008 5:07 PM
To: Sullivan, Matthew; Blumberg Alan
Cc: Ware, Jacqueline H
Subject: RE: N — (lacosamide) - information request

b(4)

Hi Matt,

We have received your request and have the following questions for clarification.

On our teleconference on March 4, 2008, we would propose to supply the lab files which include the additional variable that was requested in the teleconference and provided earlier this month. Is this acceptable? We understand your request below to have the chemistry file separated into 4 individual files and the hematology file separated into 4 individual files, is this correct? Is it also requested that the same to be done for the urinalysis file?

Thanks,

Misty

From: Sullivan, Matthew [mailto:Matthew.Sullivan@fda.hhs.gov]
Sent: Monday, March 31, 2008 1:14 PM
To: Dottavio Misty; Blumberg Alan
Cc: Ware, Jacqueline H
Subject: N — (lacosamide) - information request

b(4)

Alan and Misty –

From the DAARP folks:

Due to the large size of the ISS lab1.xpt and lab2.xpt datasets, we are unable to open them.

Please resubmit this data in separate files as follows:

Controlled Trials (Neuropathic Pain)

5/27/2008

N — (Iacosamide) - information request

Page 2 of 2

Uncontrolled Trials (Neuropathic Pain)

b(4)

Controlled Trials (Epilepsy)

Uncontrolled Trials (Epilepsy)

(I didn't necessarily believe this when the Medical Officer sent it to me. But, sure enough, JMP crashes each time I try to load
of these files, whether from the server or saved locally.)

Thanks
matt

5/27/2008

Ware, Jacqueline H

From: Sullivan, Matthew
Sent: Monday, March 31, 2008 2:14 PM
:
:
subject: N — (acosamide) - information request

b(4)

Alan and Misty –

From the DAARP folks:

Due to the large size of the ISS lab1.xpt and lab2.xpt datasets, we are unable to open them.

Please resubmit this data in separate files as follows:

- Controlled Trials (Neuropathic Pain)
- Uncontrolled Trials (Neuropathic Pain)
- Controlled Trials (Epilepsy)
- Uncontrolled Trials (Epilepsy)

(I didn't necessarily believe this when the Medical Officer sent it to me. But, sure enough, JMP crashes each time I try to load one of these files, whether from the server or saved locally.)

Thanks
matt

Ware, Jacqueline H

From: Sullivan, Matthew
Sent: Friday, March 21, 2008 12:07 PM
Dottavio Misty; Blumberg Alan
Cc: Ware, Jacqueline H
Subject: Lacosamide SP874 question

Alan and Misty –

From the DAARP team:

We note in your January 23, 2008 Safety Update submission, the inclusion of information from Study SP874, a Phase 3 trial in patients with painful diabetic peripheral neuropathy. Is it your intention to use this trial in support of the safety of lacosamide?

Thanks,
Matt

Matthew W. Sullivan, M.S.
Regulatory Project Manager
Division of Anesthesia, Analgesia
and Rheumatology Products
Food and Drug Administration
P. 301-796-1245
Fax 301-796-9722 / 9723
matthew.sullivan@fda.hhs.gov



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-253
NDA 22-254

INFORMATION REQUEST LETTER

(/)
b(4)

Schwarz Biosciences
P.O. Box 110167
Research Triangle Park, NC 27709

Attention: Alan Blumberg, Ph.D. Senior Director
Regulatory Affairs

Dear Dr. Blumberg:

Please refer to your New Drug Applications (NDAs) submitted September 28, 2007, received September 28, 2007, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for lacosamide.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submissions and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDAs.

DRUG SUBSTANCE

(/) (/) (/) (/)
(/) (/) (/)

b(4)

b(4)



7 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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NDA 22-253  
NDA 22-254

/ ( **b(4)**  
Page 4

If you have any questions, call Jacqueline H. Ware, Pharm.D., Regulatory Health Project Manager, at (301) 796-1160.

Sincerely,

*See attached electronic signature page*

Ramesh Sood, Ph.D.  
Branch Chief  
Division of Pre-Marketing Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

-----  
**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/

-----  
Ramesh Sood  
3/20/2008 07:20:56 AM

**Ware, Jacqueline H**

---

**From:** Sullivan, Matthew  
**Sent:** Thursday, March 13, 2008 1:51 PM  
Blumberg Alan  
**Cc:** Ware, Jacqueline H; DOttavio Misty  
**Subject:** Information Request - NDA (3/13/08)

b(4)

Alan -

The Stats reviewer looking at the abuse liability study is still having some issues with the dataset (although she's at least in the right file now.)

See below her most recent email to me:

It is very difficult for me to understand the variable names using the sponsor's labels for those variables. For example, QSSEQ is labeled "sequence number". I found that there are 207 different sequence numbers. No other variable in the dataset is used to identify 5 sequences in the study design. "Sequence" is an important fixed factor in my study model.

In addition, seventy five patient records are in the dataset. Based on the sponsor's clinical trial report, 76 patients were randomized in Qualification Phase. In the sponsor's report, 30 out of 76 patients completed study. However, I could not find an identifier for completers. This dataset has 232,184 observations with 46 variables. Without clarification of the definitions of those variables, I would not be able to do my analyses.

I need the definition for each variable in dataset qs.xpt.

Can you provide any assistance?

T  
M.

**Ware, Jacqueline H**

---

**From:** Sullivan, Matthew  
**Sent:** Tuesday, March 11, 2008 3:23 PM  
Blumberg Alan; DOttavio Misty  
**Cc:** Ware, Jacqueline H  
**Subject:** help finding dataset

Alan -

Can you help me find the right dataset for this statistical reviewer? She's looking at Study 903, the abuse liability study.

I did check the datasets at \\cdsesub1\evsprod\NDA022253\0000\m5\datasets\sp903. There are many datasets in there. I spent a lot of time to look for the dataset I need. However, I could not find it. Would you please ask the sponsor which dataset they used for analyses of VAS and ARCI variables (their primary and secondary endpoints)?

I'm not exactly sure what she needs, but if you can just let me know the location and filename, we should be all set.

Thanks  
Matt

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Matthew W. Sullivan, M.S.  
Regulatory Project Manager  
Division of Anesthesia, Analgesia  
and Rheumatology Products  
Food and Drug Administration  
Phone 301-796-1245  
Fax 301-796-9722 / 9723  
matt.w.sullivan@fda.hhs.gov

5/27/2008

**Ware, Jacqueline H**

---

**From:** Sullivan, Matthew  
**Sent:** Tuesday, March 11, 2008 3:19 PM  
Blumberg Alan; DOttavio Misty  
**Cc:** Ware, Jacqueline H  
**Subject:** RE: FDA Request for Information - NDA 22-253, 22-254, \_\_\_\_\_ /Lacosamide Tabs, Injection \_\_\_\_\_ b(4)

Alan -

I'm sending this on behalf of Jackie, who is out of the office much of this week.

1. Regarding your March 10<sup>th</sup> question below, please provide two analyses: one for TG  $\geq 1.5$  X ULN and other for TG  $\geq 2$  X ULN.

Additionally, we are requesting the following:

2. Please provide analyses of transaminase levels  $\geq 2$  X ULN in EP pool S1.

3. Your e \_\_\_\_\_ mentions 7 subjects who dropped out of the migraine study because of potentially cardiovascular-related adverse events during the last year. Please provide additional information from the cases who dropped from the migraine study because of MI, syncope, chest pain, high blood pressure and palpitations. b(4)

As usual, please submit your responses to these requests in electronic archival format as an amendment to the above NDAs. It is acceptable for you to email your responses to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

T. .s,

Matt (for Jackie)

---

**From:** Blumberg Alan [mailto:Alan.Blumberg@ucb-group.com]  
**Sent:** Monday, March 10, 2008 12:12 PM  
**To:** Ware, Jacqueline H; DOttavio Misty  
**Cc:** Sullivan, Matthew  
**Subject:** RE: FDA Request for Information - NDA 22-253, 22-254 \_\_\_\_\_ /Lacosamide Tabs, Injection, \_\_\_\_\_ b(4)

Dear Jackie,

Regarding the March 3 request 2. (see below), we believe defining markedly abnormal triglyceride as  $\geq 2$  X ULN ( $\geq 500$ mg/dL or 5.64mmol/L) is appropriate as the labs in our studies were not collected during fasting conditions. Does DNP's clinical team agree? Once we reach agreement we can begin the programming for the analyses.

Thanks,  
Alan

---

**From:** Ware, Jacqueline H [mailto:jacqueline.ware@fda.hhs.gov]  
**Sent:** Monday, March 03, 2008 9:34 PM  
**To:** Blumberg Alan; DOttavio Misty  
Ware, Jacqueline H; Sullivan, Matthew  
**Subject:** FDA Request for Information - NDA 22-253, 22-254, \_\_\_\_\_ /Lacosamide Tabs, Injection, \_\_\_\_\_ b(4)

5/27/2008

b(4)

Dear Alan,

Below are several requests from DNP's clinical team related to their ongoing review of the lacosamide applications. Please submit your responses to these requests in electronic archival format as an amendment to the above NDAs. It is acceptable for you to email your responses to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

1. Your Feb 19, 2008 response lists 11 patients from EP Pool S2 who received LCM doses >800 mg daily. It is our impression that the maximum dose recommended in the open label studies was 800 mg daily. Please clarify:
  - a. Whether dosing >800 mg daily was accidental or intentional,
  - b. Whether dosing >800 mg daily was associated with adverse events in these patients,
  - c. Whether any case suggests potential for drug abuse.
2. Table EP. 7.15.1 (Incidence of treatment emergent marked abnormalities during the treatment phase -chemistry) in Pool S1 submitted with the original NDA seems to be missing the analysis of Triglycerides. Please provide such analysis.
3. As per AE dataset, Subject 754011401 patient developed QTC prolongation on day 1, on LCM 100 mg/day. The reviewer has not been able to find the narrative and CRF for this patient. Please submit or direct the reviewer to the exact location of this information.

Thank you,  
Jackie Ware

\*\*\*\*\*

Jacqueline H. Ware, Pharm.D., RAC  
Commander, United States Public Health Service  
Regulatory Project Manager Team Leader

Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4348  
Silver Spring, MD 20993-0002

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email: jacqueline.ware@fda.hhs.gov

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5/27/2008

**Ware, Jacqueline H**

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**From:** Sullivan, Matthew  
**Sent:** Tuesday, March 11, 2008 3:11 PM  
DOttavio Misty; Blumberg Alan  
**Cc:** Ware, Jacqueline H  
**Subject:** RE: N (lacosamide) - information request 3/6/08

Misty -

Here is our response to the questions in your 3/7/08 email, below:

Clarification #1

Appendix F of the CV report evaluates only those events coded to the Preferred Terms: syncope, loss of consciousness, and depressed level of consciousness.

We are asking for additional information for patients with events coded to a broader range of terms and therefore beyond what is provided in the report.

Clarification #2

Regarding the following request: *"For each study population (DPN, postherpetic neuralgia etc.), provide tables that compare the frequency of the events by treatment group. Data from open-label and double-blind placebo-controlled studies should be presented separately."*

Please present the information using tables.

P S2 includes both placebo-controlled and open-label trials. We would like the information from the c label trials presented separately from the placebo-controlled trials.

---

**From:** DOttavio Misty [mailto:Misty.DOttavio@ucb-group.com]  
**Sent:** Friday, March 07, 2008 12:30 PM  
**To:** Sullivan, Matthew; Blumberg Alan  
**Cc:** Ware, Jacqueline H  
**Subject:** RE: N (lacosamide) - information request 3/6/08

Hi Matt,

Based on our telephone call earlier today, I am providing you with the location of the Cardiovascular Document that was submitted within the eCTD and making reference to Appendix F which addresses syncope.

The location of the CV document is provided below and Appendix F is located within the report.

5.3.5.3 Reports of Analyses of Data from More than One Study/Cardiac Safety Report - Cardiac Safety Report/Legacy Study Report/Cardiac Safety Report

One addition question based on the last paragraph of your request provided below in blue. Does the reference to treatment group include Pool S1 only or Pool S1 and Pool S2? Should the data requested be presented in tables or in datasets?

For each study population (DPN, postherpetic neuralgia etc.), provide tables that compare the frequency of the events by treatment group. Data from open-label and double-blind placebo-controlled studies should be presented separately.

Thank you for the clarification. Please let me know if you have any questions.

5/27/2008

Regards,

Misty

---

**From:** Sullivan, Matthew [mailto:Matthew.Sullivan@fda.hhs.gov]

**Sent:** Thursday, March 06, 2008 2:48 PM

**To:** Blumberg Alan; DOTTAVIO Misty

**Cc:** Ware, Jacqueline H

**Subject:** N — (lacosamide) - information request 3/6/08

b(4)

Alan and Misty —

Please see below a request from the DAARP team:

For all neuropathic pain populations (including DPN, mixed neuropathic pain, and postherpetic neuralgia), provide the unique subject ID numbers and case report forms, and generate a patient narrative for all patients who reported adverse events consistent with syncope or presyncope. Indicate whether the events were considered cardiac or non-cardiac in origin.

Events should include (but not necessarily be limited to) those coded to the LLTs of: blackout, blackout spell, fainting, felt faint, lightheadedness, loss of consciousness, near syncope, presyncope, syncopal attack, syncope, unconsciousness, and woozy.

The unique subject ID numbers should be submitted as a SAS transport (.xpt) file.

For each study population (DPN, postherpetic neuralgia etc.), provide tables that compare the frequency of the events by treatment group. Data from open-label and double-blind placebo-controlled studies should be presented separately.

As usual, an exact electronic copy in advance of the official submission is requested.

Thanks

Matt

---

Matthew W. Sullivan, M.S.

Regulatory Project Manager

Division of Anesthesia, Analgesia

and Rheumatology Products

Food and Drug Administration

Phone 301-796-1245

Fax 301-796-9722 / 9723

matthew.sullivan@fda.hhs.gov

5/27/2008

## Ware, Jacqueline H

---

**From:** Ware, Jacqueline H  
**Sent:** Tuesday, March 11, 2008 1:28 AM  
Delasko, Jeanne  
Sullivan, Matthew; Ware, Jacqueline H  
**Subject:** RE: GRMP Pilot: NDA 22-253 (Lacosamide)

Jeanne,  
We'll be glad to send labeling when it's available. However, it won't be anytime soon. We have not done any work on labeling at this point in the review. As you know, the PDUFA goal date is 7/28/08; I doubt we will take an action much prior to that date. I am not sure yet what type of action it will be.

Hope this helps,  
Jackie

\*\*\*\*\*

Jacqueline H. Ware, Pharm.D., RAC  
Commander, United States Public Health Service  
Regulatory Project Manager Team Leader

Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4348  
Silver Spring, MD 20993-0002

phone: 301-796-1160  
fax: 301-796-9842  
email: jacqueline.ware@fda.hhs.gov

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---

**From:** Delasko, Jeanne  
**Sent:** Monday, March 10, 2008 2:41 PM  
**To:** Ware, Jacqueline H  
**Subject:** GRMP Pilot: NDA 22-253 (Lacosamide)

Hi Jackie,

I am the PLR content reviewer from SEALD (labeling team) that has been assigned to the Lacosamide application that is due on 7/28/08. SEALD conducts content reviews **AFTER** the division review team completes their initial draft review **BUT BEFORE** labeling content comments are sent to the applicant. Could please send me the most recent version of the marked-up label (Highlights, Contents, and FPI) once your team has finished editing? An MS word file is preferable.

Also, do you have an estimate as to when you might take an action on this application and what type of action you will be taking? If you are planning to take an AE or NA action, we will wait until the next review cycle to complete our review, unless you plan on conducting labeling negotiations with the firm this cycle.

Thanks in advance for your time and help.

Jeanne Delasko on behalf of CDER SEALD LABELING

b(4)

**Ware, Jacqueline H**

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**From:** Sullivan, Matthew  
**Sent:** Monday, March 10, 2008 3:18 PM  
Hershkowitz, Norman; Villalba, Lourdes  
**Cc:** Ware, Jacqueline H  
**Subject:** FW: FDA Request for Information - NDA 22-253, 22-254, /Lacosamide Tabs, Injection, and

b(4)

**Attachments:** emfalert.txt

Since Jackie is out of the office, I'm attempting to cover Lacosamide for her.

Please see below a request for clarification from the Sponsor regarding the information request she sent last Monday.

Please let me know your thoughts.

Thanks  
Matt

---

**From:** Blumberg Alan [mailto:Alan.Blumberg@ucb-group.com]  
**Sent:** Monday, March 10, 2008 12:12 PM  
**To:** Ware, Jacqueline H; DOTTAVIO Misty  
**Cc:** Sullivan, Matthew  
**Subject:** RE: FDA Request for Information - NDA 22-253, 22-254, /Lacosamide Tabs, Injection,

b(4)

Dear Jackie,  
Regarding the March 3 request 2. (see below), we believe defining markedly abnormal triglyceride as  $\geq 2 \times \text{ULN}$  ( $\geq 500 \text{mg/dL}$  or  $\geq 5 \text{mmol/L}$ ) is appropriate as the labs in our studies were not collected during fasting conditions. Does DNP's clinical team agree? Once we reach agreement we can begin the programming for the analyses.

Thanks,  
Alan

---

**From:** Ware, Jacqueline H [mailto:jacqueline.ware@fda.hhs.gov]  
**Sent:** Monday, March 03, 2008 9:34 PM  
**To:** Blumberg Alan; DOTTAVIO Misty  
**Cc:** Ware, Jacqueline H; Sullivan, Matthew  
**Subject:** FDA Request for Information - NDA 22-253, 22-254, /Lacosamide Tabs, Injection,

b(4)

Dear Alan,  
Below are several requests from DNP's clinical team related to their ongoing review of the lacosamide applications. Please submit your responses to these requests in electronic archival format as an amendment to the above NDAs. It is acceptable for you to email your responses to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

1. Your Feb 19, 2008 response lists 11 patients from EP Pool S2 who received LCM doses  $> 800 \text{ mg}$  daily. It is our impression that the maximum dose recommended in the open label studies was  $800 \text{ mg}$  daily. Please clarify:
  - a. Whether dosing  $> 800 \text{ mg}$  daily was accidental or intentional,
  - b. Whether dosing  $> 800 \text{ mg}$  daily was associated with adverse events in these patients,

5/27/2008

- c. Whether any case suggests potential for drug abuse.
2. Table EP. 7.15.1 (Incidence of treatment emergent marked abnormalities during the treatment phase –chemistry) in Pool S1 submitted with the original NDA seems to be missing the analysis of Triglycerides. Please provide such analysis.
3. As per AE dataset, Subject 754011401 patient developed QTC prolongation on day 1, on LCM 100 mg/day. The reviewer has not been able to find the narrative and CRF for this patient. Please submit or direct the reviewer to the exact location of this information.

Thank you,  
Jackie Ware

\*\*\*\*\*

Jacqueline H. Ware, Pharm.D., RAC  
Commander, United States Public Health Service  
Regulatory Project Manager Team Leader

Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4348  
Silver Spring, MD 20993-0002

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**Ware, Jacqueline H**

---

**From:** Ware, Jacqueline H  
**Sent:** Friday, March 07, 2008 6:56 PM  
'Blumberg Alan'; 'Dottavio Misty'  
Sullivan, Matthew; Ware, Jacqueline H  
**Subject:** FDA Request for Information - NDA 22-253, 22-254 Lacosamide Tabs, **b(4)**  
Injection, \_\_\_\_\_

Dear Alan,

Below are several requests from DNP's clinical team related to their ongoing review of the lacosamide applications. Please submit your responses to these requests in electronic archival format as an amendment to the above NDAs. It is acceptable for you to email your responses to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

- Subject ID# 75411401 discontinued from the trial because of QTc prolongation. However, the reason for discontinuation for this patient was "Protocol violation" because the prolongation was present at baseline and the patient had been randomized by error.

As per the amended CRF, three ECGs were done prior to administration of trial medication, at 14:16, 14:31 and 14:49 on May 19, 2004. However, the first LCM dose is recorded as given at 11.:30. Please clarify why the timing of the ECGa was amended on June 18, 2004, whether the baseline ECGs were done before or after the first LCM dose and whether the patient continued taking LCM until May 24, 2004.

- Additionally, a footnote to the table in pg 103 of the Cardiac report indicates that non-compliance for ECG measurements was found in site 012. Please clarify what kind of non-compliance was found at that site.

Thank you,  
Jackie Ware

\*\*\*\*\*

Jacqueline H. Ware, Pharm.D., RAC  
Commander, United States Public Health Service  
Regulatory Project Manager Team Leader

Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4348  
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**Ware, Jacqueline H**

---

**From:** Sullivan, Matthew  
**Sent:** Friday, March 07, 2008 9:13 AM  
Blumberg Alan; DOttavio Misty  
**Subject:** Information Request - NDA (3/7/08)

b(4)

Alan and Misty –

Please see below a request from the DAARP clinical pharmacology review team.

As usual, an exact electronic copy in advance of the official submission is requested.

Thanks  
Matt

---

Provide assay validation data for lacosamide for the following studies:

- SP835 - lacosamide in plasma
- SP836 - lacosamide in urine and plasma
- SP588 - lacosamide in urine and plasma

---  
Matthew W. Sullivan, M.S.  
Regulatory Project Manager  
Division of Anesthesia, Analgesia  
and Rheumatology Products  
Food and Drug Administration  
Phone 301-796-1245  
Fax 301-796-9722 / 9723  
matthew.sullivan@fda.hhs.gov

## Ware, Jacqueline H

---

**From:** Bonson, Katherine R  
**Sent:** Thursday, March 06, 2008 9:28 AM  
Hershkovitz, Norman; Ware, Jacqueline H  
Al Hakim, Ali H; Bhattaram, Atul; Brounstein, Daniel; Christodoulou, Danae D; Doddapaneni, Suresh; Fadiran, Emmanuel O; Fisher, J Edward; Freed, Lois M; Gobburu, Jogarao V; Grant, Stephen; Gunther, Sheryl; Hayes, Belinda; Heimann, Martha R; Hertz, Sharon H; Jenkins, Darrell; Jin, Kun; Kashoki, Mwango; Katz, Russell G; Kortepeter, Cindy; Lee, Lauren; Locicero, Colleen L; Massie, Tristan; Meaker, Katherine B; Mellon, Dan; Park, Judy; Pokrovnichka, Anjelina; Price, Dionne; Rappaport, Bob A; Ripper, Leah W; Rosebraugh, Curtis; Shiromani, Prafull; Sullivan, Matthew; Tandon, Veneeta; Taylor, Kellie; Temple, Robert; Thomson, Steven F; Uppoor, Ramana S; Villalba, Lourdes; Yasuda, Sally; Zhu, Hao  
**Subject:** RE: Follow-up to Lacosamide Mid-cycle Meeting

Thanks, Norm --

As I said in the meeting, CSS has some concerns about the abuse potential of lacosamide, but at this point we are not ready to convey this to the Sponsor. We have sent the human abuse potential study out for consult to Stats and we won't be able to comment until after we have their assessment at the end of the month. At that point, we will also have had a chance to more thoroughly review the animal abuse studies and the AE profile in the clinical efficacy studies to see if there is an abuse signal.

Kit

---

**From:** Hershkovitz, Norman  
**Sent:** Thursday, March 06, 2008 8:13 AM  
**To:** Ware, Jacqueline H  
**Cc:** Al Hakim, Ali H; Bhattaram, Atul; Bonson, Katherine R; Brounstein, Daniel; Christodoulou, Danae D; Doddapaneni, Suresh; Fadiran, Emmanuel O; Fisher, J Edward; Freed, Lois M; Gobburu, Jogarao V; Grant, Stephen; Gunther, Sheryl; Hayes, Belinda; Heimann, Martha R; Hertz, Sharon H; Jenkins, Darrell; Jin, Kun; Kashoki, Mwango; Katz, Russell G; Kortepeter, Cindy; Lee, Lauren; Locicero, Colleen L; Massie, Tristan; Meaker, Katherine B; Mellon, Dan; Park, Judy; Pokrovnichka, Anjelina; Price, Dionne; Rappaport, Bob A; Ripper, Leah W; Rosebraugh, Curtis; Shiromani, Prafull; Sullivan, Matthew; Tandon, Veneeta; Taylor, Kellie; Temple, Robert; Thomson, Steven F; Uppoor, Ramana S; Villalba, Lourdes; Yasuda, Sally; Zhu, Hao  
**Subject:** RE: Follow-up to Lacosamide Mid-cycle Meeting

Jackie et al,

It seems to me that we have 3 potential issues that may need to be communicated (impurity, syncope narratives and OCP). As they are mostly under investigation now, perhaps we should establish a deadline of about 2 weeks till those involved in the primary review of the issues decide what needs to be communicated. At that time we can have a small meeting with pertinent individual to determine what should be communicated. We can also deal with the broad safety review issue at that meeting. I feel we should set up the meeting now. One last thing, I seem to recall that CSS may have some issues that might need to be communicated. Can CSS comment on this?

Norm

Norman Hershkovitz MD, PhD  
Senior Medical Officer (Acting Team Leader)  
Division of Neurology Products  
CDER, FDA

---

**From:** Ware, Jacqueline H  
**Sent:** Wednesday, March 05, 2008 10:18 PM  
**To:** Al Hakim, Ali H; Bhattaram, Atul; Bonson, Katherine R; Brounstein, Daniel; Christodoulou, Danae D; Doddapaneni, Suresh; Fadiran, Emmanuel O; Fisher, J Edward; Freed, Lois M; Gobburu, Jogarao V; Grant, Stephen; Gunther, Sheryl; Hayes, Belinda; Heimann, Martha R; Hershkovitz, Norman; Hertz, Sharon H; Jenkins, Darrell; Jin, Kun; Kashoki, Mwango; Katz, Russell G; Kortepeter, Cindy; Lee, Lauren; Locicero, Colleen L; Massie, Tristan; Meaker, Katherine B; Mellon, Dan; Park, Judy;

Pokrovnichka, Anjelina; Price, Dionne; Rappaport, Bob A; Ripper, Leah W; Rosebraugh, Curtis; Shiromani, Prafull; Sullivan, Matthew; Tandon, Veneeta; Taylor, Kellie; Temple, Robert; Thomson, Steven F; Uppoor, Ramana S; Villalba, Lourdes; Ware, Jacqueline H; Yasuda, Sally; Zhu, Hao  
Follow-up to Lacosamide Mid-cycle Meeting

**Subject:**

Hi all,

Below is the list of action items that I captured at the Lacosamide Mid-cycle meeting. Admittedly they are very rough, but please review, comment, confirm, edit, and/or delete as appropriate.

**Actions:**

1. Dan will assist CMC in addressing impurity comment to address potential qualification issue.
2. Pharm/tox to figure out coverage issue with impurity — **b(4)**
3. OCP may have request for assay validation for several studies.
4. Send all slides out to all team members.
5. ??? Do we want to request syncope & LOC & depressed level of consciousness for DPN controlled trials (Neurological AEs)? And/or for entire NDA safety database?
6. CDTLs should discuss shared review responsibilities for a broad safety evaluation.
7. Clinical may want to investigate verbatim terms for certain neuron/psych AEs.

Also, we need to think about having some sort of mid-cycle communication with the applicant. [GRMP encourages communication with the applicant throughout the review process, and the OND GRMP Activity Description document recommends a mid-cycle communication, similar to the filing communication.] So can folks please think about what this communication should consist of and share your thoughts with the team?

Thanks,  
Jackie

**APPEARS THIS WAY  
ON ORIGINAL**

**Ware, Jacqueline H**

---

**From:** Ware, Jacqueline H  
**Sent:** Monday, March 03, 2008 9:34 PM  
'Blumberg Alan'; 'Dottavio Misty'  
Ware, Jacqueline H; Sullivan, Matthew  
**subject:** FDA Request for Information - NDA 22-253, 22-254 \_\_\_\_\_ /Lacosamide Tabs, Injection, \_\_\_\_\_

b(4)

Dear Alan,

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  - a. Whether dosing >800 mg daily was accidental or intentional,
  - b. Whether dosing >800 mg daily was associated with adverse events in these patients,
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2. Table EP. 7.15.1 (Incidence of treatment emergent marked abnormalities during the treatment phase –chemistry) in Pool S1 submitted with the original NDA seems to be missing the analysis of Triglycerides. Please provide such analysis.
3. As per AE dataset, Subject 754011401 patient developed QTC prolongation on day 1, on LCM 100 mg/day. The reviewer has not been able to find the narrative and CRF for this patient. Please submit or direct the reviewer to the exact location of this information.

Thank you,  
Jackie Ware

\*\*\*\*\*

Jacqueline H. Ware, Pharm.D., RAC  
Commander, United States Public Health Service  
Regulatory Project Manager Team Leader

Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
10903 New Hampshire Avenue; WO22 Rm. 4348  
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**APPEARS THIS WAY  
ON ORIGINAL**

**APPEARS THIS WAY  
ON ORIGINAL**

**APPEARS THIS WAY  
ON ORIGINAL**

**Ware, Jacqueline H**

---

**From:** Ware, Jacqueline H  
**Sent:** Tuesday, February 26, 2008 7:37 AM  
:  
:  
**subject:** FDA Request for Information - NDA 22-253, 22-254, \_\_\_\_\_ Lacosamide Tabs, Injection \_\_\_\_\_

b(4)

Dear Alan,

Below is a request from DNP's clinical pharmacology team related to their ongoing review of the lacosamide applications. Please submit your response to this request in electronic archival format as an amendment to the above NDAs. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

- Please explain why the lacosamide Tmax values were greater than the infusion duration (1 - 3 hours) in about 25% of the subjects in the 15, 30 and 60 minutes infusion groups in studies SP645 and SP658.

Thank you,  
Jackie Ware

\*\*\*\*\*

Jacqueline H. Ware, Pharm.D., RAC  
Commander, United States Public Health Service  
Regulatory Project Manager Team Leader

Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
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**Ware, Jacqueline H**

---

**From:** Sullivan, Matthew  
**Sent:** Wednesday, February 20, 2008 12:22 PM  
 Blumberg Alan; DOttavio Misty  
**Cc:** Ware, Jacqueline H  
**Subject:** RE: NDA — IR 2/20/08 **b(4)**

And number 2 for today:

In the ISS adverse event dataset (ae.xpt), the following codes could be used to identify the phases and/or studies during which an event occurred: STUDYID, POOL\_S1/S2 and PART.

Using LCMCODE, POOL-S1/S2 to select for studies of interest, and then PART to further identify when an event occurred, we find that there are patients with events coded under "DB/OL." Attempts to specify whether an event occurred during a double-blind or open-label extension trial (using TP\_L, MP\_L, TRN-L, TAP\_L, CRELSTDY, and CRELSTDO) were not successful. The data entered under the respective variables are inconsistent and/or unclear.

For example, subject 742010304 (study ID 742, LCM 200 mg/d) had 4 events: Dizziness and ECG PR prolongation (coded under DB and OL phases, respectively) and areflexia and weight decreased each coded under DB/OL phase.

CRELSTDY = "relative day of AE onset." However, it is not stated what time point the event is relative to. Thus this variable cannot be used to assist in determining when during study SP742, the event occurred, or if it occurred in an open-label extension study.

CRELSTDO = AE start relative to first OL date. The variable TP\_L shows that the event of dizziness occurred during the extension phase of the double-blind phase (PART=DB). However, the variable CRELSTDO indicates that the event occurred 4 days after the first open-label date.

Explain the apparent inconsistencies in the adverse event dataset.

---

**From:** Sullivan, Matthew  
**Sent:** Wednesday, February 20, 2008 10:49 AM  
**To:** 'Blumberg Alan'; 'DOttavio Misty'  
**Cc:** Ware, Jacqueline H  
**Subject:** NDA 22-284 IR 2/20/08

Alan and Misty –

Please see the below information request from the DAARP clinical team:

Section 4.1.2 of the ISS states, with respect to the pooling of diabetic neuropathic pain (DNP) trials:

*"...the following pooled analysis sets were used for assessing safety:*

- *DNP Pool S1 (primary safety pool) – Treated subjects from all double-blind placebo controlled trials (SP614, SP742, SP743, and SP768)*
- *DNP Pool S2 (long-term safety pool) – All subjects who were treated with LCM in double-blind trials SP614, SP742, SP743, and SP768 and subjects who received at least 1 dose of LCM in open-label trials SP665, SP745, SP746, and SP830. All post-Baseline data contributing to this pool was restricted to that observed while subjects were exposed to LCM. Subjects who received treatment with LCM in more than 1 trial are counted only once.*

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*The safety results of the SP746 subtrial were presented separately from the above safety pools since the subtrial was different in design and conduct."*

Grouping of the ISS adverse event dataset (ae.xpt) by the variable "POOL\_S1" and then by "PART," shows that there are adverse event data from double-blind (DB) and open-label (OL and DB/OL) phases. However, because POOL\_S1 contains only double-blind trials, there should be no adverse events reported during an open-label phase. Please clarify.

In the ISS adverse event dataset (ae.xpt), the variable "POOL\_S2" should identify the trials included in Pool S2. Grouping by POOL\_S2 and then again by STUDY ID shows that only studies SP614, 742, 743, 768, 830, and 874 are included. Data from studies SP665, 745, and 746 are not included.

Also, in the ISS ae.xpt dataset, the variables TP\_L(F), MP\_L(F), TRN\_L(F), and TAP\_L(N) indicate the study phase during which an adverse event occurred. Data for these variables are not complete (i.e. some cells are blank).

Provide a revised integrated adverse event dataset for all DNP trials that, in addition to the current variables, includes the following:

- Data from studies SP665, 745, and 746
- A flag indicating whether the AE occurred during the double-blind placebo controlled trials (titration, maintenance, or taper phase), or during the open-label studies
- Complete data entry for the TP\_L(F), MP\_L(F), TRN\_L(F), and TAP\_L(F). If this is not possible, provide your explanation for this.
- A flag indicating whether or not a patient entered into one of the open-label safety studies

As usual, please provide an advance electronic copy as long as you assure us that it is an exact duplicate to what will be officially life-cycled.

Thanks  
matt

---  
Matthew W. Sullivan, M.S.  
Regulatory Project Manager  
Division of Anesthesia, Analgesia  
and Rheumatology Products  
Food and Drug Administration  
Phone 301-796-1245  
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matthew.sullivan@fda.hhs.gov

5/27/2008

**Ware, Jacqueline H**

---

**From:** Ware, Jacqueline H  
**Sent:** Thursday, February 14, 2008 8:51 AM  
: 'Blumberg Alan'; 'Dottavio Misty'  
: Ware, Jacqueline H; Sullivan, Matthew  
**subject:** FDA Request for Information - NDA 22-253, 22-254, \_\_\_\_\_ Lacosamide Tabs, Injection, \_\_\_\_\_

b(4)

Dear Alan,

Below are several requests from DNP's clinical team related to their ongoing review of the lacosamide applications. Please submit your responses to these requests in electronic archival format as an amendment to the above NDAs. It is acceptable for you to email your responses to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

- We have reviewed your comment and response to FDA 1/14/08 Question 6 (included below for ease of reference) and have the following clarification.

**Comment/Response from Schwarz:** "In reference to FDA 1/14/08 Question 6: We acknowledge that the disposition and AE datasets submitted with the original application include maximum treatment dose columns, but they provide a dose range, not the actual maximum dose received by each patient. Please provide the maximum dose taken at any time during the double blind and the OL periods for each patient in EP Pool 1 and 2.

Sponsor's Response:

The Integrated EXPOSURE analysis file has the variable MAXOVER which is the maximum LCM dose taken at any time during exposure to LCM for the combined double-blind and OL periods for each subject in EP Pool S2. This is a 1 record per subject file for epilepsy and can be easily merged with the Disposition and/or AE files."

**FDA clarification:** This response does not fully address our request. Please provide the listing of subjects who received LCM doses higher than the randomization dose in the EP Pool S1 and subjects who received LCM doses above 800 mg/day in EP S2.

- With regard to your February 11, 2008 email, which requests feedback about our January 14, 2008 Question 4, we agree that the analysis by dose at onset in S2 is difficult to interpret. Therefore, we ask that you respond to the following request instead of the original request described in FDA 1/14/08 Question 4.

Please provide the analysis of TAES that resulted in early discontinuation or dose reduction by dose at onset and by randomization dose in Pool EP S1.

Thank you,  
Jackie Ware

\*\*\*\*\*  
Jacqueline H. Ware, Pharm.D., RAC  
Commander, United States Public Health Service  
Regulatory Project Manager Team Leader

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b(4)

**Ware, Jacqueline H**

---

**From:** Blumberg Alan [Alan.Blumberg@ucb-group.com]  
**Sent:** Thursday, February 07, 2008 10:04 AM  
Ware, Jacqueline H  
**Cc:** DOTTAVIO Misty  
**Subject:** RE: FDA Request for Information - NDA 22-253, 22-254, \_\_\_\_\_ Lacosamide Tabs, Injection, \_\_\_\_\_ b(4)

**Attachments:** Report.doc; emfinfo.txt

Jackie,  
Attached is a screen shot of where the report is located within the CTD. Do I need to lifecycle this? I do not think so, but who am I?

Best regards,  
Alan

---

**From:** Ware, Jacqueline H [mailto:jacqueline.ware@fda.hhs.gov]  
**Sent:** Thursday, February 07, 2008 9:28 AM  
**To:** Blumberg Alan; DOTTAVIO Misty  
**Cc:** Ware, Jacqueline H; Sullivan, Matthew  
**Subject:** FDA Request for Information - NDA 22-253, 22-254, \_\_\_\_\_ 'Lacosamide Tabs, Injection, \_\_\_\_\_ b(4)

Dear Alan,  
Below is a request from DNP's clinical pharmacology team related to their ongoing review of the lacosamide e... ations. Please submit your response to this request in electronic archival format as an amendment to ti... above NDAs. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

- For Study SP657, the within study bioanalytical report has been provided for assessing lacosamide and its metabolite in human saliva. The within study bioanalytical report for assessing the drug in human plasma could not be located. Please provide this. If already submitted, please indicate its location.

Thank you,  
Jackie Ware

\*\*\*\*\*  
Jacqueline H. Ware, Pharm.D., RAC  
Commander, United States Public Health Service  
Regulatory Project Manager Team Leader

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Center for Drug Evaluation and Research, FDA  
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e: jacqueline.ware@fda.hhs.gov

**Ware, Jacqueline H**

---

**From:** Sullivan, Matthew

**Sent:** Wednesday, February 06, 2008 1:44 PM

Blumberg Alan

**Cc:** DOttavio Misty; Ware, Jacqueline H

**Subject:** Feb 6 2008 - FDA Request for Information - NDA 22-253, 22-254, /Lacosamide Tabs, Injection, b(4)

Alan -

Please see below another request for information from the DAARP review team:

The following request pertains to studies SP742, SP743, and SP768.

/ / / / /

b(4)

Thanks  
Matt

Matthew W. Sullivan, M.S.

Regulatory Project Manager

Division of Anesthesia, Analgesia

and Rheumatology Products

Food and Drug Administration

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matthew.sullivan@fda.hhs.gov

5/27/2008

**Ware, Jacqueline H**

---

**From:** Ware, Jacqueline H  
**Sent:** Thursday, January 31, 2008 3:36 PM  
'Blumberg Alan'; 'Dottavio Misty'  
Sullivan, Matthew; Ware, Jacqueline H  
**subject:** RE: FDA Request for Information #2 on 1/31/08 - NDA 22-253, 22-254. /Lacosamide Tabs, Injection.

b(4)

Dear Alan,  
In my below message, I forgot to include a response date. As such, we ask that Schwarz respond to these requests by February 19, 2008.

Thanks,  
Jackie

\*\*\*\*\*

Jacqueline H. Ware, Pharm.D., RAC  
Commander, United States Public Health Service  
Regulatory Project Manager Team Leader

Division of Neurology Products  
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Silver Spring, MD 20993-0002

phone: 301-796-1160  
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---

**From:** Ware, Jacqueline H  
**Sent:** Thursday, January 31, 2008 2:55 PM  
**To:** 'Blumberg Alan'; 'Dottavio Misty'  
**Cc:** Ware, Jacqueline H; Sullivan, Matthew  
**Subject:** FDA Request for Information #2 on 1/31/08 - NDA 22-253, 22-254, ,Lacosamide Tabs, Injection

Dear Alan,  
Below are several requests from DNP's clinical team related to their ongoing review of the lacosamide applications. Please submit your responses to these requests in electronic archival format as an amendment to the above NDAs. It is acceptable for you to email your responses to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

b(4)

1. The epilepsy placebo-controlled safety pool (EP Pool S1) includes 364 patients randomized to placebo. Tables EP 6.47.1 (Incidence of common treatment emergent adverse events [TEAEs] resulting in discontinuation in EP pool S1 by dose at onset) and EP 6.49.1 of the ISS (Incidence of TAEs during the treatment phase by dose at onset in population Pool S1), show 781 patients receiving placebo. Please clarify.

2. The number of AEs in the "LCM total" group in table 6.47.1 of the ISS (Incidence of common TEAEs resulting in early discontinuation from the treatment phase in population Pool S1 by dose at onset) do not match some of the numbers in EP.6.29.1 of the ISS (Incidence of TEAEs resulting in early discontinuation from the treatment phase in population Pool S1 by randomized dose). For instance, in table 6.29.1, there are 9 patients who underwent drug discontinuation in the "Investigations" SOC in the "LCM total" column. However, table 6.47.1 only lists two

discontinuations due to Investigations in this population, one at the 100 mg/d dose and one at the 200 mg/day dose. Please clarify this discrepancy.

3. Please submit a summary table of Serious TAEs during treatment phase by dose at onset in EP Pools S1 and S2 or direct the reviewer to the exact location in the submission where this information is located.

4. Please clarify whether AEs that occurred within 30 days after the last dose of study medication were included in the analyses of the epilepsy studies. If so, in which pool and study phase?

Thank you,  
Jackie Ware

\*\*\*\*\*

Jacqueline H. Ware, Pharm.D., RAC  
Commander, United States Public Health Service  
Regulatory Project Manager Team Leader

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**Ware, Jacqueline H**

---

**From:** Sullivan, Matthew  
**Sent:** Thursday, January 31, 2008 12:16 PM  
'Blumberg Alan'; 'DOttavio Misty'  
Ware, Jacqueline H  
**subject:** FDA Request for Information - NDA 22-253, 22-254, /Lacosamide Tabs, Injection, b(4)

Alan and Misty –

Please find below a request from DAARPs clinical review team:

For the Phase 3 efficacy trials in painful diabetic neuropathy, provide a new disposition dataset that includes the following variables:

USUBJID; STUDYID; SITEID; TRTGRP; TRTCAT; RS; FAS; CS; SS; ES; CTITR\_F; CMAIN\_F; CTRAN\_F; CTAPER\_F; COMPLETE;

The dataset should also contain:

- A variable indicating the reason for dropout (adverse event, lack of efficacy, lost to follow-up, patient request, etc.)
- A flag to indicate at which stage of the trial a patient prematurely discontinued (e.g. run-in, titration, maintenance, taper)
- A variable indicating the number of weeks on therapy at which each patient prematurely discontinued.

Note: for patient's listed as discontinuing due to "patient request," the comments in the CRF should be reviewed to determine whether the patients actually requested to stop the trial due to an adverse event or lack of efficacy. The reason for dropout should be recoded accordingly. Patients for whom the reason for dropout is revised should be flagged.

As with other requests, an advance response via email is desirable, as long as it is followed by an official submission of the exact information.

Thanks  
Matt

---  
Matthew W. Sullivan, M.S.  
Regulatory Project Manager  
Division of Anesthesia, Analgesia  
and Rheumatology Products  
Food and Drug Administration  
Phone 301-796-1245  
Fax 301-796-9722 / 9723  
matthew.sullivan@fda.hhs.gov

**Ware, Jacqueline H**

---

**From:** Ware, Jacqueline H  
**Sent:** Tuesday, January 29, 2008 8:06 AM  
'Blumberg Alan'; 'DOttavio Misty'  
**Subject:** Ware, Jacqueline H; Sullivan, Matthew  
FDA Request for Information - NDA 22-253, 22-254 /Lacosamide Tabs, Injection, b(4)

Dear Alan,

Below is an additional request from DNP's clinical team related to their ongoing review of the lacosamide applications. Please submit your response to this request in electronic archival format as an amendment to the above NDAs. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

- Regarding item #4 of our January 14, 2008 request (included below for reference), please also submit a summary table of AE that led to dose reduction and/or discontinuation by SOC and PT in Pool EP S1 by dose at onset.

Thank you,  
Jackie Ware

\*\*\*\*\*  
Jacqueline H. Ware, Pharm.D., RAC  
Commander, United States Public Health Service  
Regulatory Project Manager Team Leader

Division of Neurology Products  
Center for Drug Evaluation and Research, FDA  
103 New Hampshire Avenue; WO22 Rm. 4348  
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phone: 301-796-1160  
fax: 301-796-9842  
email: jacqueline.ware@fda.hhs.gov

---

**From:** Ware, Jacqueline H  
**Sent:** Monday, January 14, 2008 3:49 PM  
**To:** 'Blumberg Alan'; 'DOttavio Misty'  
**Cc:** Ware, Jacqueline H; Sullivan, Matthew  
**Subject:** FDA Request for Information - NDA 22-253, 22-254, /Lacosamide Tabs, Injection, b(4)

Dear Alan,

Below are several requests from DNP's clinical team related to their ongoing review of the lacosamide applications. Please submit your responses to these requests in electronic archival format as an amendment to the above NDAs. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

1. Your description of the safety pools in page 17 of the Clinical Summary indicates that the EP S2 pool includes studies SP607 and SP615. However, the ISS dataset does not include patients from studies 607 and 615. Please clarify why. Also provide Lacosamide tablets exposure in patient years as presented in page 22 of the Clinical Summary, without these two studies.

2. You state that 1327 unique patients were exposed to the oral tablet formulation in the phase 2/3 epilepsy studies. It is unclear how many of these rolled over into extension/open label studies from the active and placebo groups in placebo-controlled studies, and how many were new patients. Please clarify.
3. Please provide line listings of patients with adverse events that led to dose reduction in the EF trials, including the dose at which the event occurred, the outcome (resolved or eventually led to discontinuation) and the final dose at the end of the study or time of withdrawal in the S1 and S2 pools.
4. Provide a summary table of adverse events that led to dose reduction and/or discontinuation by SOC and PT term (similar to tables EP 6.29.1 and EP 6.30.1 of the Clinical Summary of Safety, respectively, but with dose reduction + discontinuation instead of only discontinuations). If these analyses have already been submitted, please direct the reviewer to the exact location.
5. Please clarify how many patients discontinued because of consent withdrawal and had had an adverse event that required dose reduction.
6. We acknowledge that the disposition and AE datasets submitted with the original application include maximum treatment dose columns, but they provide a dose range, not the actual maximum dose received by each patient. Please provide the maximum dose taken at any time during the double blind and the OL periods for each patient in EP Pool 1 and 2.
7. Patient 756/754012317 was found dead at home. Please provide some supportive evidence to your assumption that this was a case of SUDEP. Otherwise, it could have been plain sudden death.
8. There are discrepancies between some of the ages listed in the summary table of deaths in pg. 120 of the Summary of Clinical Safety, and the ages stated in the narratives. Similarly, there are discrepancies between the days on treatment at the time of death listed in the summary table and those mentioned in the narratives. Please clarify and revise accordingly.
9. As per the summary table of deaths, patient 667/667012803 died on relative day 21 of LCM treatment. However, the narrative states that it is unclear whether the patient was taking medication or not during the last 3 weeks in the trial. A calculation of days on treatment based on the starting date in the disposition dataset suggests that the duration of treatment was either 68 days or 127 days. Please clarify where the day #21 came from.

Thank you,  
Jackie Ware

\*\*\*\*\*

*Jacqueline H. Ware, Pharm.D., CDR USPHS  
Senior Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA*

*10903 New Hampshire Avenue; WO22 Rm. 4348  
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**Ware, Jacqueline H**

**From:** Ware, Jacqueline H  
**Sent:** Tuesday, January 15, 2008 2:09 PM  
 'Blumberg Alan'; 'Dottavio Misty'  
**Cc:** Ware, Jacqueline H; Sullivan, Matthew  
**Subject:** FDA Request for Information - NDA 22-253, 22-254, /Lacosamide Tabs, Injection, **b(4)**

Dear Alan,

Below are the responses from DNP's clinical team to your questions about our 1/14/08 information request.

- **Sponsor Question:** For number 1 (below), What do you mean by ISS dataset? Which dataset in particular?

***FDA Response:** We were referring to the ISS AE dataset. However, upon further review, We have realized that AE from these studies are in fact included in the AE dataset. Please disregard request #1.*

- **Sponsor Question:** For number 3 (below), What do you mean by end of the study for pool S2? We assume you mean the cut off date for the interim reports. Is this correct?

***FDA Response:** Yes.*

If further clarification is needed, please let me know.

Regards,

Jackie

\* /\*\*\*\*\*

Jacqueline H. Ware, Pharm.D., CDR USPHS  
 Senior Regulatory Project Manager  
 Division of Neurology Products  
 Center for Drug Evaluation and Research, FDA

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 fax: 301-796-9842  
 NEW email: jacqueline.ware@fda.hhs.gov

-----Original Message-----

**From:** Blumberg Alan  
**Sent:** Tuesday, January 15, 2008 11:30 AM  
**To:** 'Ware, Jacqueline H'  
**Cc:** Dottavio Misty  
**Subject:** RE: FDA Request for Information - NDA 22-253, 22-254, /Lacosamide Tabs, Injection,

Hi Jackie,

I know you are off-site today so do not expect a quick response to these clarifications on your requests.

For number 1 (below), What do you mean by ISS dataset? Which dataset in particular? We are also curious about why you are asking for lacosamide tablets exposure in patient years as presented in page 22 of the Clinical Summary, **without these two**

5/27/2008

**studies.**

For number 3 (below), What do you mean by end of the study for pool S2? We assume you mean the cut off date for the interim reports. Is this correct?

Thanks for your assistance and will speak to you about the European inspection tomorrow at 1:30 PM.

Thanks,  
Alan

-----Original Message-----

**From:** Ware, Jacqueline H [mailto:jacqueline.ware@fda.hhs.gov]

**Sent:** Monday, January 14, 2008 3:49 PM

**To:** Blumberg Alan; DOTTAVIO Misty

**Cc:** Ware, Jacqueline H; Sullivan, Matthew

**Subject:** FDA Request for Information - NDA 22-253, 22-254, Lacosamide Tabs, Injection,

Dear Alan,

Below are several requests from DNP's clinical team related to their ongoing review of the lacosamide applications. Please submit your responses to these requests in electronic archival format as an amendment to the above NDAs. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

1. Your description of the safety pools in page 17 of the Clinical Summary indicates that the EP S2 pool includes studies SP607 and SP615. However, the ISS dataset does not include patients from studies 607 and 615. Please clarify why. Also provide Lacosamide tablets exposure in patient years as presented in page 22 of the Clinical Summary, without these two studies.
2. You state that 1327 unique patients were exposed to the oral tablet formulation in the phase 2/3 epilepsy studies. It is unclear how many of these rolled over into extension/open label studies from the active and placebo groups in placebo-controlled studies, and how many were new patients. Please clarify.
3. Please provide line listings of patients with adverse events that led to dose reduction in the EP trials, incl the dose at which the event occurred, the outcome (resolved or eventually led to discontinuation) and the final dose at the end of the study or time of withdrawal in the S1 and S2 pools.
4. Provide a summary table of adverse events that led to dose reduction and/or discontinuation by SOC and PT term (similar to tables EP 6.29.1 and EP 6.30.1 of the Clinical Summary of Safety, respectively, but with dose reduction + discontinuation instead of only discontinuations). If these analyses have already been submitted, please direct the reviewer to the exact location.
5. Please clarify how many patients discontinued because of consent withdrawal and had had an adverse event that required dose reduction.
6. We acknowledge that the disposition and AE datasets submitted with the original application include maximum treatment dose columns, but they provide a dose range, not the actual maximum dose received by each patient. Please provide the maximum dose taken at any time during the double blind and the OL periods for each patient in EP Pool 1 and 2.
7. Patient 756/754012317 was found dead at home. Please provide some supportive evidence to your assumption that this was a case of SUDEP. Otherwise, it could have been plain sudden death.
8. There are discrepancies between some of the ages listed in the summary table of deaths in pg. 120 of the Summary of Clinical Safety, and the ages stated in the narratives. Similarly, there are discrepancies between the days on treatment at the time of death listed in the summary table and those mentioned in the narratives. Please clarify and revise accordingly.
9. As per the summary table of deaths, patient 667/667012803 died on relative day 21 of LCM treatment. However, the narrative states that it is unclear whether the patient was taking medication or not during the last

b(4)

weeks in the trial. A calculation of days on treatment based on the starting date in the disposition dataset suggests that the duration of treatment was either 68 days or 127 days. Please clarify where the day #21 came from.

Thank you,  
Jackie Ware

\*\*\*\*\*

*Jacqueline H. Ware, Pharm.D., CDR USPHS  
Senior Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA*

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---

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Mail P.O. Box 110167 - Research Triangle Park - NC 27709 - USA

Via Courier 8010 Arco Corporate Drive - Suite 100 - Raleigh - NC 27617 - USA

Phone +1 919 767 2555 - Fax +1 919 767 2570 - E-mail [info@schwarzpharma.com](mailto:info@schwarzpharma.com)

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ar no liability for any damage caused by any virus transmitted by this electronic mail. (Ref: #\*BI1107)

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**Ware, Jacqueline H**

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**From:** Ware, Jacqueline H  
**Sent:** Monday, January 07, 2008 10:58 AM  
'Blumberg Alan'; 'Dottavio Misty'  
Ware, Jacqueline H; Sullivan, Matthew  
**Subject:** FDA Request for Information - NDA 22-253, 22-254, \_\_\_\_\_ #Lacosamide Tabs, Injection, \_\_\_\_\_

b(4)

Dear Alan,

Below is a request from DNP's clinical and statistical team related to their ongoing review of the lacosamide applications. Please submit your response to this request in electronic archival format as an amendment to the above NDAs. It is acceptable for you to email your response to me in advance of a formal, archival submission as long as both communications (email & archive) contain identical information.

- Please provide a single adverse events dataset and a single disposition dataset for all placebo-controlled studies with lacosamide (excluding the open-label phase, for both indications).

Thank you,  
Jackie Ware

\*\*\*\*\*

*Jacqueline H. Ware, Pharm.D., CDR USPHS  
Senior Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA*

*10903 New Hampshire Avenue; WO22 Rm. 4348  
Silver Spring, MD 20993-0002*

*phone: 301-796-1160  
fax: 301-796-9842  
NEW email: jacqueline.ware@fda.hhs.gov*

**Ware, Jacqueline H**

---

**From:** Ware, Jacqueline H  
**Sent:** Thursday, January 03, 2008 8:07 PM  
**To:** Grant, Stephen  
**Cc:** Kozeli, Devi; Ware, Jacqueline H; Sullivan, Matthew  
**Subject:** FW: DFS Email - N \_\_\_\_\_ 28-Sep-2007 - Forms

b(4)

Hi Steve,

Please see the below specific request from DAARP regarding the cardiology consult sent for lacosamide. Note: this drug is under review in 2 divisions - DNP for epilepsy and DAARP for diabetic peripheral neuropathy. However, all the data resides in 1 NDA (22-253). If you'd like for me to resend the NDA electronic link, please just let me know.

I will send an amended consult with this additional request.

Thanks,  
Jackie

-----Original Message-----

**From:** Kashoki, Mwango  
**Sent:** Thursday, January 03, 2008 4:08 PM  
**To:** Ware, Jacqueline H; Hershkowitz, Norman; Villalba, Lourdes; Yasuda, Sally  
**Cc:** Sullivan, Matthew; Hertz, Sharon H; Pokrovnichka, Anjelina  
**Subject:** RE: DFS Email - N \_\_\_\_\_ 28-Sep-2007 - Forms

b(4)

Jackie -

We would also like Cardio-Renal to evaluate the cardiac-related adverse event data. Specifically, we would like a consult sent with the following question:

We note the previous consults from DCRP regarding the effects on lacosamide on cardiac conduction. In the safety database for lacosamide, there are multiple reports of cardiac-related events, including arrhythmias (bradycardias and tachycardias), myocardial infarction/cardiac arrest, and syncope. The safety database includes patients with diabetes. Please review the adverse event data and comment on whether or not, in the context of a background of risk factors for cardiac disease, treatment with lacosamide is associated with a greater risk of cardiac events.

Thanks,

Mwango

-----Original Message-----

**From:** Ware, Jacqueline H  
**Sent:** Wednesday, January 02, 2008 10:37 AM  
**To:** Hershkowitz, Norman; Kashoki, Mwango; Villalba, Lourdes; Yasuda, Sally; Pokrovnichka, Anjelina  
**Cc:** Sullivan, Matthew; Hertz, Sharon H  
**Subject:** FW: DFS Email - N \_\_\_\_\_ 28-Sep-2007 - Forms

b(4)

Hi folks,

Do you all have any other specific cardiac safety concerns for lacosamide other than effects on cardiac conduction and QTc intervals (which is what was identified on the consult request)? I'm trying to respond to the cardio-renal reviewer's request (see below).

Thanks,  
Jackie

-----Original Message-----

**From:** Grant, Stephen

Sent: Wednesday, January 02, 2008 10:31 AM  
To: Ware, Jacqueline H  
Cc: Kozeli, Devi  
Subject: RE: DFS Email - N \_\_\_\_\_ 28-Sep-2007 - Forms

b(4)

Hi Jackie...I see this product has had numerous DCRP consults. The QT-IRT has already provided a consult and I have nothing further to add. Would you please let me know what specific concern your reviewers have about the cardiovascular safety of this drug.

Thanks!  
Steve Grant

-----Original Message-----

From: Kozeli, Devi  
Sent: Wednesday, 02 January, 2008 10:25  
To: Ware, Jacqueline H  
Cc: Grant, Stephen; Kozeli, Devi  
Subject: FW: DFS Email - N ' \_\_\_\_\_ 28-Sep-2007 - Forms

b(4)

Hi Jackie,

The assigned review for this consult request is Dr. Stephen Grant. Please contact him with any additional information or questions.

Thank you,

Devi Kozeli  
Regulatory Project Manager  
Assistant to the Division Director  
QT Interdisciplinary Review Team  
Division of Cardiovascular and Renal Products Office of Drug Evaluation I Office of New  
Drugs Center of Drug Evaluation and Research U.S. Food and Drug Administration  
10903 New Hampshire Avenue, WO-22, Suite 4183 Silver Spring, MD 20993-0002

Phone: (301) 796-1128  
Fax: (301) 796-9841  
Note new email address: devi.kozeli@fda.hhs.gov

-----Original Message-----

From: cderdocadmin@cder.fda.gov [mailto:cderdocadmin@cder.fda.gov]  
Sent: Thursday, December 27, 2007 3:21 PM  
To: Kozeli, Devi; Fromm, Edward J; Villalba, Lourdes; Yasuda, Sally; Hershkovitz, Norman;  
Kashoki, Mwango; Pokrovnichka, Anjelina; Sullivan, Matthew; Ware, Jacqueline H; Hertz,  
Sharon H  
Subject: DFS Email - N \_\_\_\_\_ , 28-Sep-2007 - Forms

b(4)

Document room update the following:

|                            | Decision Date | Decision Code |
|----------------------------|---------------|---------------|
| N _____                    | _____         | :             |
| N _____                    | _____         | : b(4)        |
| N 022254 N 000 28-Sep-2007 | 27-Dec-2007   | :             |
| N 022253 N 000 28-Sep-2007 | 27-Dec-2007   | :             |

Document Type: Forms  
Form Group: CONSULT  
Form Name: General Consult Request  
Submission Description: DCRP consult request - cardiac safety

Author(s)/Discipline(s)

-----  
1. Jackie Ware, CSO

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Signer(s)

- 1. Jackie Ware  
Sent at request of Dr. Hershkowitz and Dr. Hertz  
27-Dec-2007

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Supervisory Signer(s)

- 1. Jackie Ware  
Sent at request of Dr. Hershkowitz and Dr. Hertz  
27-Dec-2007

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ON ORIGINAL**

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this page is the manifestation of the electronic signature.**  
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/s/

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Jackie Ware  
1/10/2008 05:08:45 PM

## DSI CONSULT: Request for Clinical Inspections

**Date:** January 2, 2008

**To:** Leslie Ball  
(Acting) Director, Division of Scientific Investigations, HFD-45  
  
Constance Lewin  
Branch Chief, Good Clinical Practice Branch I, HFD-46

**Through:** Russell Katz, MD, Director  
Division of Neurology Products, HFD-120  
  
Norman Hershkowitz, MD, (Acting) Neurology Team Leader,  
Division of Neurology Products, HFD-120

**From:** Jackie Ware, Regulatory Health Project Manager  
Division of Neurology Products, HFD-120

**Subject:** **Request for Clinical Site Inspections – epilepsy indication**  
NDA 22-253/Vimpat (Lacosamide) Tablets  
Applicant: Schwarz Biosciences, Inc.  
Contact: Alan Blumberg, PhD, 919-767-3513

### I. General Information

Drug: Vimpat (lacosamide) Tablets  
NME: Yes  
Standard or Priority: Standard  
Study Population < 18 years of age: No; studies are in adults  
Pediatric exclusivity: No

PDUFA: July 28, 2008  
Inspection Summary Goal Date: May 28, 2008

### II. Background Information

NDA 22-253 is a new drug marketing application. Lacosamide is a new chemical entity being developed as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 16 years and older and for the management of neuropathic pain associated with diabetic peripheral neuropathy. — different pharmaceutical formulations containing lacosamide are proposed to be marketed:

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

b(4)

b(4)

The recommended maintenance dose of lacosamide is 200 — mg per day, administered in two equally divided doses.

In the 3 adequate and well-controlled trials (SP667, SP754, and SP755), LCM 200mg/day (SP667 and SP755 only), 400mg/day (SP667, SP754, and SP755), and 600mg/day (SP667 and SP754 only) were investigated to determine LCM’s efficacy and safety as an adjunctive therapy in subjects with partial-onset seizures with or without secondary generalization. Trials SP667, SP754, and SP755 had similar trial designs and endpoints, are considered the primary efficacy trials in this submission, and met the definition of an adequate and well-controlled trial for registration. SP667 was conducted in the United States (US) and Europe, SP754 was conducted in the US, and SP755 was conducted in Europe and Australia.

The following table presents the trial numbers, trial design, dosing, number of subjects randomized to receive LCM and placebo, and duration of treatment for subjects with partial-onset seizures exposed to trial medication in the double-blind, placebo-controlled Phase 2/3 trials.

**Adequate and well-controlled trials of LCM as adjunctive therapy in adults with partial-onset seizures – primary efficacy trials**

| Trial number/clinical development phase/trial design                                                                                                                  | Number of subjects randomized to receive LCM <sup>a</sup>        | Number of subjects randomized to receive placebo <sup>a</sup> | Maximum duration of treatment <sup>b</sup> |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------|---------------------------------------------------------------|--------------------------------------------|
| SP667/Phase 2/multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of LCM (200, 400, and 600mg/day) | 200mg/day: 107<br>400mg/day: 108<br>600mg/day: 106               | 97                                                            | 21 weeks                                   |
| SP754/Phase 3/multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of LCM (400 and 600mg/day)       | 400mg/day: 204<br>600mg/day: 97                                  | 104                                                           | 21 weeks                                   |
| SP755/Phase 3/multicenter, double-blind, randomized, placebo-controlled, parallel-group trial to investigate the efficacy and safety of LCM (200 and 400mg/day)       | 200mg/day: 163<br>400mg/day: 159                                 | 163                                                           | 18 weeks                                   |
| <b>Total</b>                                                                                                                                                          | 200mg/day: 270<br>400mg/day: 471<br>600mg/day: 203<br>Total: 944 | 364                                                           | NA                                         |

LCM=lacosamide

a Because of audit findings suggesting noncompliance with the SP667 protocol, all 3 randomized and treated subjects at Site 12 were removed from the Safety Set (SS). As a result, 418 subjects were included in the SS.

b All 3 trials had a 12-week Maintenance Phase.

Data source: 5.3.5.1.1 EP: SP667 Table 3; 5.3.5.1.2 EP: SP754 Table 2.3.1; 5.3.5.1.3 EP: SP755 Table 2.3.1

**III. Protocol/Site Identification**

| Site # (Name,Address, Phone number, email, fax#)                                                                                                                          | Protocol #     | Number of Subjects             | Indication |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|--------------------------------|------------|
| Michael Sperling MD<br>Thomas Jefferson University<br>Hospital<br>Jefferson Comprehensive<br>Epilepsy<br>Center<br>900 Walnut Street, Suite 200<br>Philadelphia, PA 19107 |                | Enrolled 22 with<br>ITT of 18. | Epilepsy   |
| / /                                                                                                                                                                       | Study<br>SP754 | / /                            | Epilepsy   |
| Krauss, Gregory, MD<br>Johns Hopkins Hospital<br>600 N Wolfe Street<br>Meyer 2-147<br>Baltimore, MD 21287-7247                                                            |                | Enrolled 17 with<br>ITT of 15. | Epilepsy   |
| / /                                                                                                                                                                       |                | / /                            | Epilepsy   |
| Dr. Zdravka Poljakovic<br>University Hospital Center<br>Zagreb<br>Department of Neurology<br>Ctr. For Epilpesy<br>Kispaticeva 12<br>10000 Zagreb<br>Croatia               | Study<br>SP755 | Enrolled 20, 18 in<br>ITT      | Epilepsy   |
| / /                                                                                                                                                                       |                | / /                            | Epilepsy   |

b(5)

b(5)

b(5)

b(5)

| Site # (Name, Address, Phone number, email, fax#)                                                                                                     | Protocol #     | Number of Subjects        | Indication |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|---------------------------|------------|
| Dr Sanja Hajnsek<br>University Hospital Center<br>Zagreb<br>Department of Neurology<br>Ctr. For Epilpesy<br>Kispaticeva 12<br>10000 Zagreb<br>Croatia | Study<br>SP755 | Enrolled 16, 16 in<br>ITT | Epilepsy   |

**IV. Site Selection/Rationale**

- Sites in the above table present this division’s recommendations for inspection. Only two sites need to be inspected for each study. One study is completely domestic and one completely foreign, meaning two domestic and two foreign sites will require inspection. More than two sites are presented above so as to give DSI some discretion in the choice of site for inspection which can be based upon their convenience.
- As no sites obviously stood out based upon effect size or differences between recruitment and randomization, recommendations are principally determined ITT population size

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

**International Inspections:**

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify): **See bulleted comments above.**

Page 5-NDA 22-253 Request for Clinical Inspections – epilepsy indication

Should you require any additional information, please contact Jackie Ware, RPM at Ph: 301-796-1160 or Norman Hershkowitz, Medical Officer at Ph: 301-796-1088.

Concurrence: (as needed)

       X      Medical Team Leader (Norman Hershkowitz)  
       X      Medical Reviewer (Norman Hershkowitz)  
       X      Director (Russell Katz) (for foreign inspection requests only)

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/s/

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Jackie Ware

1/2/2008 02:23:56 PM

Sent at request of Drs. Katz and Hershkowitz

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |                                                                                                                                                                                         |                                                                                                |                                        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|----------------------------------------|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                    | REQUEST FOR CONSULTATION                                                                                                                                                                |                                                                                                |                                        |
| TO (Division/Office):<br>Division of Cardio-Renal Products                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                    | FROM:<br>Division of Neurology Products (DNP) and Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)                                                                  |                                                                                                |                                        |
| DATE<br>January 10, 2008<br>(original consult dated December 27, 2007)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | IND NO.                            | NDA NO.<br>22-253, 22-254,                                                                                                                                                              | TYPE OF DOCUMENT<br>Amended consult request -<br>New original NME NDAs                         | DATE OF DOCUMENT<br>September 28, 2007 |
| NAME OF DRUG<br>Vimpat (lacosamide) Tablets,<br>Injection, _____                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | PRIORITY CONSIDERATION<br>Standard | CLASSIFICATION OF DRUG<br>1                                                                                                                                                             | DESIRED COMPLETION DATE<br>May 1, 2008 - (due to GRMP pilot)<br>PDUFA goal date: July 28, 2008 |                                        |
| NAME OF FIRM: Schwarz Pharma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                    |                                                                                                                                                                                         |                                                                                                |                                        |
| REASON FOR REQUEST                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                    |                                                                                                                                                                                         |                                                                                                |                                        |
| I. GENERAL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                    |                                                                                                                                                                                         |                                                                                                |                                        |
| <input type="checkbox"/> NEW PROTOCOL<br><input type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE/ADDITION<br><input type="checkbox"/> MEETING PLANNED BY                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                    |                                                                                                                                                                                         |                                                                                                |                                        |
| <input type="checkbox"/> PRE-NDA MEETING<br><input type="checkbox"/> END OF PHASE II MEETING<br><input type="checkbox"/> RESUBMISSION<br><input checked="" type="checkbox"/> SAFETY/EFFICACY<br><input type="checkbox"/> PAPER NDA<br><input type="checkbox"/> CONTROL SUPPLEMENT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                    |                                                                                                                                                                                         |                                                                                                |                                        |
| <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW):                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                    |                                                                                                                                                                                         |                                                                                                |                                        |
| II. BIOMETRICS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                    |                                                                                                                                                                                         |                                                                                                |                                        |
| STATISTICAL EVALUATION BRANCH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                    | STATISTICAL APPLICATION BRANCH                                                                                                                                                          |                                                                                                |                                        |
| <input checked="" type="checkbox"/> TYPE A OR B NDA REVIEW<br><input type="checkbox"/> END OF PHASE II MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW):                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                    | <input type="checkbox"/> CHEMISTRY REVIEW<br><input type="checkbox"/> PHARMACOLOGY<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER (SPECIFY BELOW):      |                                                                                                |                                        |
| III. BIOPHARMACEUTICS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                    |                                                                                                                                                                                         |                                                                                                |                                        |
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE IV STUDIES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                    | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST                            |                                                                                                |                                        |
| IV. DRUG EXPERIENCE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                    |                                                                                                                                                                                         |                                                                                                |                                        |
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                    | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS |                                                                                                |                                        |
| V. SCIENTIFIC INVESTIGATIONS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                    |                                                                                                                                                                                         |                                                                                                |                                        |
| <input type="checkbox"/> CLINICAL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                    | <input type="checkbox"/> PRECLINICAL                                                                                                                                                    |                                                                                                |                                        |
| <p><b>REQUEST:</b> NDAs 22-253/Lacosamide Tablets (administratively split to include NDA _____ has been submitted for review to DAARP and DNP (electronic link \\CDSESUB1\EVSPROD\NDA022253\022253.ENX) for the treatment of neuropathic pain and epilepsy. Because both Divisions have concerns about the cardiac safety of lacosamide, we ask that DCRP <b>please review the cardiac safety report (section 5.3.5.3 of the eCTD) and any other relevant information in the NDA, and comment on the effects of lacosamide on cardiac conduction and QTc intervals. See page 2 for an additional specific request.</b></p> <p><b>Background:</b> DCRP has provided previous consult responses regarding lacosamide [previously named harkoseride] on 10/30/02 and 3/16/04 _____ ) and on 7/25/07 (IND 57,939).</p> |                                    |                                                                                                                                                                                         |                                                                                                |                                        |
| SIGNATURE OF REQUESTER<br>Jackie Ware, Pharm.D., Regulatory Project Manager                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                    | METHOD OF DELIVERY (Check one)<br><input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DFS & Email                                                                         |                                                                                                |                                        |
| SIGNATURE OF RECEIVER                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                    | SIGNATURE OF DELIVERER                                                                                                                                                                  |                                                                                                |                                        |

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**DSI CONSULT**  
**Request for Biopharmaceutical Inspections**

**DATE:** December 27, 2007

**TO:** CT Viswanathan, Branch Chief  
 Good Laboratory Practice and Bioequivalence Branch  
 Division of Scientific Investigations, HFD-48

**THROUGH:** Russell Katz, Director, Division of Neurology Products

**FROM:** Jackie Ware, Regulatory Project Manager, Division of Neurology Products

**SUBJECT:** Request for Biopharmaceutical Inspections  
 NDA 22-254  
 Vimpat (lacosamide) Injection  
 Schwarz Biosciences, Inc.

**Study/Site Identification:**

DNP is requesting inspection of the following studies/sites pivotal to approval:

| Study #                                                          | Clinical Site (name, address, phone, fax, contact person, if available)                                                                                    | Analytical Site (name, address, phone, fax, contact person, if available)                                                                                                              |
|------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| SP658<br>(BE study for 30 and 60 minute infusions versus tablet) | Investigators: _____<br>Sub-Investigators: _____<br><br>Trial site: _____<br><br>Biostatistical analyses were performed by the Trial Statistician of _____ | Analysis of bioanalytical samples was carried out in the Bioanalytics Department of the sponsor<br>Dr. _____<br>Schwarz Biosciences, GmbH<br>Alfred-Nobel-Straße 10<br>D-40789 Monheim |
| SP645                                                            | Investigators: _____                                                                                                                                       |                                                                                                                                                                                        |

b(4)

|                                                         |                                                                                                                                                                                                                                       |                                     |
|---------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
| <p>(BE study for 15 minute infusion versus tablets)</p> | <p>Sub-Investigators: _____<br/>_____<br/>_____</p> <p>Trial site(s): _____<br/>/ /</p> <p>Statistical analysis was planned to be performed by _____ according to the Trial Protocol but was performed by the CRO _____<br/>/ / /</p> | <p>b(4)</p> <p>b(4)</p> <p>b(4)</p> |
|---------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|

**International Inspections:**

(Please note: International inspections require sign-off by the ORM Division Director or DPE Division Director.)

We have requested an international inspection because:

There is a lack of domestic data that solely supports approval;

Other (please explain):

**Goal Date for Completion:**

We request that the inspections be conducted and the Inspection Summary Results be provided by **May 28, 2008**. We intend to issue an action letter on this application by July 28, 2008.

Should you require any additional information, please contact Jackie Ware, Regulatory Project Manager, at 301-796-1160 or [jacqueline.ware@fda.hhs.gov](mailto:jacqueline.ware@fda.hhs.gov)

Concurrence:

Veneeta Tandon, Ph.D., Clinical Pharmacology Reviewer

Ramana Uppoor, Ph.D., Clinical Pharmacology Team Leader

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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/

-----  
Jackie Ware  
12/27/2007 03:44:15 PM

**REQUEST FOR CONSULTATION**

TO (Division/Office):  
**Division of Cardio-Renal Products**

FROM:  
**Division of Neurology Products (DNP) and Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)**

DATE  
December 27, 2007

IND NO.

NDA NO.  
22-253, 22-254,

TYPE OF DOCUMENT  
New original NME NDAs

DATE OF DOCUMENT  
September 28, 2007

NAME OF DRUG  
Vimpat (lacosamide) Tablets,  
Injection

PRIORITY CONSIDERATION  
Standard

CLASSIFICATION OF DRUG  
1

DESIRED COMPLETION DATE  
May 1, 2008 - (due to GRMP pilot)  
PDUFA goal date: July 28, 2008

NAME OF FIRM: Schwarz Pharma

**REASON FOR REQUEST**

**I. GENERAL**

- |                                                        |                                                     |                                                        |
|--------------------------------------------------------|-----------------------------------------------------|--------------------------------------------------------|
| <input type="checkbox"/> NEW PROTOCOL                  | <input type="checkbox"/> PRE-NDA MEETING            | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT               | <input type="checkbox"/> END OF PHASE II MEETING    | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE            | <input type="checkbox"/> RESUBMISSION               | <input type="checkbox"/> LABELING REVISION             |
| <input type="checkbox"/> DRUG ADVERTISING              | <input checked="" type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT       | <input type="checkbox"/> PAPER NDA                  | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT         | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY            |                                                     |                                                        |

**II. BIOMETRICS**

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW  
 END OF PHASE II MEETING  
 CONTROLLED STUDIES  
 PROTOCOL REVIEW  
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW  
 PHARMACOLOGY  
 BIOPHARMACEUTICS  
 OTHER (SPECIFY BELOW):

**III. BIOPHARMACEUTICS**

- DISSOLUTION  
 BIOAVAILABILITY STUDIES  
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE  
 PROTOCOL-BIOPHARMACEUTICS  
 IN-VIVO WAIVER REQUEST

**IV. DRUG EXPERIENCE**

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL  
 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES  
 CASE REPORTS OF SPECIFIC REACTIONS (List below)  
 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY  
 SUMMARY OF ADVERSE EXPERIENCE  
 POISON RISK ANALYSIS

**V. SCIENTIFIC INVESTIGATIONS**

CLINICAL

PRECLINICAL

**REQUEST:** NDAs 22-253/Lacosamide Tablets (administratively split to include NDA \_\_\_\_\_ ) has been submitted for review to DAARP and DNP (electronic link \\CDSESUB1\EVSPROD\NDA022253\022253.ENX) for the treatment of neuropathic pain and epilepsy. Because both Divisions have concerns about the cardiac safety of lacosamide, we ask that DCRP **please review the cardiac safety report (section 5.3.5.3 of the eCTD) and any other relevant information in the NDA, and comment on the effects of lacosamide on cardiac conduction and QTc intervals.**

**Background:** DCRP has provided previous consult responses regarding lacosamide [previously named harkoseride] on 10/30/02 and 3/16/04 \_\_\_\_\_ and on 7/25/07 (IND 57,939).

SIGNATURE OF REQUESTER  
Jackie Ware, Pharm.D., Regulatory Project Manager

b(4)

METHOD OF DELIVERY (Check one)

MAIL

DFS & Email

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

b(4)

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/s/

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Jackie Ware  
12/27/2007 03:20:41 PM  
Sent at request of Dr. Hershkowitz and Dr. Hertz

10



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-253

NDA 22-254

b(4)

Schwarz Biosciences, Inc.  
Attention: Alan Blumberg  
Sr. Director, US Regulatory Affairs  
P.O. Box 110167  
Research Triangle Park, NC 27709

Dear Mr. Blumberg:

Please refer to your new drug application (NDA) dated September 28, 2007, received September 28, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Lacosamide Tablets, Lacosamide Injection \_\_\_\_\_ b(4)

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is July 28, 2008.

During our filing review of your application, we have identified the following potential review issues:

**Clinical Pharmacology**

1. The bioanalytical report for Study SP645 could not be located within the study report. The bioanalytical tests were performed at \_\_\_\_\_, but the report is not included. Please submit this information soon (e.g., within 2 weeks). b(4)
2. The PK-PD modeling report for epilepsy is not under the Folder 5.3.4 (reports for human PD studies). It is also not present in the tabular listing of all studies. It was found in the Folder 5.3.5 (reports for efficacy and safety studies). Please verify that all studies/ Modeling reports submitted to the NDA are listed under the Tabular listing of studies.

**Product Quality**

3. The formulation of the 50 mg lacosamide clinical tablets is not provided in the original NDA (22-253). Provide the quantitative unit composition for all strengths of each formulation that was used in clinical studies to support this application.

b(4)

4. For lacosamide tablets, the container closure documentation for PVC/PVDC-Aluminum blisters and HDPE bottles is provided in the application. Clarify whether the blisters will be used for commercial distribution or professional samples and provide the appropriate container labels for review.
5. For lacosamide injection (NDA 22-254), with respect to product labeling, we recommend that \_\_\_\_\_

b(4)

**Clinical**

We have the following requests for additional information that will facilitate our review.

6. Please provide summary tables of serious adverse events in placebo-controlled studies for both epilepsy and diabetic neuropathic pain together, by MedDRA SOC and by dose. The table should be similar to the table below, but include data for *both* S1 pools (epilepsy and diabetic neuropathic pain) considered together.

Treatment-emergent SAEs during the Treatment Phase in subjects with partial-onset seizures (EP Pool S1)

| MedDRA* SOC/preferred term                  | Placebo<br>N=364 | LCM<br>200mg/day<br>N=270 | LCM<br>400mg/day<br>N=471 | LCM<br>600mg/day<br>N=203 | LCM<br>Total<br>N=944 |
|---------------------------------------------|------------------|---------------------------|---------------------------|---------------------------|-----------------------|
|                                             | n (%)            |                           |                           |                           |                       |
| <b>Blood and lymphatic system disorders</b> |                  |                           |                           |                           |                       |
| Thrombocytopenia                            | 0                | 0                         | 1 (0.2)                   | 0                         | 1 (0.1)               |
| <b>Cardiac disorders</b>                    |                  |                           |                           |                           |                       |
| Sinus bradycardia                           | 0                | 0                         | 1 (0.2)                   | 0                         | 1 (0.1)               |
| Bradycardia                                 | 1 (0.3)          | 0                         | 0                         | 0                         | 0                     |

6. Please also provide summary tables of discontinuations due to adverse events in placebo-controlled studies for both epilepsy and diabetic neuropathic pain together, by MedDRA SOC and by dose.
7. Please provide a joint Adverse Event dataset for placebo-controlled studies in both epilepsy and diabetic neuropathic pain.
8. Please clarify whether the MedDRA version used in this application is Version 9.1.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

b(4)

**Pediatrics**

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for these applications for pediatric patients who are less than ← years old.

b(4)

If you have any questions, call Jacqueline H. Ware, Pharm.D., RAC, Senior Regulatory Project Manager, at (301) 796-1160.

Sincerely,

*{See appended electronic signature page}*

Russell Katz, M.D.  
Director  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Russell Katz  
12/10/2007 04:54:24 PM

7

1 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

       Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

**Ware, Jacqueline H**

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**From:** Uppoor, Ramana S  
**Sent:** Wednesday, November 28, 2007 10:18 AM  
Ware, Jacqueline H  
Tandon, Veneeta  
**Subject:** Lacosamide DSI consult

Jackie,

Just a reminder for sending a DSI consult for the Lacosamide IV BE study. I don't know whether Veneeta sent you any information following the filing meeting or not. Thanks!

***Ramana S. Uppoor, Ph.D.***

Deputy Director (& Clinical Pharmacology Team Leader, Neurology Drug Products)  
Division of Clinical Pharmacology-I  
OCP, CDER, FDA  
HFD-860, rm 3626, White Oak bldg 21  
10903 New Hampshire Avenue  
Silver Spring, Maryland 20993-0002  
Phone: 301-796-1619; Fax: 301-796-9736  
ramana.uppoor@fda.hhs.gov

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**From:** Ware, Jacqueline H  
**Sent:** Wednesday, November 28, 2007 8:46 AM  
**To:** CDER-DNDP-CSO'S; CDER-DNDP-SUPERVISORS  
**Subject:** Working at home today (11/28)

Please email if needed. I will be checking periodically.  
Thanks,  
Jackie

\*\*\*\*\*  
*Jacqueline H. Ware, Pharm.D., CDR USPHS  
Senior Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA*

*10903 New Hampshire Avenue; WO22 Rm. 4348  
Silver Spring, MD 20993-0002*

*phone: 301-796-1160  
fax: 301-796-9842  
NEW email: jacqueline.ware@fda.hhs.gov*



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/s/

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|---------------------------------------|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION                                                                                                                                                                                                                                                  |                                                                              | <b>REQUEST FOR CONSULTATION</b>                                                                                                                                                 |                                         |                                       |
| TO (Office/Division): David Hussong/Jim McVey/Sylvia Gantt<br>NEW DRUG MICROBIOLOGY STAFF<br>OC/OO/CDER/OPS/NDMS - HFD-805                                                                                                                                                                                                                        |                                                                              | FROM (Name, Office/Division, and Phone Number of Requestor): Wendy Wilson PhD through Scott N. Goldie, Ph.D., Office of New Drug Quality Assessment, 301 796-2055               |                                         |                                       |
| DATE<br>November 20, 2007                                                                                                                                                                                                                                                                                                                         | IND NO.                                                                      | NDA NO.<br>22-254                                                                                                                                                               | TYPE OF DOCUMENT<br>Original NDA        | DATE OF DOCUMENT<br>28 September 2007 |
| NAME OF DRUG<br>Iacosamide                                                                                                                                                                                                                                                                                                                        | PRIORITY CONSIDERATION<br>Standard - GRMP<br>PILOT                           | CLASSIFICATION OF DRUG                                                                                                                                                          | DESIRED COMPLETION DATE<br>May 21, 2007 |                                       |
| NAME OF FIRM: Schwarz Biosciences                                                                                                                                                                                                                                                                                                                 |                                                                              |                                                                                                                                                                                 |                                         |                                       |
| <b>REASON FOR REQUEST</b>                                                                                                                                                                                                                                                                                                                         |                                                                              |                                                                                                                                                                                 |                                         |                                       |
| <b>I. GENERAL</b>                                                                                                                                                                                                                                                                                                                                 |                                                                              |                                                                                                                                                                                 |                                         |                                       |
| <input type="checkbox"/> NEW PROTOCOL                                                                                                                                                                                                                                                                                                             | <input type="checkbox"/> PRE-NDA MEETING                                     | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER                                                                                                                          |                                         |                                       |
| <input type="checkbox"/> PROGRESS REPORT                                                                                                                                                                                                                                                                                                          | <input type="checkbox"/> END-OF-PHASE 2a MEETING                             | <input type="checkbox"/> FINAL PRINTED LABELING                                                                                                                                 |                                         |                                       |
| <input type="checkbox"/> NEW CORRESPONDENCE                                                                                                                                                                                                                                                                                                       | <input type="checkbox"/> END-OF-PHASE 2 MEETING                              | <input type="checkbox"/> LABELING REVISION                                                                                                                                      |                                         |                                       |
| <input type="checkbox"/> DRUG ADVERTISING                                                                                                                                                                                                                                                                                                         | <input type="checkbox"/> RESUBMISSION                                        | <input checked="" type="checkbox"/> ORIGINAL NEW CORRESPONDENCE                                                                                                                 |                                         |                                       |
| <input type="checkbox"/> ADVERSE REACTION REPORT                                                                                                                                                                                                                                                                                                  | <input type="checkbox"/> SAFETY / EFFICACY                                   | <input type="checkbox"/> FORMULATIVE REVIEW                                                                                                                                     |                                         |                                       |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION                                                                                                                                                                                                                                                                                          | <input type="checkbox"/> PAPER NDA                                           | <input type="checkbox"/> OTHER (SPECIFY BELOW):                                                                                                                                 |                                         |                                       |
| <input type="checkbox"/> MEETING PLANNED BY                                                                                                                                                                                                                                                                                                       | <input type="checkbox"/> CONTROL SUPPLEMENT                                  |                                                                                                                                                                                 |                                         |                                       |
| <b>II. BIOMETRICS</b>                                                                                                                                                                                                                                                                                                                             |                                                                              |                                                                                                                                                                                 |                                         |                                       |
| <input type="checkbox"/> PRIORITY P NDA REVIEW                                                                                                                                                                                                                                                                                                    | <input type="checkbox"/> CHEMISTRY REVIEW                                    |                                                                                                                                                                                 |                                         |                                       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING                                                                                                                                                                                                                                                                                                   | <input type="checkbox"/> PHARMACOLOGY                                        |                                                                                                                                                                                 |                                         |                                       |
| <input type="checkbox"/> CONTROLLED STUDIES                                                                                                                                                                                                                                                                                                       | <input type="checkbox"/> BIOPHARMACEUTICS                                    |                                                                                                                                                                                 |                                         |                                       |
| <input type="checkbox"/> PROTOCOL REVIEW                                                                                                                                                                                                                                                                                                          | <input type="checkbox"/> OTHER (SPECIFY BELOW):                              |                                                                                                                                                                                 |                                         |                                       |
| <input type="checkbox"/> OTHER (SPECIFY BELOW):                                                                                                                                                                                                                                                                                                   |                                                                              |                                                                                                                                                                                 |                                         |                                       |
| <b>III. BIOPHARMACEUTICS</b>                                                                                                                                                                                                                                                                                                                      |                                                                              |                                                                                                                                                                                 |                                         |                                       |
| <input type="checkbox"/> DISSOLUTION                                                                                                                                                                                                                                                                                                              | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE                          |                                                                                                                                                                                 |                                         |                                       |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES                                                                                                                                                                                                                                                                                                  | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS                         |                                                                                                                                                                                 |                                         |                                       |
| <input type="checkbox"/> PHASE 4 STUDIES                                                                                                                                                                                                                                                                                                          | <input type="checkbox"/> IN-VIVO WAIVER REQUEST                              |                                                                                                                                                                                 |                                         |                                       |
| <b>IV. DRUG SAFETY</b>                                                                                                                                                                                                                                                                                                                            |                                                                              |                                                                                                                                                                                 |                                         |                                       |
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                                                                                                                                                                                                                                                                               | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |                                                                                                                                                                                 |                                         |                                       |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES                                                                                                                                                                                                                                                                | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |                                                                                                                                                                                 |                                         |                                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)                                                                                                                                                                                                                                                                          | <input type="checkbox"/> POISON RISK ANALYSIS                                |                                                                                                                                                                                 |                                         |                                       |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP                                                                                                                                                                                                                                                                        |                                                                              |                                                                                                                                                                                 |                                         |                                       |
| <b>V. SCIENTIFIC INVESTIGATIONS</b>                                                                                                                                                                                                                                                                                                               |                                                                              |                                                                                                                                                                                 |                                         |                                       |
| <input type="checkbox"/> CLINICAL                                                                                                                                                                                                                                                                                                                 | <input type="checkbox"/> NONCLINICAL                                         |                                                                                                                                                                                 |                                         |                                       |
| COMMENTS / SPECIAL INSTRUCTIONS: Microbiology review requested of new NDA application. THIS APPLICATION IS A GRMP PILOT APPLICATION. Injection dosage form. NDA 22-253 contains all microbiology information, and is cross referenced from NDA 22-254 Please direct questions to Wendy Wilson at 6-1651. Submission is in electronic form in EDR. |                                                                              |                                                                                                                                                                                 |                                         |                                       |
| SIGNATURE OF REQUESTOR<br>{See appended electronic signature page}                                                                                                                                                                                                                                                                                |                                                                              | METHOD OF DELIVERY (Check one)<br><input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND |                                         |                                       |
| PRINTED NAME AND SIGNATURE OF RECEIVER                                                                                                                                                                                                                                                                                                            |                                                                              | PRINTED NAME AND SIGNATURE OF DELIVERER                                                                                                                                         |                                         |                                       |

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Scott Goldie  
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|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION                                                                                                                                                                                                                                                                        |                                                                              | <b>REQUEST FOR CONSULTATION</b>                                                                                                                                                 |                                                                                                                                                                              |                                       |
| TO (Office/Division): David Hussong/Jim McVey/Sylvia Gantt<br>NEW DRUG MICROBIOLOGY STAFF<br>JC/OO/CDER/OPS/NDMS - HFD-805                                                                                                                                                                                                                                              |                                                                              |                                                                                                                                                                                 | FROM (Name, Office/Division, and Phone Number of Requestor): Prafull<br>Shiromani PhD through Scott N. Goldie, Ph.D., Office<br>of New Drug Quality Assessment, 301 796-2055 |                                       |
| DATE<br>November 20, 2007                                                                                                                                                                                                                                                                                                                                               | IND NO.                                                                      | NDA NO.<br>22-253 and —<br>—<br>b(4)                                                                                                                                            | TYPE OF DOCUMENT<br>Original NDA                                                                                                                                             | DATE OF DOCUMENT<br>28 September 2007 |
| NAME OF DRUG<br>Iacosamide                                                                                                                                                                                                                                                                                                                                              | PRIORITY CONSIDERATION<br>Standard - GRMP<br>PILOT                           | CLASSIFICATION OF DRUG                                                                                                                                                          | DESIRED COMPLETION DATE<br>May 21, 2007                                                                                                                                      |                                       |
| NAME OF FIRM: Schwarz Biosciences                                                                                                                                                                                                                                                                                                                                       |                                                                              |                                                                                                                                                                                 |                                                                                                                                                                              |                                       |
| <b>REASON FOR REQUEST</b>                                                                                                                                                                                                                                                                                                                                               |                                                                              |                                                                                                                                                                                 |                                                                                                                                                                              |                                       |
| <b>I. GENERAL</b>                                                                                                                                                                                                                                                                                                                                                       |                                                                              |                                                                                                                                                                                 |                                                                                                                                                                              |                                       |
| <input type="checkbox"/> NEW PROTOCOL                                                                                                                                                                                                                                                                                                                                   | <input type="checkbox"/> PRE-NDA MEETING                                     | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER                                                                                                                          |                                                                                                                                                                              |                                       |
| <input type="checkbox"/> PROGRESS REPORT                                                                                                                                                                                                                                                                                                                                | <input type="checkbox"/> END-OF-PHASE 2a MEETING                             | <input type="checkbox"/> FINAL PRINTED LABELING                                                                                                                                 |                                                                                                                                                                              |                                       |
| <input type="checkbox"/> NEW CORRESPONDENCE                                                                                                                                                                                                                                                                                                                             | <input type="checkbox"/> END-OF-PHASE 2 MEETING                              | <input type="checkbox"/> LABELING REVISION                                                                                                                                      |                                                                                                                                                                              |                                       |
| <input type="checkbox"/> DRUG ADVERTISING                                                                                                                                                                                                                                                                                                                               | <input type="checkbox"/> RESUBMISSION                                        | <input checked="" type="checkbox"/> ORIGINAL NEW CORRESPONDENCE                                                                                                                 |                                                                                                                                                                              |                                       |
| <input type="checkbox"/> ADVERSE REACTION REPORT                                                                                                                                                                                                                                                                                                                        | <input type="checkbox"/> SAFETY / EFFICACY                                   | <input type="checkbox"/> FORMULATIVE REVIEW                                                                                                                                     |                                                                                                                                                                              |                                       |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION                                                                                                                                                                                                                                                                                                                | <input type="checkbox"/> PAPER NDA                                           | <input type="checkbox"/> OTHER (SPECIFY BELOW):                                                                                                                                 |                                                                                                                                                                              |                                       |
| <input type="checkbox"/> MEETING PLANNED BY                                                                                                                                                                                                                                                                                                                             | <input type="checkbox"/> CONTROL SUPPLEMENT                                  |                                                                                                                                                                                 |                                                                                                                                                                              |                                       |
| <b>II. BIOMETRICS</b>                                                                                                                                                                                                                                                                                                                                                   |                                                                              |                                                                                                                                                                                 |                                                                                                                                                                              |                                       |
| <input type="checkbox"/> PRIORITY P NDA REVIEW                                                                                                                                                                                                                                                                                                                          | <input type="checkbox"/> CHEMISTRY REVIEW                                    |                                                                                                                                                                                 |                                                                                                                                                                              |                                       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING                                                                                                                                                                                                                                                                                                                         | <input type="checkbox"/> PHARMACOLOGY                                        |                                                                                                                                                                                 |                                                                                                                                                                              |                                       |
| <input type="checkbox"/> CONTROLLED STUDIES                                                                                                                                                                                                                                                                                                                             | <input type="checkbox"/> BIOPHARMACEUTICS                                    |                                                                                                                                                                                 |                                                                                                                                                                              |                                       |
| <input type="checkbox"/> PROTOCOL REVIEW                                                                                                                                                                                                                                                                                                                                | <input type="checkbox"/> OTHER (SPECIFY BELOW):                              |                                                                                                                                                                                 |                                                                                                                                                                              |                                       |
| <input type="checkbox"/> OTHER (SPECIFY BELOW):                                                                                                                                                                                                                                                                                                                         |                                                                              |                                                                                                                                                                                 |                                                                                                                                                                              |                                       |
| <b>III. BIOPHARMACEUTICS</b>                                                                                                                                                                                                                                                                                                                                            |                                                                              |                                                                                                                                                                                 |                                                                                                                                                                              |                                       |
| <input type="checkbox"/> DISSOLUTION                                                                                                                                                                                                                                                                                                                                    | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE                          |                                                                                                                                                                                 |                                                                                                                                                                              |                                       |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES                                                                                                                                                                                                                                                                                                                        | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS                         |                                                                                                                                                                                 |                                                                                                                                                                              |                                       |
| <input type="checkbox"/> PHASE 4 STUDIES                                                                                                                                                                                                                                                                                                                                | <input type="checkbox"/> IN-VIVO WAIVER REQUEST                              |                                                                                                                                                                                 |                                                                                                                                                                              |                                       |
| <b>IV. DRUG SAFETY</b>                                                                                                                                                                                                                                                                                                                                                  |                                                                              |                                                                                                                                                                                 |                                                                                                                                                                              |                                       |
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                                                                                                                                                                                                                                                                                                     | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |                                                                                                                                                                                 |                                                                                                                                                                              |                                       |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES                                                                                                                                                                                                                                                                                      | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |                                                                                                                                                                                 |                                                                                                                                                                              |                                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)                                                                                                                                                                                                                                                                                                | <input type="checkbox"/> POISON RISK ANALYSIS                                |                                                                                                                                                                                 |                                                                                                                                                                              |                                       |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP                                                                                                                                                                                                                                                                                              |                                                                              |                                                                                                                                                                                 |                                                                                                                                                                              |                                       |
| <b>V. SCIENTIFIC INVESTIGATIONS</b>                                                                                                                                                                                                                                                                                                                                     |                                                                              |                                                                                                                                                                                 |                                                                                                                                                                              |                                       |
| <input type="checkbox"/> CLINICAL                                                                                                                                                                                                                                                                                                                                       |                                                                              | <input type="checkbox"/> NONCLINICAL                                                                                                                                            |                                                                                                                                                                              |                                       |
| COMMENTS / SPECIAL INSTRUCTIONS: Microbiology review requested of new NDA application. THIS APPLICATION IS A GRMP PILOT APPLICATION. Tablet dosage form - this application contains all microbiology information, and is cross referenced from NDA 22-254 and — please direct questions to Prafull Shiromani at 62133. Submission is in electronic form in EDR.<br>b(4) |                                                                              |                                                                                                                                                                                 |                                                                                                                                                                              |                                       |
| SIGNATURE OF REQUESTOR<br>{See appended electronic signature page}                                                                                                                                                                                                                                                                                                      |                                                                              | METHOD OF DELIVERY (Check one)<br><input checked="" type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND |                                                                                                                                                                              |                                       |
| PRINTED NAME AND SIGNATURE OF RECEIVER                                                                                                                                                                                                                                                                                                                                  |                                                                              | PRINTED NAME AND SIGNATURE OF DELIVERER                                                                                                                                         |                                                                                                                                                                              |                                       |

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/s/

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Scott Goldie  
11/20/2007 03:51:29 PM

**Ware, Jacqueline H**

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**From:** Ware, Jacqueline H  
**Sent:** Tuesday, November 20, 2007 11:17 AM  
'Blumberg Alan'; 'Dottavio Misty'  
Ware, Jacqueline H; Malandro, Lisa  
**Subject:** FDA Request - NDA 22-253, 22-254, \_\_\_\_\_, Lacosamide Tabs, Injection, \_\_\_\_\_

Dear Alan,

Below is a request from CDER's clinical pharmacology group related to their initial filing review of the lacosamide applications. Please provide your response to this request by Tuesday, Nov. 27th, and submit the information in archival format as an amendment to the 4 NDAs listed above. If you are unable to meet the requested timeframe for submission, please call me.

- Under individual subject listing for each study, the data listing dataset folder has numerous datasets. The definition of these data sets should be provided. We acknowledge the definition of the data columns within these data sets has been provided, but description of datasets like ALCO, CAFF etc have not been provided. Under analysis dataset, the description of PC, PP and PC-E have not been given. Please provide these.
- Please submit the applicable data from the following to support ALL population PK analyses and concentration-response relationship analyses:
  - All datasets used for model development and validation should be submitted as SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
  - Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt).
  - A model development decision tree and/or table which gives an overview of modeling steps.
  - For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Thank you,  
Jackie

\*\*\*\*\*  
*Jacqueline H. Ware, Pharm.D., CDR USPHS  
Senior Regulatory Project Manager  
Division of Neurology Products  
Center for Drug Evaluation and Research, FDA*

*10903 New Hampshire Avenue; WO22 Rm. 4348  
Silver Spring, MD 20993-0002*

*one: 301-796-1160*

fax: 301-796-9842  
NEW email: [jacqueline.ware@fda.hhs.gov](mailto:jacqueline.ware@fda.hhs.gov)

**APPEARS THIS WAY  
ON ORIGINAL**

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                    |                                                                                                                                                                                                                      |                                                                          |                                        |
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| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                    | REQUEST FOR CONSULTATION                                                                                                                                                                                             |                                                                          |                                        |
| TO (Division/Office):<br>Division of Biostatistic VI<br>Attention: Karl Lin                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                    | FROM:<br>Division of Neurology Products (DNP), HFD-120<br>WO 22 Rm. 4350                                                                                                                                             |                                                                          |                                        |
| DATE<br>November 5, 2007                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | IND NO.                            | NDA NO.<br>22-253, 22-254, _____                                                                                                                                                                                     | TYPE OF DOCUMENT<br>New original NME NDAs                                | DATE OF DOCUMENT<br>September 28, 2007 |
| NAME OF DRUG<br>Vimpat (lacosamide) Tablets,<br>Injection, _____                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | PRIORITY CONSIDERATION<br>Standard | CLASSIFICATION OF DRUG<br>1                                                                                                                                                                                          | DESIRED COMPLETION DATE<br>May 1, 2008<br>PDUFA goal date: July 28, 2008 |                                        |
| NAME OF FIRM: Schwarz Pharma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                    |                                                                                                                                                                                                                      |                                                                          |                                        |
| REASON FOR REQUEST<br>I. GENERAL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                    |                                                                                                                                                                                                                      |                                                                          |                                        |
| <input type="checkbox"/> NEW PROTOCOL<br><input type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE/ADDITION<br><input type="checkbox"/> MEETING PLANNED BY                                                                                                                                                                                                                                                                                                                                                                                                                 |                                    |                                                                                                                                                                                                                      |                                                                          |                                        |
| <input type="checkbox"/> PRE-NDA MEETING<br><input type="checkbox"/> END OF PHASE II MEETING<br><input type="checkbox"/> RESUBMISSION<br><input type="checkbox"/> SAFETY/EFFICACY<br><input type="checkbox"/> PAPER NDA<br><input type="checkbox"/> CONTROL SUPPLEMENT                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                    |                                                                                                                                                                                                                      |                                                                          |                                        |
| <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW):                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                    |                                                                                                                                                                                                                      |                                                                          |                                        |
| II. BIOMETRICS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                    |                                                                                                                                                                                                                      |                                                                          |                                        |
| STATISTICAL EVALUATION BRANCH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                    | STATISTICAL APPLICATION BRANCH                                                                                                                                                                                       |                                                                          |                                        |
| <input type="checkbox"/> TYPE A OR B NDA REVIEW<br><input type="checkbox"/> END OF PHASE II MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW):                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                    | <input type="checkbox"/> CHEMISTRY REVIEW<br><input checked="" type="checkbox"/> PHARMACOLOGY - CAC statistical data<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |                                                                          |                                        |
| III. BIOPHARMACEUTICS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                    |                                                                                                                                                                                                                      |                                                                          |                                        |
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE IV STUDIES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                    | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST                                                         |                                                                          |                                        |
| IV. DRUG EXPERIENCE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                    |                                                                                                                                                                                                                      |                                                                          |                                        |
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                    | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS                              |                                                                          |                                        |
| V. SCIENTIFIC INVESTIGATIONS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                    |                                                                                                                                                                                                                      |                                                                          |                                        |
| <input type="checkbox"/> CLINICAL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                    | <input type="checkbox"/> PRECLINICAL                                                                                                                                                                                 |                                                                          |                                        |
| <p><b>REQUEST:</b> NDA 22-253/Lacosamide Tablets (administratively split to include NDA _____ has been submitted for review to DAARP and DNP (electronic link \\CDSESUB1\EVSPROD\NDA022253\022253.ENX). Also, _____ lacosamide dosage forms (injection _____) have been proposed under NDA 22-254 _____ and cross-reference data in NDA 22-253. Lacosamide (previously named harkosaride) has been developed for the treatment of neuropathic pain (DAARP) and epilepsy (DNP). <b>Please review and comment on the acceptability of the carcinogenicity statistical information submitted in NDA 22-253.</b> The filing meeting for NDA 22-253 is scheduled for 11/20 at 10am (WO 22 Rm. 3270) if you or someone from your group would like to attend.</p> |                                    |                                                                                                                                                                                                                      |                                                                          |                                        |
| <p><b>NOTE:</b> NDA 22-253 has been identified as DNP's GRMP pilot NME application for FY08. As such, we ask that this review be completed by May 1, 2008 because all primary discipline reviews must be completed by May 28, 2008 (month 8 of the review cycle). For questions, please contact Jackie Ware, DNP Project Manager, at 301-796-1160 or Lisa Malandro, DAARP Project Manager, at 301-796-1251.</p>                                                                                                                                                                                                                                                                                                                                            |                                    |                                                                                                                                                                                                                      |                                                                          |                                        |
| SIGNATURE OF REQUESTER<br>Jackie Ware, Pharm.D., Regulatory Project Manager                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                    | METHOD OF DELIVERY (Check one)<br><input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DFS & Email                                                                                                      |                                                                          |                                        |
| SIGNATURE OF RECEIVER                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                    | SIGNATURE OF DELIVERER                                                                                                                                                                                               |                                                                          |                                        |

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/s/

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Jackie Ware  
11/9/2007 12:36:53 PM

| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |         | REQUEST FOR CONSULTATION               |                                                                                                                                                                                         |                                                                          |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------|----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|--|
| TO (Division/Office):<br><b>Director, Division of Medication Errors and<br/>Technical Support (DMETS), HFD-420<br/>WO 22 Rm. 4421</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |                                        | FROM:<br><b>Division of Neurology Products (DNP), HFD-120<br/>WO 22 Rm. 4350</b>                                                                                                        |                                                                          |  |
| DATE<br>October 31, 2007                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | IND NO. | NDA NO.<br>22-253, 22-254, <b>b(4)</b> | TYPE OF DOCUMENT<br>New original NME NDAs                                                                                                                                               | DATE OF DOCUMENT<br>September 28, 2007                                   |  |
| NAME OF DRUG<br>Vimpat (lacosamide) Tablets<br>Injection, <b>b(4)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         | PRIORITY CONSIDERATION<br>Standard     | CLASSIFICATION OF DRUG<br>1                                                                                                                                                             | DESIRED COMPLETION DATE<br>May 1, 2008<br>PDUFA goal date: July 28, 2008 |  |
| NAME OF FIRM: Schwarz Pharma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |         |                                        |                                                                                                                                                                                         |                                                                          |  |
| REASON FOR REQUEST                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |         |                                        |                                                                                                                                                                                         |                                                                          |  |
| I. GENERAL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |         |                                        |                                                                                                                                                                                         |                                                                          |  |
| <input type="checkbox"/> NEW PROTOCOL<br><input type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE/ADDITION<br><input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING<br><input type="checkbox"/> END OF PHASE II MEETING<br><input type="checkbox"/> RESUBMISSION<br><input type="checkbox"/> SAFETY/EFFICACY<br><input type="checkbox"/> PAPER NDA<br><input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Proprietary name review |         |                                        |                                                                                                                                                                                         |                                                                          |  |
| II. BIOMETRICS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |         |                                        |                                                                                                                                                                                         |                                                                          |  |
| STATISTICAL EVALUATION BRANCH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |         |                                        | STATISTICAL APPLICATION BRANCH                                                                                                                                                          |                                                                          |  |
| <input type="checkbox"/> TYPE A OR B NDA REVIEW<br><input type="checkbox"/> END OF PHASE II MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW):                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |         |                                        | <input type="checkbox"/> CHEMISTRY REVIEW<br><input type="checkbox"/> PHARMACOLOGY<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER (SPECIFY BELOW):      |                                                                          |  |
| III. BIOPHARMACEUTICS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |                                        |                                                                                                                                                                                         |                                                                          |  |
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE IV STUDIES                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |                                        | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST                            |                                                                          |  |
| IV. DRUG EXPERIENCE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |         |                                        |                                                                                                                                                                                         |                                                                          |  |
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |         |                                        | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS |                                                                          |  |
| V. SCIENTIFIC INVESTIGATIONS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |         |                                        |                                                                                                                                                                                         |                                                                          |  |
| <input type="checkbox"/> CLINICAL                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |         |                                        | <input type="checkbox"/> PRECLINICAL                                                                                                                                                    |                                                                          |  |
| <p><b>REQUEST:</b> Please review and comment the acceptability of Schwarz's propriety name, Vimpat, as well as the 2 alternate proposed names. Although included as part of their NDA submission dated 9/28/07 (electronic link \\CDSESUB1\EVSPROD\NDA022253\022253.ENX ; in Module 1 under 1.6 "Correspondence regarding Meetings", "EP-table of Sponsor-Agency communications" [page 4 06 July 2007]), these names were previously submitted for DMETS review on 7/20/07 under IND 57,939 (copy attached).</p> <p><b>NOTE:</b> NDA 22-253 has been identified as DNP's GRMP pilot NME application for FY08. As such, we ask that this review be completed by May 1, 2008 because all primary discipline reviews must be completed by May 28, 2008 (month 8 of the review cycle).</p>                                                                                                                                                                                 |         |                                        |                                                                                                                                                                                         |                                                                          |  |
| If additional information regarding this consult request is needed, please contact Jackie Ware, Project Manager, at 301-796-1160 or warej@cder.fda.gov.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |         |                                        |                                                                                                                                                                                         |                                                                          |  |
| SIGNATURE OF REQUESTER<br>Jackie Ware, Pharm.D., Regulatory Project Manager                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |         |                                        | METHOD OF DELIVERY (Check one)<br><input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DFS & Email                                                                         |                                                                          |  |
| SIGNATURE OF RECEIVER                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |         |                                        | SIGNATURE OF DELIVERER                                                                                                                                                                  |                                                                          |  |

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/s/

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Jackie Ware  
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| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                       | <b>REQUEST FOR CONSULTATION</b>                                                                                                                                          |                                              |                                        |
| TO (Division/Office):<br>Controlled Substance Staff (HFD-009)<br>Attn: Corrine Moody                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                       | FROM:<br>Division of Anesthesia, Analgesia and Rheumatology<br>Products (HFD-170); Dr. Bob Rappaport<br>And<br>Division of Neurology Products (HFD-120); Dr. Russel Katz |                                              |                                        |
| DATE<br>October 25, 2007                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | IND NO.<br>See below                  | NDA NO. <b>b(4)</b><br>22-253                                                                                                                                            | TYPE OF DOCUMENT<br>NDA                      | DATE OF DOCUMENT<br>September 28, 2007 |
| NAME OF DRUG<br>Lacosamide                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | PRIORITY<br>CONSIDERATION<br>Standard | CLASSIFICATION OF<br>DRUG<br>1S                                                                                                                                          | DESIRED COMPLETION<br>DATE<br>April 29, 2008 |                                        |
| NAME OF FIRM: Schwarz Biosciences, Inc                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                       |                                                                                                                                                                          |                                              |                                        |
| <b>REASON FOR REQUEST</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                       |                                                                                                                                                                          |                                              |                                        |
| <b>I. GENERAL</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                       |                                                                                                                                                                          |                                              |                                        |
| <input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> RESPONSE TO DEFICIENCY<br><input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> END OF PHASE II MEETING                      LETTER<br><input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ADVERSE REACTION REPORT <input checked="" type="checkbox"/> ELECTRONIC NDA <input type="checkbox"/> ORIGINAL NEW<br><input type="checkbox"/> MANUFACTURING <input type="checkbox"/> CONTROL SUPPLEMENT                      CORRESPONDENCE<br><input type="checkbox"/> CHANGE/ADDITION <input type="checkbox"/> FORMULATIVE REVIEW<br><input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> OTHER (SPECIFY BELOW): |                                       |                                                                                                                                                                          |                                              |                                        |
| <b>COMMENTS/SPECIAL INSTRUCTIONS:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                       |                                                                                                                                                                          |                                              |                                        |
| <p>Please provide guidance on the on the abuse potential of lacosamide. This NDA has been administratively split into two applications by indication: NDA 22-253 (epilepsy, standard review, HFD-120) and NDA _____ (neuropathic pain associated with diabetic peripheral neuropathy, HFD-170). Associated INDs are I 57,939, _____ 68,407, I 73,809 _____</p> <p>The network path location is: \\CDSESUB1\EVSPROD\NDA022253\0000A<br/>It is now available on the network. You can review this submission by entering EDR in your browser.</p> <p><b>A joint filing meeting between HFD-170 and HFD-120 is scheduled for November 20, 2007 at 9:00 am. The filing date for the applications is December 30, 2003. The PDUFA goal date .</b></p> <p>Please contact Lisa Malandro (HFD-170, 6-1251) or Jackie Ware (HFD-120,6-1160) for additional information.</p>                                                                                                                           |                                       |                                                                                                                                                                          |                                              |                                        |
| SIGNATURE OF REQUESTER                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                       | METHOD OF DELIVERY (Check one)<br><input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND                                                                 |                                              |                                        |
| SIGNATURE OF RECEIVER                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                       | SIGNATURE OF DELIVERER                                                                                                                                                   |                                              |                                        |

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this page is the manifestation of the electronic signature.**  
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/s/

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Lisa Malandro  
10/25/2007 05:07:16 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-253

NDA \_\_\_\_\_

b(4)

**NDA ACKNOWLEDGMENT**

Schwarz Biosciences, Inc.  
Attention: Alan Blumberg  
Sr. Director, US Regulatory Affairs  
P.O. Box 110167  
Research Triangle Park, NC 27709

Dear Mr. Blumberg:

We refer to your new drug application (NDA), dated September 28, 2007, received on September 28, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Lacosamide Tablets, 50 mg, 100 mg, 150 mg, 200 mg, 250 mg, and 300 mg

We have administratively split your NDA into two applications according to indication. The details for the split applications are as follows:

|                       |                                                                                    |                                                                               |
|-----------------------|------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Our Reference Number: | NDA 22-253                                                                         | NDA _____ b(4)                                                                |
| Indication:           | Adjunctive therapy in patients with partial onset seizures aged 16 years and older | Management of neuropathic pain associated with diabetic peripheral neuropathy |
| Responsible Division: | Division of Neurology Products (DNP)                                               | Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)          |

Unless we notify you within 60 days of the receipt date that these applications are not sufficiently complete to permit a substantive review, we will file them on November 27, 2007 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

NDA 22-253

NDA \_\_\_\_\_

Page 2

b(4)

The NDA numbers provided above should be cited at the top of the first page of all submissions to these applications. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
DNP and DAARP  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call either of us at the following numbers:

Jacqueline H. Ware – (301) 796-1160; Lisa Malandro – (301) 796-1251

Sincerely,

*{See appended electronic signature page}*

*{See appended electronic signature page}*

Jacqueline H. Ware, Pharm.D., RAC (US)  
Senior Regulatory Project Manager  
Division of Neurology Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Lisa Malandro, MBA  
Senior Regulatory Project Manager  
Division of Anesthesia, Analgesia, and  
Rheumatology Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**  
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/s/

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Jackie Ware  
10/22/2007 07:55:03 AM

Lisa Malandro  
10/22/2007 09:58:14 AM

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                            |                                     |                                                                       |                                   |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|-------------------------------------|-----------------------------------------------------------------------|-----------------------------------|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES<br>PUBLIC HEALTH SERVICE<br>FOOD AND DRUG ADMINISTRATION                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                            | <b>REQUEST FOR CONSULTATION</b>     |                                                                       |                                   |
| TO (Division/Office): HFD-420/Director, Division of Medication Errors and Technical Support                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                            |                                     | FROM: HFD-120/Division of Neurology Products                          |                                   |
| DATE:<br>July 11, 2007                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | IND NO.:                                                   | NDA NO.:<br>IND 57,939              | TYPE OF DOCUMENT: Name<br>Review Request                              | DATE OF DOCUMENT:<br>July 6, 2007 |
| NAME OF DRUG:<br>Lacosamide (SPM)Tablets                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | PRIORITY CONSIDERATION:<br>NDA to be filed<br>September 07 | CLASSIFICATION OF DRUG:<br>Epilepsy | DESIRED COMPLETION DATE:<br>October 2007                              |                                   |
| NAME OF FIRM: Schwarz                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                            |                                     |                                                                       |                                   |
| <p><b>COMMENTS/SPECIAL INSTRUCTIONS:</b></p> <p><b>Proposed Proprietary Name:</b> Please evaluate the following 3 names in order of preference by the sponsor:<br/> 1. Vimpat _____ <b>b(4)</b></p> <p><b>Trademark registration status/Countries registered(if known):</b> Registered but country unknown</p> <p><b>Other proprietary names by same firm for companion products:</b> none</p> <p><b>United States Adopted Name, dosage form, strength and dosing schedule:</b><br/> Lacosamide tablets, IV, _____ - Recommended doses, dosing schedules and available dosage strengths are in the attached package.<br/> <b>b(4)</b></p> <p><b>Indication for use:</b><br/> In the treatment of epilepsy</p> |                                                            |                                     |                                                                       |                                   |
| SIGNATURE OF REQUESTER:<br><br>Melina Griffis (301-796-1078)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                            |                                     | METHOD OF DELIVERY (Check one):<br>MAIL <input type="checkbox"/> HAND |                                   |
| SIGNATURE OF RECEIVER:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                            |                                     | SIGNATURE OF DELIVERER:                                               |                                   |

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/s/

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Melina Griffis  
7/20/2007 11:24:33 AM

From: "Calder, Courtney" <courtney.calder@fda.hhs.gov>  
To: "Misty Williams" <Misty.Williams@schwarzbiosciences.com>  
Date: 8/8/2006 1:55:50 PM  
Subject: RE: pre NDA premtg

Hi, Attached are our minutes. Thanks, Courtney

\*\*\*\*\*  
Courtney R. Calder, Pharm.D., LT USPHS  
Regulatory Project Manager  
Division of Neurology Products, HFD-120  
Center For Drug Evaluation and Research, FDA  
Office of Drug Evaluation I  
Ph: (301) 796-1050  
Fax: (301) 796-9842  
Email: courtney.calder@fda.hhs.gov

-----Original Message-----

From: Misty Williams [mailto:Misty.Williams@schwarzbiosciences.com]  
Sent: Friday, July 21, 2006 11:37 AM  
To: Calder, Courtney  
Cc: Byron Scott  
Subject: RE: pre NDA premtg

Hi Courtney,

I have attached the slide that we presented in the meeting as a pdf and a word doc. Please let me know if you anything else.

Kind Regards,

Misty

>>> "Calder, Courtney" <courtney.calder@fda.hhs.gov> 07/21/06 10:11 AM  
>>>

Hi, Would it be possible to e-mail me the slides regarding the analysis

plan for the \_\_\_\_\_ indication?

We are going to discuss this internally Monday.

b(4)

Thanks, have a good weekend, Courtney

\*\*\*\*\*  
Courtney R. Calder, Pharm.D., LT USPHS  
Regulatory Project Manager  
Division of Neurology Products, HFD-120  
Center For Drug Evaluation and Research, FDA  
Office of Drug Evaluation I  
Ph: (301) 796-1050  
Fax: (301) 796-9842  
Email: courtney.calder@fda.hhs.gov

APPEARS THIS WAY  
ON ORIGINAL

CC: "Byron Scott" <Byron.Scott@schwarzbiosciences.com>

APPEARS THIS WAY  
ON ORIGINAL

Meeting Minutes

**Meeting Date: July 19, 2006**

**Sponsor: Schwarz Pharma**

**Pre NDA Mtg : I 57,939**

**Product: Lacosamide (SPM 927)**

**FDA Attendees:**

John Feeney, M.D., Team Leader

Norman Hershkowitz, M.D., Medical Officer

Lois Freed, PhD, Pharm/Tox Supervisor

John Duan, Ph.D., Clin.Pharm.

Kun Jin, PhD, Biometrics TL

Courtney Calder, PharmD., Project Manager

Ohidul Siddiqui, PhD, Biometrics

Ed Fisher, PhD, Pharm/Tox

Katherine Bonson, MD, CSS

**Sponsor Attendees:**

Alan Blumberg, PhD., Sr Director, Regulatory Affairs, US

Elena Cleary, PhD., Director, Medical Writing, US

Pam Doty, PhD, Clinical Program Director, Neurology, US

David Hebert, PhD, Sr. Statistician, US

Pejo Kux, PhD, Project Team Leader, Germany

David Rudd, RPh, Sr. Director Clinical Development, Neurology, US

Robert Ryan, PhD, Vice President, Global Regulatory Affairs

Byron Scott, RPh, Sr. Director, Regulatory Affairs, US

Kenneth Sommerville, MD, Vice President, Clinical Development, Neurology

Niels Krebsfaenger, PhD, Senior Toxicologist, PHTox , Germany

Tim Sullivan, MD, Clinical Program Medical Scientist, Neurology, US

Dirk Thomas, MD, Sr. Scientist, Clinical Pharmacology, Germany

Misty Williams, RN, Regulatory Specialist, US

This meeting was held to provide FDA guidance on NDA submissions for Lacosamide tablets, IV,

**The pre-meeting questions and answers are followed by the actual meeting discussion.**

**Questions and Issues for Discussion**

**Nonclinical**

1. Does the Division agree with the outlines for the dose range finding study and main juvenile toxicity study to assess juvenile toxicity with specified assessments of cardiovascular toxicity? (Appendix 1) Could FDA elaborate their concerns leading to the request for a second juvenile toxicity study?

- The proposed juvenile dog study appears generally adequate based on the submitted outline; however, the outline provides insufficient detail upon which to base overall concurrence. It will be important to conduct detailed histopathological examinations of the heart and brain at termination, and to conduct a thorough neurological examination. In addition, it is recommended that bone densitometry be included. While the observed effects of lacosamide on cardiac conduction (in adult dog and humans) provide a basis for focusing on cardiovascular parameters in juvenile dogs, the request for juvenile animal toxicity evaluations in two species is routine for this drug category (i.e., antiepileptic).

**Controlled Substance**

2. Does the Division agree that with the completed studies on dependence and abuse liability (Sections 4.3.7.4, 4.1.1.1.1, and 4.1.2.1.1 in the Investigator's Brochure) and the ongoing drug discrimination study and the self-administration study (Appendix 2 and 3), the preclinical evaluation of lacosamide's abuse potential is sufficient?

No.

\* The Abuse Potential Section of an NDA includes the following:

Chemistry (including chemical similarity to other drugs of abuse and ability to extract the drug of abuse from the preparation)

Pharmacokinetics and pharmacodynamics (including full data on receptor binding)

Primary data from abuse potential studies in animals and humans

Adverse events in clinical studies related to abuse potential

Integrated summaries of safety and efficacy (ISS and ISE)

Information related to overdose

Prospective assessment of the incidence of misuse, abuse, physical dependence/withdrawal syndrome, tolerance, diversion during clinical studies

\* Thus, in addition to the studies outlined in the question, the Sponsor should conduct studies and provide primary data regarding chemistry, receptor binding, toxicity levels and physical dependence and tolerance of lacosamide.

\* Additionally, the protocols for the drug discrimination and self-administration studies are incomplete -- a justification for the comparator/training drugs and the selected doses for all drugs should be provided.

3. Does the Division agree with the list of clinical trials to be evaluated and the planned search strategy to evaluate signs of abuse liability or dependence as outlined in the attached plan (Appendix 4)?

No.

#### Assessment of Physical Dependence and Tolerance

\* Clinical trials should include prospective evaluations of physical dependence and withdrawal as well as the development of tolerance. Assessments should occur prospectively, using objective, standard metrics for these phenomena.

#### MedDRA terms

\* Appendix 4 does not contain a list of clinical trials to be evaluated, but does delineate the search strategy using MedDRA terms.

\* The strategy provided by the Sponsor for assessing abuse-related MedDRA adverse events terms states that "all placebo-controlled trials in Phases 1-3, which are completed by the time of analysis" will be included in the search. However, the search should not be conducted until all trials to be included in the NDA are complete. Additionally, all trials, regardless of whether they are placebo-controlled, should also be included and listed separately.

\* CSS does not agree with the exclusions proposed for the MedDRA terms that will be used to search adverse events that occur during clinical trials. These MedDRA terms were provided by FDA to the Sponsor in the pre-NDA meeting in December 2005. All listed terms are potentially useful for capturing the full range of abuse-related psychiatric and CNS responses to lacosamide.

\* The Sponsor maintains that certain MedDRA terms should be excluded because the occurrence of any one of these adverse events cannot be understood without appropriate context. However, the

Pre-NDA Meeting

Lacosamide

broader list of psychiatric MedDRA terms proposed by FDA provides such a context, so the justification for exclusion is not valid.

\* Additionally, the full list of MedDRA terms proposed by FDA provide a method of examining abuse-related terms in MedDRA that are subsumed under HLT's or HLT's.

\* CSS evaluates all data, from both preclinical and clinical studies, in making the final determination of whether a drug has abuse liability.

**Adverse Events Indicative of Abuse Liability**

\* The Investigator's Brochure states that nervous system and psychiatric adverse events observed in previous clinical trials with lacosamide included euphoric mood, visual hallucinations and disturbances, as well as amnesia, memory impairment, confusional states, balance and speech disorders and disturbances in attention. No information was provided regarding the frequency or intensity of these adverse events in the clinical trials.

\* However, these adverse effects are either directly indicative of abuse liability or are psychiatric or neurological effects associated with known drugs of abuse.

\* Given the adverse events profile of lacosamide, and given that the drug has a unique mechanism of action, a human laboratory abuse liability study is needed.

\* The Sponsor is encouraged to submit data regarding the frequency and intensity of the adverse events noted above and to consult with CSS (through correspondence with the Division) for feedback on the design of the protocol.

Clinical

4. Does the Division agree that the Clinical Development Program reflected by the clinical trials presented in the tabulated overview of clinical trials is acceptable for the NDA-filing?

- The application is acceptable for filing from a clinical trials perspective.

5. At the time of the NDA's safety data cut off (April 2006) with an anticipated filing date of March/April 2007, there will be unique exposures to lacosamide for approximately 600 healthy subjects, 1300 patients with partial seizures, and 1580 patients with neuropathic pain. Exposure data by dose for the epilepsy population for at least 6 months and 1 year will be presented in a tabulated summary of exposure. Does the Division agree that the number of patients with partial seizures exposed to lacosamide for 6 and 12 months is sufficient for filing the initial NDA?

Pre-NDA Meeting

Lacosamide

- Generally numbers are adequate. Should, however, have adequate exposure at 6 months and 1 year exposures which are not noted in the submission. ICH guidelines recommends 300-600 and 100 patients respectively. The majority patients fulfilling these ICH recommended sample sizes should be made up by patients with epilepsy.
6. Does the Division agree that the efficacy results of 200mg/day lacosamide in SP667 and SP755 (see Section 4.3.1) support 200 and 400mg/day lacosamide as effective doses in the labeling?
- (see page 22) This question cannot be answered at the present time as it is a review issue. It is noteworthy that the division answered a similar question at the end of phase 2 meeting at which time the division noted, "this is a possibility, but it is dependent upon the strength of the result."
7. Does the Division agree that if the \_\_\_\_\_ ) is positive that the indication for lacosamide can be \_\_\_\_\_

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( / / / / / )

8. A statistical analysis plan to support the integrated analyses of safety and efficacy data has been provided in the meeting package.

a. Does the Division concur with the proposal for pooling as described in Section 2 of the attached ISAP (Appendix 5) and with the proposal for marked abnormalities for clinical laboratory measurements and vital signs?

• The pain pool should be separately analyzed, as you are planning but should also be divided into two separate analyses as you are planning for the epilepsy populations: i.e. 1) placebo versus drug analysis from the controlled pain studies 2) all pain patients from the complete pain database (controlled and open label studies) . Also see note on the ISS below.

b. Does the Division suggest any additional alternative analyses to be included in this Integrated Statistical Analysis Plan?

The iv evaluation should include a placebo versus drug examination of adverse events from controlled tolerability studies. Note, there should separate section in the ISS discussing liver toxicity (elevated LFTs), skin reactions; cardiovascular and EKG related events, psychiatric effects (an examination of suicide and suicidality should specifically discussed.

9. Schwarz proposes to provide narratives and CRFs for lacosamide and placebo cases (for healthy subjects, renally or hepatically impaired subjects, patients with epilepsy or neuropathic pain) for all SAEs and AE drops. In addition, narratives will also be provided for lacosamide and placebo cases (for the same subjects and patients identified above) that include the following adverse events defined as other significant AEs by the development program:

- rash, rash generalized, rash maculopapular, rash pruritic
- alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase, blood alkaline phosphatase increased, blood bilirubin increased, blood lactate dehydrogenase increased, gamma- glutamyltransferase increased, hepatic enzyme abnormal, hepatic enzyme increased, hepatic function abnormal, hepatic steatosis, liver disorder, liver function test abnormal, transaminases increased, urine bilirubin increased, urobilin urine present, and

angina pectoris, angina unstable, arrhythmia, atrial bigeminy, atrial fibrillation, atrial flutter, atrio-ventricular block- second degree, AV block complete, AV dissociation, bradyarrhythmia, bradycardia, bundle branch block, bundle branch block left, bundle branch block right, cardiac arrest, chest discomfort, chest pain, depressed level of consciousness, ECG P wave inverted, ECG signs of myocardial ischemia, electrocardiogram abnormal, electrocardiogram change, electrocardiogram pr prolongation, electrocardiogram QRS complex prolonged, electrocardiogram QT corrected interval prolonged, electrocardiogram QT prolonged, electrocardiogram ST segment depression, electrocardiogram ST-T segment abnormal, electrocardiogram T wave abnormal, electrocardiogram T wave inversion, extrasystoles, loss of consciousness, nodal rhythm, palpitations, QRS axis abnormal, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, syncope, tachycardia, ventricular extrasystoles, ventricular fibrillation

Does the Division agree with this proposal?

- The proposal appears adequate. Additional adverse events narrations that are included which are not part of the serious database or cause discontinuations should be easily identified as such. When submitting narrations it is helpful to include all narration in one section as an appendix to the ISS and divide narrations into the subsections( serious events (including deaths), discontinuations and "other significant AEs").

Please note that narrative summaries of important adverse events (e.g., deaths, events leading to discontinuation, other serious adverse events) should provide the detail necessary to permit an adequate understanding of the nature of the adverse event experienced by the study subject. Narrative summaries should not merely provide, in text format, the data that are already presented in the case report tabulation, as this adds little value. A valuable narrative

The summary would provide a complete synthesis of all available clinical data and an informed discussion of the case, allowing a better understanding of what the patient experienced. The following is a list of components that would be found in a useful narrative summary:

- Patient age and gender
- Signs and symptoms related to the adverse event being discussed
- An assessment of the relationship of exposure duration to the development of the adverse event
- Pertinent medical history
- Concomitant medications with start dates relative to the adverse event

- Pertinent physical exam findings
  - Pertinent test results (e.g., lab data, ECG data, biopsy data). This should not only consist of all significant positives but significant negative (e.g. a case of elevated liver function tests should include bilirubin even if normal, a case of pre-syncope should include EKG and vital signs even if normal).
  - Discussion of the diagnosis as supported by available clinical data
  - For events without a definitive diagnosis, a list of the differential diagnoses
  - Treatment provided
  - Re-challenge results (if performed)
  - Outcomes and follow-up information
10. SCHWARZ BIOSCIENCES plans to submit analysis files in the form of SAS datasets for the Phase 2b/3 trials and Oracle Clinical CRF files in the form of SAS datasets for all other trials and therefore, does not intend to submit Case Report Form tabulations (patient line listings) as part of the eCTD format NDA. Does the Division agree with this plan?
- Yes.
11. Does the Division agree with the proposed risk assessment outline for lacosamide as described in Appendix 6?
- This generally looks adequate. However, included as an additional note at the end of this document, is a guide to the elements that are generally required in an ISS. The Sponsor should confirm that these are included. Issues in section 2.2 (hepato-toxicity, cardiovascular effects, suicidality etc) should be very thoroughly examined.
12. SCHWARZ intends to include an update of the lacosamide safety data submitted to the Division on 21 April 2006 (serial no. 0393) in the NDA. Based on the Division's review of the data to date, does the Division recommend any additions or revisions of the analytical approaches or data displays?
- No

**Additional comments:**

Outline of the summary section of the HPBIO section is provided. We request that the sponsor provide such summary section as a review aid for Clinical Pharmacology and Biopharmaceutics

Pre-NDA MeetingLacosamide

reviewer. At the time of NDA submission the sponsor can use this template to write the summary of the Clinical Pharmacology and Biopharmaceutics section of the NDA or provide it to the agency as a review aid. This summary section should be submitted electronically with appropriate hyperlinks to the relevant supporting data (Document attached).

Regulatory

13. If the SP754 clinical trial report were to be submitted at the time of the 120 day safety update rather than with the initial NDA, would an updated integrated analysis of safety and efficacy data be expected? Would this submission be considered a major amendment to the NDA?

- No. It would not be considered a major amendment, but the division is not committed to review the efficacy of this additional study as part of the submission within the PDUFA deadline. Safety Information, however, will be reviewed as part of the safety update. An updated ISS should be provided but you must very clearly identify those new cases not previously described in the original NDA that involve discontinuations or serious (including deaths) adverse events.

14. This submission will contain      formulations, an oral tablet, intravenous solution     

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     Is this acceptable under one NDA number and one user fee?

- It should be submitted as      NDAs. The tablet formulation will require a full user fee for review of the safety and efficacy, and a half user fee will be required for      intravenous solution for PK examination.

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Electronic Submissions

15. Due to the multiple indications and formulations for lacosamide, the Agency has indicated that the regulatory submissions for this compound will be submitted under multiple NDA numbers. This will result in multiple eCTD folder structures on the FDA server. Multiple eCTD folder structures present a number of technical difficulties for electronically cross-referencing studies that support multiple applications. SCHWARZ would like to avoid duplicate submission of studies that support multiple NDAs in each eCTD folder structure. SCHWARZ has developed a potential solution to this problem and will submit a request for a separate meeting or teleconference to discuss jointly a proposal with each review division and the Electronic Regulatory Submissions and Review group. Does the Division agree with this approach?

- A future meeting to discuss this issue is acceptable. The meeting should include representatives of Dr. Randy Levin's group (Office of Information Management).

*Additional notes by the Division:*

As a guide this division is providing you with the elements that are generally required as part of an ISS. Please confirm that your submission contains all the elements described below:

**1 THE FOLLOWING ITEMS SHOULD BE INCLUDED IN THE ISS**

- *The ISS should clearly state what safety assessments were carried out in each study included in the ISS. A tabular presentation of schedule of events might be helpful.*
- *All deaths that occurred in the clinical development program or found during a literature search and from various commercial and non-commercial databases (ex AERS) should be described in a single section and individual deaths should be listed in a table.*
- *All non-fatal serious adverse events, regardless of assigned causality, that occurred during the clinical development program or were reported from secondary sources (i.e. literature and/or post marketing reports) should be described in a single section. Serious adverse events may, in addition to signs, symptoms, and diagnosable events, include changes in laboratory parameters, vital signs, ECG, or other parameters of sufficient magnitude to meet the regulatory definition of a serious adverse event [21 CFR 312.32(a); 314.80(a)].*
- *Dropouts due to adverse events should be clearly described in a single section of the ISS. CRF/narratives should be provided for all dropouts. An overall profile of these patients by reason for dropping out (e.g. adverse events, treatment failures, lost to follow up) should be provided. For the more common adverse events associated with dropouts, the ISS should present the incidence of these adverse events, preferably in a table. Investigator causality assessment can be described but should be justified. The ISS should also describe any dose-response, time dependency of the dropout, drug-demographic, drug-disease, and drug-drug interactions. With respect to rarer events that could represent an important adverse event, the ISS should critically assess whether any of these may represent treatment-induced injury. Finally the ISS should consider these events individually with narratives and reference to other data as appropriate.*
- *The ISS should contain a section entitled "Other Significant Adverse Events." This section should describe significant safety findings such as marked hematological or other lab abnormalities not meeting the definition of serious, any events that led to an adverse dropout or any other intervention such as dose reduction or significant additional concomitant therapy (an expansion of the adverse dropout concept) and potentially important abnormalities not meeting the above definition of serious and not leading to death or modification of therapy (e.g., a single seizure, syncopal episode, orthostatic symptoms). Those adverse events that did not lead to discontinuation but otherwise meet the definition described above should be described in this section.*
- *If preclinical pharmacology/toxicology, post-marketing and/or literature reports provide insight into possible safety signals with the investigational drug product the ISS should describe any findings relative to these signals. This is especially important for new chemical entities. Similarly, if there are particular safety concerns evident from other drug products that are members of the same pharmacological class as the investigational drug product, the ISS should describe a thorough safety analysis of these concerns.*

- *The ISS should contain a section entitled "Common Adverse Events". You should include a table (or tables) that presents the best overall display of commonly occurring adverse events, generally those occurring at a rate of 1% or more (but lower rates can be presented for very large data bases). This table or tables will be the basis for the ADR table in labeling, which may, however, use a higher cut off if this does not lose important information, and will eliminate ADRs that are equally common on drug and placebo. This table or tables should compare the incidence of common adverse events between cohorts regardless of the investigator's assignment of causality from the pooled studies. You should justify any decision for not including a particular study in the pooled adverse event incidence tables. For development programs with a significant amount of severe adverse events it would be helpful to include a table that compares the incidence of severe adverse events between cohorts from the pooled studies.*
- *For adverse events that seem clearly drug related (i.e., consistent difference from control across studies, evidence of dose response etc.) you should provide the following additional analysis as appropriate:*
  1. *exploration for dose dependency, exploration of time to onset (for those that show a delay in onset)*
  2. *exploration of adaptation (for common, troublesome events such as somnolence, nausea)*
  3. *explorations of demographic interactions, explorations of drug-disease and drug-drug interactions (if there is a strong signal for an interaction, or a good rationale for expecting an interaction)*
  4. *selective exploration of individual cases in an attempt to better characterize the events.*
- *For each trial described in the ISS you should include a brief discussion on how adverse events were captured (i.e. checklist, open-ended questions on follow up visits etc.). The frequency of assessments should also be described.*
- *For each trial described in the ISS you should clearly state which translation dictionary (MedDRA, COSTART) was used to categorize verbatim adverse event terms.*
- *The ISS should include a discussion of the less common adverse events of significant concern seen across all studies in the clinical development program. Since the overall database is typically very heterogeneous, it is unlikely to lend itself to meaningful estimations of rates or assessments of causality. Thus it may be sufficient to group these events by incidence and by body system. For example, it may be useful to categorize less common adverse events in order of decreasing frequency within certain ranges: e.g.  $\leq 1\%$ , between 0.1% and 1%;  $\leq 0.1\%$ .*
- *The ISS should clearly provide an overview of what laboratory testing (chemistry, hematology, and urinalysis) was carried out in each study. It is best to summarize the overall approach, rather than provide detailed comments about laboratory testing for each study. The ISS should also describe any discrepancies between planned analyses and those actually conducted, as well as the procedures used to evaluate abnormal values. Provide a summary table identifying the numbers of patients exposed to test drug who had baseline laboratory values and follow-up assessments.*
- *The ISS should include an integrated discussion of significant laboratory findings from the clinical development program. Controlled comparisons generally provide the best data for*

*deciding whether there is a signal of an effect of a drug on a laboratory test. However placebo-controlled trials are generally short term, and unsuitable for assessing late-developing abnormalities, so that longer term data need to be therefore examined also. If there is no concomitant control in the long term studies the comparison may need to be with similar populations outside the NDA. The ISS should explain which studies were pooled relative to the evaluation of laboratory findings and why they were selected.*

- *The ISS should generally include three standard approaches to the analysis of laboratory data. The first two analyses are based on comparative trial data. The third analysis should focus on all patients in the phase 2-3 experience. Analyses are intended to be descriptive and should not be thought of as hypothesis testing. P-values or confidence intervals can provide some evidence of the strength of the finding, but unless the trials are designed for hypothesis testing (rarely the case), these should be thought of as descriptive. The analysis of all laboratory findings should include a comparative description of mean or median changes from baseline across treatment groups. The ISS should include a discussion on individual patients whose laboratory values deviate substantially from the reference range and describe what criteria were used to identify outliers. Additional analyses may be appropriate for certain laboratory findings, including analyses for dose dependency, time dependency, and also drug-demographic, drug-disease, and drug-drug interactions. The ISS should discuss the rationale for additional explorations, the methods used, and the results and interpretations.*
- *The ISS should include an evaluation of vital sign assessment using a similar approach as described for laboratory data (i.e, description of vital sign assessment in each study, measures of central tendencies, analysis focused on shifts from normal to abnormal, discussion of outliers etc).*
- *The ISS should include an evaluation of ECG findings using a similar approach as described for laboratory data (i.e, description of ECG assessments in each study, measures of central tendencies, analysis focused on shifts from normal to abnormal, discussion of outliers etc). Particular attention should be given to ECG findings where the timing of the assessment was done at or near the time of maximum concentration for the drug product (generally during phase I or phase II studies) in order to assess QT prolongation effects. A brief discussion on any preclinical cardiac findings would be helpful in orienting the reviewer to any potential concerns.*
- *The ISS should include a discussion of the impact of immunogenicity (if applicable) on safety, efficacy and/or clinical pharmacology and pharmacokinetics.*
- *The ISS should include a brief discussion of human carcinogenicity data if available. A systematic discussion of all human tumors reported during drug development can provide useful safety information, particularly in the case of drugs or biologics that have positive genotoxicity or animal carcinogenicity findings, or those that are known immune modulators.*
- *The ISS should include a summary of any studies designed to evaluate a specific safety concern(s). These studies may include:*
  1. *studies to assess whether a drug has safety concerns common to its pharmacological class*
  2. *studies in topical products to assess cumulative irritancy, contact sensitizing potential, photosensitivity, and photoallergenicity*

3. *studies to characterize the effect on the QT interval (part of most modern development efforts)*
  4. *studies intended to demonstrate a safety advantage over therapeutic alternatives*
- *The ISS should contain a discussion of abuse potential and any apparent withdrawal symptoms seen during the clinical development program. This discussion should contain a summary of findings from any non-clinical and clinical abuse liability studies (if done), problems in medication accounting encountered while monitoring the investigational supply of medication, chemistry and pharmacology issues that relate to abuse potential, and relevant adverse events and epidemiologic data. The ISS should describe any adverse events that emerge after discontinuation of the drug in order to determine whether they may indicate a withdrawal phenomenon. If studies evaluated the potential for withdrawal phenomena, the ISS should indicate whether there was a prospective or post-hoc assessment of withdrawal emergent signs and symptoms (during drug taper or following discontinuation) and discuss the implications of the approach used on the reliability of the findings.*
  - *The ISS should include a discussion of all pregnancies that occur during the clinical development program. A brief description of each pregnancy should include outcome, duration on therapy, use of drug relative to trimester.*
  - *The ISS should summarize all overdose experience with the investigational drug/biologic in humans. The summary should include a description of the constellation of signs and symptoms that might be associated with overdose. A description of phase I or phase II safety findings in subjects exposed to doses higher than planned for marketing should be included. Patients with certain physiological differences that would compromise their ability to clear the drug (e.g. renal impairment, limited CYP450 2D6 activity for a drug cleared by this isozyme) may provide relevant data to the clinical implications of overdose.*
  - *The ISS should include relevant findings from U.S. and foreign post-marketing experience if available.*
  - *The ISS should include a clear description of all patient exposures from the entire clinical development program. The exposure summary should describe various demographic subsets such as race, gender and age. Additionally the summary should include a clear description of dose and duration of exposure. Tables and graphs may be helpful in describing the data sources for the ISS. If applicable the ISS should describe any secondary sources of safety data (ex. studies not conducted under the IND and not meeting the standards for inclusion as primary, post marketing data, and/or literature reports). Secondary sources should be briefly described. Original articles and study reports should be provided.*
  - *The ISS should briefly describe the findings from any preclinical studies that were conducted in order to explore certain potential adverse events, using preclinical models based either on a drug's pharmacology or on clinical findings that emerged early in clinical development. For example, for a drug anticipated to cause QT prolongation because of its drug class or because QT prolongation was seen in phase I studies, were there any preclinical (in-vitro) studies done to evaluate this potential.*

Pre-NDA MeetingLacosamide

- *The ISS should include a discussion of any in vitro and in vivo studies done to evaluate how a drug is metabolized and excreted. Issues to be included should include the following:*
  1. *The enzymatic pathways responsible for clearance of the drug and the effects of inhibition of those pathways, notably CYP450 enzymes and p-glycoproteins.*
  2. *The effect of the drug on CYP450 enzymes (inhibition, induction) and the effects of the drug on the PK of model compounds.*
  3. *The major potential safety consequences of drug-drug interactions.*
- *The ISS should describe the general methodology used to construct the integrated safety review. This discussion should include a rationale for pooling safety data (if done) and the method employed. For example a justification for pooling safety data may include an argument that a larger data base will permit explorations of possible drug-demographic or drug-disease interactions in subgroups of the population or pooling data from different studies can improve the precision of an incidence estimate (i.e., narrow the confidence intervals by enlarging the sample size). In pooling safety data, usually the numerator events and denominators for the selected studies are simply combined. If other more formal weighting methods are used (e.g., weighting studies on the basis of study size or inversely to their variance) the ISS should justify why and how it was done. Information on baseline risk factors of concern should be retrievable from the case report tabulations.*
- *Since adverse reaction rates may differ considerably from one patient population to another and may change over time the ISS should explore factors that may affect the safety profile of a drug. For example the ISS could explore common drug related predictive factors, such as dose, plasma level, duration of treatment and concomitant medications, and patient related predictive factors such as age, sex, race, concomitant illnesses. In general, these explorations are meaningful only for adverse reactions that appear to be drug-related. The ISS may present these explorations using the following subheadings: exploration of dose-dependency for adverse findings, explorations for time dependency for adverse findings, exploration for drug-demographic interactions, exploration for drug-disease interactions and exploration for drug drug interactions. It may be helpful to link individual safety observations with other on-therapy data such as dose, duration of treatment, concomitant therapy, other adverse effects, lab data or effectiveness results.*

Meeting Discussion

- **Regarding Question 1, Schwarz stated that bone densitometry will be included in their juvenile study protocol. They also agreed that there would be a detailed histopathological examination of the heart and brain of the dogs in addition to the standard histopathological examination of a full battery of tissues. The histopathology examination of main study animals should be conducted at the end of the dosing period. The Agency stated that Schwarz will need to perform neurobehavioral assessment on a group of animals during the recovery period. Additional animals will need to be added to the recovery group in order to have 4-6 animals/sex/group available for**

neurobehavioral assessment. Schwarz asked if they may request a teleconference to discuss the results of the dosing range-finding study. The Agency stated that the protocol should be submitted as a regular submission, and a teleconference would be scheduled following review, if needed.

- Regarding question 2, the division said they couldn't comment on the completeness of the abuse liability studies until they see the data and justification for doses. They need the full receptor binding profile to make an assessment of behavior studies. CSS is willing to look at the binding studies before they submit them in the NDA. The clinical human abuse study is the gold standard for assessment of abuse liability, and the monkey self-administration study might not be needed if that study is adequate.
- In clinical trials in patients with epilepsy and diabetic neuropathy, Schwartz incorporated a 2 week tapering period from a 600mg/day dose to a 200mg/day dose. They evaluated for rebound seizures and other adverse events. They also monitored for withdrawal in patients taken off drug. The drug acts on sodium channels, and, according to the sponsor, there is a lack of signal for abuse/dependence in clinical trials. Also, the company conducted one trial at 400mg/day that terminated patients immediately from drug with 1 week of follow-up. Schwartz inquired whether this information would be adequate for dependence and tolerance information. Concern was expressed that patients were tapered off of medication, which may not allow an examination of withdrawal phenomena. The division thought no taper was necessary if normal (non-seizure) patients were studied with this non- GABAergic drug. The Sponsor noted that a QT study has examined the rapid ("cold turkey") drug discontinuation.
- The division also instructed Schwartz to submit a list of the data they have assessing withdrawal and physical dependence. The agency is looking for behavioral manifestations following withdrawal of their drug, including flu-like or CNS symptoms. What the company has already completed may be adequate. Schwartz stated that their clinical trials are over and asked what the minimum duration a patient should be on the drug to assess withdrawal from the drug. FDA controlled substance staff needs to see all of Schwartz's data involving events following completion of the drug course.
- Schwartz plans on submitting the NDA in March or April 2007. The agency requires an abuse liability trial in humans. Schwartz inquired if it would be possible to submit the clinical trial report and updated abuse section around the time of the 120 day safety update of the NDA. The FDA will get back to Schwartz on this issue.
- Controlled substance staff would be happy to look at Schwartz's abuse liability protocol before the study begins. There is usually a 30 day turnaround time.
- The MedDRA list of terms that was provided to the Sponsor in the pre-NDA meeting minutes is not negotiable because the terms relate to abuse liability, safety, and/or pharmacology of lisdexamphetamine.



- The diabetic neuropathy subjects should be pooled into two separate pools: placebo versus drug analysis from the controlled diabetic pain studies and all diabetic pain patients from the complete pain database. The epilepsy ISS should contain a full safety analysis of these pools. It is noteworthy that upon reading pre-meeting minutes regarding this question a typo may have obscured the the correct answer to this question. The response should have stated: "The pain pool should be separately analyzed and included in the ISS. It should also be divided into two separate analyses as you are planning for the epilepsy populations: i.e. 1) placebo versus drug analysis from the controlled pain studies 2) all pain patients from the complete pain database (controlled and open label studies)."
- The cutoff for the safety data from the pain trials will be February 2006 and the cutoff for the epilepsy data is April 2006. The division asks that they concentrate on the cases that are serious or result in discontinuations in the 120 day safety update.
- The narratives will be in an appendix in the back of the ISS. Epilepsy and pain data will be organized by trial in subsections. In narratives with more than one section, they go in most severe section with hyperlinks. The division responded that this seems to be what we are asking for.
- The cardiac data is under review by the FDA's cardiologists. The division believes the prolongation of the PR interval is real, but a more significant problem for diabetic patients. In the SP768 trial, the maximum daily dose has been lowered to 400mg/day.
- Schwartz will submit identical NDAs — to the agency, but have different tables of contents and cover letters for each NDA. b(4)
- It would be helpful to the medical officer to include a copy of his ISS template with pertinent sections of the template hyperlinked to the actual NDA. This review aid while very helpful is not required. The medical officer can supply the template.
- The division asked if the renal impairment study was completed. It is complete and will be in the next version of the IB.

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this page is the manifestation of the electronic signature.**

/s/

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Russell Katz  
8/8/2006 11:10:01 AM

**Kim Overton - Meeting Minutes; IND 57,939**

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**From:** "Griffis, Melina" <GriffisM@cdcr.fda.gov>  
**To:** "Byron.Scott@schwarzbiosciences.com" <Byron.Scott@schwarzbiosciences.com>  
**Date:** 12/1/2004 8:29 AM  
**Subject:** Meeting Minutes; IND 57,939

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Hi Byron,

Attached are the EOP2 mtg minutes for IND 57,939. Regarding IND 68,407, I will be in training on the 9<sup>th</sup> so another project manager, Richardae Taylor will be covering the meeting for me. You should call her at 301-594-5793 just prior to the meeting and she will bring you upstairs.

Take care

\*\*\*\*\*  
Melina Griffis, R.Ph, LCDR-USPHS  
Senior Regulatory Project Manager  
Division of Neuropharmacological Drug Products  
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(301) 594-5526  
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## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** November 3, 2004  
**Application:** IND 57,939; SPM 927  
**Indication:** Epilepsy  
**Type of Meeting:** EOP2  
**Meeting Chair:** Russell Katz, M.D.  
**Meeting Recorder:** Melina Griffis, R.Ph.

### FDA Attendees:

|                                           |                                |
|-------------------------------------------|--------------------------------|
| Russell Katz, M.D., Division Director     | John Feeney, M.D., Team Leader |
| Norman Hershkowitz, M.D., Medical Officer | Sharon Yan, Ph.D., Biometrics  |
| Ed Fisher, Ph.D., Pharm/tox               | Lois Freed, Ph.D., Pharm/tox   |
| Ramana Uppoor, Ph.D., Biopharm            | John Duan, Ph.D., Biopharm     |
| Melina Griffis, R.Ph., Project Manager    |                                |

### Sponsor Attendees:

|                           |                          |
|---------------------------|--------------------------|
| Elena Cleary, Ph.D.       | Maria Crampen-Ant, Ph.D. |
| Pamela Doty, Ph.D.        | David Herbert, Ph.D.     |
| Rolf Horstmann, M.D.      | Harald Jordan, Ph.D.     |
| Dirk Kropeit, M.D.        | Peter-Joseph Kux, Ph.D.  |
| David Rudd, R.Ph.         | Byron Scott, R.Ph.       |
| Kenneth Sommerville, M.D. | Thomas Stoehr, Ph.D.     |

**Discussion Points:** Below are the sponsor's questions with the appropriate FDA responses.

### CMC

1. Does the Division agree with the proposed specification for SPM 927 drug substance? **The set of tests for the drug substance specifications is acceptable. We defer comment on the acceptance limits to NDA review.**
2. Does the Division agree with the proposed stability program and protocols for SPM 927 drug substance and for SPM 927 film-coated tablets? **The proposed drug substance stability protocol is sufficient to provide adequate information for NDA filing. The proposed bracket design for SPM 927 tablets does not provide for monitoring of the appearance and color of the different strengths that could be of different colors and appearance from the 50 and 300 mg strengths. It is possible for the appearance of different colored tablets made from the same \_\_\_\_\_ to change. Please address that issue.**

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### Other Comments

#### Polymorphism and Bioavailability

Please address any claims or questions concerning BCS classification of the drug substance to the biopharmaceutics review team.

**Impurities**

The structures of impurities and degradation products have not been explicitly identified. They should be provided in due course. (Cf. ICH Q3A)

**Drug Product Specifications**

Identification of the API in the drug product by a \_\_\_\_\_ IS not regarded as specific. See ICH guidance Q6A § 3.2.2 (b). An additional provision for API identity is recommended.

The Agency recognizes one set of regulatory specifications for a drug product. If tighter specifications are to be used for release testing, separate from shelf-life specifications, we recommend that they be employed as in-house specifications.

**Nonclinical**

3. Does the Division agree that the completed and ongoing nonclinical program is adequate for submission and approval of a marketing application for adjunctive treatment of adults with partial seizures? **Quantitative comparative data on metabolites across species NEED to be submitted. Additionally the rat and rabbit developmental studies may not have evaluated high enough doses. Although the high doses were not maternally toxic based on body weight gain or mortality, we recognize that clinical signs (convulsions) were considered dose-limiting. Therefore, the sponsor should make the case that these studies are adequate.**

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**Other Comments (provided to the sponsor via email on 11/16/04)**

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Clinical

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6. Does the Division agree that the completed and ongoing clinical pharmacology program is adequate for submission and approval of a marketing application for adjunctive treatment of adults with partial seizures? The completed and ongoing program covers most of the clinical pharmacology aspects. However, with limited information, the quality and the suitability of the studies can not be assessed. In addition, more information of the following aspects should be provided.

-The metabolic pathway of SPM 927 should be clarified (i.e. how this drug is metabolized).

- The inhibition of CYP2C19 by SPM 927 and its clinical significance should be further investigated. Although the sponsor claimed that the ratio of  $[I]$  to  $k_i$  was less than 0.1, we do not know the exact value of  $[I]/k_i$  in this case and can not rule out the possibility of an interaction with a CYP2C19 substrate (unless the  $[I]/k_i$  is extremely low).

-The to-be-marketed formulation is different from that used in clinical trials. The claim that SPM 927 is a Class I drug must be supported by convincing data. Otherwise, a bioequivalence study is needed.

-Since the drug has five polymorphs, the solubility of each of them should be characterized and submitted.

7. The potential for pharmacokinetic interactions between SPM 927 and other marketed antiepileptics (AEDs) is being evaluated using data from in vitro

evaluation (see Section 3.2.2.3) as well as healthy volunteer studies and adjunctive studies conducted in patients with uncontrolled partial seizures (see Section 4.2.9.1).

In vitro, SPM 927 has minimal interaction with the CYP-P450 enzyme system and a low potential for pharmacokinetic interaction with concomitant AEDs. SPM 927 exhibits low binding to plasma proteins (<15%). Four trials were conducted in healthy volunteers. SPM 927 (400 mg per day) had no effect on the pharmacokinetic disposition of carbamazepine [SP618]. Pharmacokinetics of SPM 927 were also not affected by the CYP-P450 inducer, carbamazepine (400 mg/day) [SP603]. SPM 927 (400 mg per day) did not alter the pharmacokinetic disposition of valproate [SP601]. Pharmacokinetics of SPM 927 were also not affected by the CYP-P450 inhibitor, valproate (600mg/day) [SP602]. Potential drug interactions between SPM 927 and other AEDs (carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, topiramate, valproate, etc.) were assessed by pharmacokinetic screening. In SP667, evaluation of the serum concentrations of SPM 927 and these AEDs indicated that SPM 927 does not influence the plasma concentration of the above AEDs. These same analyses will also be done for the placebo-controlled studies, SP754 and SP755. For SP754 and SP755, population pharmacokinetic analyses will be performed to characterize the pharmacokinetics of SPM 927 in patients. The analyses will be also used to identify any specific AED that affects the pharmacokinetics of SPM 927.

Does the Division agree that the above approaches provide adequate evaluation of potential AED pharmacokinetic interactions to support approval of SPM 927 for the proposed indication? Generally, the answer is yes. However, the issues raised in Question #6 should be noted. In addition, pharmacodynamic interactions can not be excluded.

8. Trial SP667 (see Section 4.3.2.3) and the 2 Phase 3 trials, SP754 and SP755 (see Section 5.5), have been designed and powered to evaluate one primary endpoint for the FDA (change in seizure frequency) and one primary endpoint for the EMBA (50% responder rate). Does the Division agree that this approach is acceptable? Yes
9. Does the Division agree that the results from the completed clinical trial (SP667) along with at least one positive adequate and well controlled trial (SP754 and/or SP755) will provide sufficient evidence of the safety and efficacy of SPM 927 for marketing approval for the following indication?

Assuming there are no review issues with the protocol design and statistic plan the phase two trial along with another positive study would be adequate. The Sponsor asked, in light of the negative results for the 200 mg/day dose in the phase II study, will the division label this dose if a second phase III study indicated a positive result

at that specific dose? The division responded that this is a possibility, but it is dependent upon the strength of the result. It was also noted that if two doses do not appear different in efficacy but different in tolerability the lower, more tolerated, dose will be labeled as the recommended dose. The Sponsor asked whether \_\_\_\_\_' guidelines are still applicable. The division noted yes but that they will always consider an argument that challenges this.

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10. An overall evaluation of ECG data obtained in Phase 1 and 2 clinical trials in different populations and after different routes of administration did not show a clinically relevant influence of SPM 927 on the electrical conductivity and the repolarization phase of the myocardium (see Sections 4.4.2.6.1 and 4.4.3). Reference is made to a fax from the Division of Anesthetic, Critical Care, and Addiction Drug Products dated 24 August 2004 stating: "Provided that the Phase 1 studies from which the data were obtained cover the maximal concentration of SPM 927 that would be observed in clinical settings, a formal QT study may not be required".

Does the Division agree with the proposed trial design and SPM 927 doses (see Section 4.2.10 and QT protocol (SP640) submitted to the Division on 10 March 2004)?

Does the Division require a formal QT trial to be submitted with the initial marketing application? An analysis of preexisting data of the EKGs obtained in the previous and ongoing trials may be sufficient. The analysis should include mean and outlier analysis that includes correlation with dose and time following drug and comparison to placebo. A concentration versus response QTc analysis should also be performed. The data should be analyzed conventional QTc analysis techniques. Both animal and clinical studies indicate the potential for conduction disturbances not necessarily related to QT alterations. For example, there have been a number of adverse reporting events for heart block and bundle branch block. For this reason the Sponsor should perform a similar analysis of other pertinent intervals (e.g. PR and QRS) in a fashion similar to that outlined for QTc analysis: i.e. correlation with dose and time after dose, concentration response analysis, along with comparison with placebo. Mean and outlier analysis should be performed: e.g. for PR outliers may be categorized as >200 and >250 and QRS outlier >120. Lastly a comparative analysis in diabetic versus epilepsy populations may be of interest. A careful analysis of cardiovascular AEs, which includes the examination of the potential association with any electrophysiological changes, should also be performed.

11. The completed program will expose 1200 patients with partial seizures to SPM 927. Of these, approximately 700 will have been exposed to SPM 927 for 6 months and 300 for 1 year or more. In a parallel development program,

approximately 1550 patients with neuropathic pain will be exposed to SPM 927 at the time of submission. Similar to patients with partial seizures, many of these neuropathic pain patients will also continue in the long-term extension trials. Thus at the time of submission:

- A total of 1200 patients with partial seizures would have been exposed to daily doses of 200mg/day or higher.
- At least 700 patients with partial seizures would have been exposed to daily doses of 400mg/day or higher
- A total of 3200 healthy subjects and patients with epilepsy and neuropathic pain will have been exposed to SPM 927.
- Of the total elderly ( $\geq 65$  yrs of age) population included in Phase 1-3 (~185 subjects), 23 will be healthy subjects from Phase 1, approximately 150 will be patients with neuropathic pain, and approximately 12 will be patients with epilepsy.

Does the Division agree that this will provide an adequate evaluation of safety for the proposed indication? Numbers are generally sufficient. There are however only a small number of elderly. It would be best to acquire more data on the elderly. The label will reflect the absence of elderly data if there is a paucity of such information.

12. Given the clinical safety data collected to date (see Section 4.4), does the Division agree with the proposed clinical safety strategy (see Section 5.7)? Are there any additional specific adverse events that require further assessment?

**Additional Safety issues raised by the division are as follows:**

- The division questioned whether the 600 mg dose was well tolerated as presently administered considering the high drop-out rate. It was suggested that a slower titration rate may be tried. The Sponsor did not feel that this would influence the tolerability.
- The case of "toxic hepatitis" was discussed. The division noted that this is a worrisome case and asked for more information. The Sponsor noted that the event appeared to occur 13 days after a 12 day multiple dose trial in normal subjects. "Dark urine" was noted according to the Sponsor but an abnormal bilirubin was not reported. According to the Sponsor, although there have been some reports of significant elevations in LFTs, there have been no cases of significantly elevated bilirubin reported to date. The Sponsor was asked to send additional information on the above noted patient and a general summary and analysis of cases of abnormal liver function.
- A large number of cases of "abnormal vision" have been reported. The division will need more specific information on these cases.
- The division is generally interested in issues of a potential association between anticonvulsants and suicide. The division will be circulating information as to how to perform a retrospective analysis of this data.
- The division has noted a very high incidence of nausea and vomiting. The Sponsor should examine this association thoroughly.

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Pediatric

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- Is the Division prepared to grant a deferral for submission of a pediatric package at the time of original submission? Deferral of the pediatric package is acceptable.

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Minutes Preparer: Melina Griffis R.Ph.

Chair Concurrence: Russell Katz, M.D.

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/s/

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Russell Katz  
12/1/04 08:11:34 AM