

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202543Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 202543

HFD # 120/Division of Neurology Products

Trade Name n/a

Generic Name Levetiracetam in Sodium Chloride Injection

Applicant Name HQ Specialty Pharma Corporation

Approval Date, If Known: November 9, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21982

Kepra (levetiracetam) Injection

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ! NO
! Explain:

Investigation #2 !
!
IND # YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES ! NO
Explain: ! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

Name of person completing form:

Jacqueline H. Ware

Senior Regulatory Project Manager

Date: November 2, 2011

Name of Office/Division Director signing form:

Russell G. Katz,

Director, Division of Neurology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

JACQUELINE H WARE
04/17/2012

RUSSELL G KATZ
04/20/2012

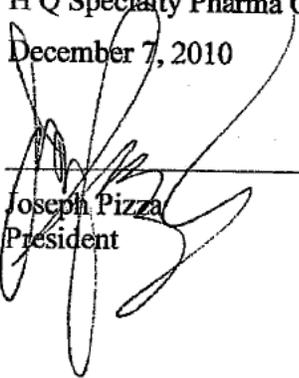


1.3.3. Debarment Certification and List of Convictions

H Q Specialty Pharma Corporation (HQ) hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306(a) or 305(b) of the United States Federal Food, Drug and Cosmetic Act ("FDCA"), or as may be amended, in connection with this application for Levetiracetam Injection, Ready-to-Infuse Solution, 500 mg/100 mL (5 mg/mL).

H Q Specialty Pharma Corporation (HQ) hereby certifies that it did not and will not use in any capacity the services of any person convicted under section 306(a) and (b) of the Federal Food Drug, and Cosmetic Act in connection with this application for Levetiracetam Injection. ^{(b) (4)} [REDACTED] ^{(b) (4)} [REDACTED] 500 mg/100 mL (5 mg/mL).

H Q Specialty Pharma Corporation
December 7, 2010



Joseph Pizza
President

Merchant, Lubna

From: Merchant, Lubna
Sent: Monday, October 31, 2011 1:01 PM
To: Ware, Jacqueline H
Subject: RE: Successfully Processed eCTD: nda202543 in DARRTS

DMEPA finds the revised container labels, overwrap, carton and insert labeling submitted by the Applicant on 10/27/11 acceptable.

Thanks,
Lubna

Lubna Merchant, M.S., Pharm.D.
Team Leader
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
Office 301.796.5162
lubna.merchant@fda.hhs.gov

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

From: Ware, Jacqueline H
Sent: Friday, October 28, 2011 2:15 PM
To: Hershkowitz, Norman; Rusinowitz, Martin; Kelley, Laurie; Merchant, Lubna; Claffey, David; Heimann, Martha R
Cc: Katz, Russell G
Subject: FW: Successfully Processed eCTD: nda202543 in DARRTS

Folks,
Please take a look at the labeling (PI, bag, overwrap, and carton) and let me know if any further edits are needed. Please reply by next Wed., Nov. 2nd.

Thanks,
Jackie

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

From: asr-dontreply@fda.hhs.gov [mailto:asr-dontreply@fda.hhs.gov]
Sent: Thursday, October 27, 2011 2:28 PM
To: Ware, Jacqueline H; CDER-OND-DNP-EDRNOTIFY; CDER-EDR ASR Document Coordinators; CDER-EDRSTAFF; CDER-EDRADMIN; CDER ESUB; Khalsa, Gurinders J; Livermore, Russell J; Thompson, Douglas L. *; CDER-EDRSTAFF
Subject: Successfully Processed eCTD: nda202543 in DARRTS

Successfully Processed eCTD: nda202543 in DARRTS. Details below:

EDR Location: \\CDSESUB1\EVSPROD\NDA202543\202543.enx

For Document Room Staff Use:
Application Type/Number: nda202543
Incoming Document Category/Sub Category: Electronic_Gateway
Supporting Document Number: 9
eCTD Sequence Number: 0008
Letter Date: 10/27/2011
Stamp Date: 10/27/2011

Receipt Date/Time from Notification: 10-27-2011, 13:53:58
Origination Date/Time from Notification: 10-27-2011, 13:48:46
DOCUMENT ID: 4955883

356H Form: \\CDSESUB1\EVSPROD\NDA202543\0008\m1\us\11-forms\fda-form-356h\form-fda-356h-sn0008.pdf

Cover Letter: \\CDSESUB1\EVSPROD\NDA202543\0008\m1\us\12-cover-letters\cover-lettersn0008.pdf

3397 Form: NOT FOUND

3674 Form: NOT FOUND

For EDR Staff Use:

The submission has already been processed. The following information is provided if verification is required. No additional action is required on your part

EDR Location: \\CDSESUB1\EVSPROD\NDA202543\0008
Submission Size: 2874930
Gateway Location: \\chdc9681\cderesub\inbound\ectd\ci1319737724148.235942@llnap12_te

Copy to EDR Status: Good-1

For CDER Project Manager Use:

The following submission received through the Electronic Submission Gateway has been processed using the following information. This information will be updated once Document Room personnel have been able to verify the content of the submission.

Application Type/Number: nda202543
Incoming Document Category/Sub Category: Electronic_Gateway
Supporting Document Number: 9
eCTD Sequence Number: 0008
Letter Date: 10/27/2011

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

/s/

LUBNA A MERCHANT
10/31/2011

Ware, Jacqueline H

From: Ware, Jacqueline H
Sent: Friday, October 14, 2011 9:32 AM
To: 'jeanne squeglia hq'; 'michele msrofani hq'; 'Susan Laffey HQ'
Cc: Choy, Fannie; Ware, Jacqueline H
Subject: RE: FDA advice: re: NDA 202543 Levetiracetam labeling comments

Attachments: N202543 Levetiracetam in Sodium Chloride Injection FDA Proposed Labeling 10.14.11 clean.doc; N202543 Levetiracetam in Sodium Chloride Injection FDA Proposed Labeling 10.14.11 marked.doc



N202543



N202543

vetiracetam in Sodiivetiracetam in Sodi

Dear Jeanne,

Attached please find FDA's proposed draft labeling for NDA 202543/Levetiracetam in Sodium Chloride Injection (clean and marked versions). The base document is the firm's version submitted on April 26, 2011.

Please share this proposed labeling with the appropriate people on your team and let me know as soon as possible if it is acceptable. If you wish to send a counter-proposal, please provide it via email as a tracked-changes WORD document using our proposed labeling as the base.

If you have any questions, please don't hesitate to let me know.

Kind regards,

Jackie Ware

Jacqueline H. Ware, Pharm.D., RAC
Captain, United States Public Health Service
Senior Regulatory Project Manager
FDA/CDER/OND/ODEI/Division of Neurology Products
phone: 301-796-1160

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

From: Ware, Jacqueline H
Sent: Wednesday, October 12, 2011 10:01 AM
To: 'jeanne squeglia hq'
Cc: Choy, Fannie
Subject: RE: FDA advice: re: NDA 202543 Levetiracetam labeling comments

Dear Jeanne,

Yes...I expect to email you our draft proposed labeling by COB on Friday, October 14, 2011. It will likely be a clean version in WORD format.

Thank you for following up.

Jackie

Jacqueline H. Ware, Pharm.D., RAC
Captain, United States Public Health Service
Senior Regulatory Project Manager
FDA/CDER/OND/ODEI/Division of Neurology Products
phone: 301-796-1160

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

From: jeanne squeglia hq [mailto:jsqueglia@hqspecialtypharma.com]
Sent: Wednesday, October 12, 2011 9:12 AM
To: Ware, Jacqueline H
Cc: Choy, Fannie
Subject: RE: FDA advice: re: NDA 202543 Levetiracetam labeling comments

Dear Jackie,

Please advise if we are still on target for the below communication.

Thanks and best regards,
Jeanne

From: Ware, Jacqueline H [Jacqueline.Ware@fda.hhs.gov]
Sent: Thursday, August 18, 2011 9:18 AM
To: jeanne squeglia hq
Cc: Choy, Fannie; Ware, Jacqueline H
Subject: RE: FDA advice: re: NDA 202543 Levetiracetam labeling comments

Dear Jeanne,

As stated in our March 25, 2011 filing communication letter, "we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by October 14, 2011." It is possible that the review team may have comments ready before then. If that happens, I will send them on to you.

Many thanks,
Jackie

Jacqueline H. Ware, Pharm.D., RAC
Captain, United States Public Health Service
Senior Regulatory Project Manager
FDA/CDER/OND/ODEI/Division of Neurology Products
phone: 301-796-1160

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

From: jeanne squeglia hq [mailto:jsqueglia@hqspecialtypharma.com]

Sent: Monday, August 15, 2011 3:54 PM
To: Choy, Fannie
Cc: Ware, Jacqueline H
Subject: RE: FDA advice: re: NDA 202543 Levetiracetam labeling comments

Dear Fannie

Please note we are finalizing the changes and should have the same to you by end of the week.

Will we be receiving comments on the package insert? If so, can you advise when?

Thanks,
Jeanne

From: Choy, Fannie [Fannie.Choy@fda.hhs.gov]
Sent: Wednesday, August 10, 2011 1:47 PM
To: jeanne squeglia hq
Cc: Ware, Jacqueline H
Subject: RE: FDA advice: re: NDA 202543 Levetiracetam labeling comments

Dear Jeanne,

In response to the new proposed established name for your pending NDA 202543 levetiracetam, the Office of New Drug Quality Assessment finds the revised name unacceptable. The Agency has discussed extensively on the nomenclature of your product, (b)(4) should not be part of the established name. We recommend the established name as presented previously.

For the 500 mg/100 mL dosage strength: "Levetiracetam in 0.82% Sodium Chloride Injection".

Please let me know if you have any questions.

Regards,
Fannie

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

From: jeanne squeglia hq [mailto:jsqueglia@hqspecialtypharma.com]
Sent: Friday, August 05, 2011 11:25 AM
To: Choy, Fannie
Cc: Ware, Jacqueline H
Subject: RE: FDA advice: re: NDA 202543 Levetiracetam labeling comments

Dear Fannie

Thank you for your comments below. We will formally submit the changes as requested shortly through the electronic gateway. However we would like to propose the following established name:

"Levetiracetam (b)(4) in 0.82 % sodium chloride injection" for 500 mg/100 mL
"Levetiracetam (b)(4) in 0.75 % sodium chloride injection" for 1000 mg/100 mL
"Levetiracetam (b)(4) in 0.54% sodium chloride injection" for 1500 mg/100 mL

We note other approved products use this terminology.

We look forward to your response.

Best regards,
Jeanne

From: Choy, Fannie [Fannie.Choy@fda.hhs.gov]
Sent: Wednesday, August 03, 2011 6:06 PM
To: jeanne squeglia hq
Cc: Ware, Jacqueline H; Choy, Fannie

Subject: FDA advice: re: NDA 202543 Levetiracetam labeling comments

Dear Ms. Squeglia:

I am responding to your inquiry regarding our review of the proposed established name for your pending NDA 202543. We have finished the initial review of your proposed established name, and proposed container/carton labeling. The Agency is providing the following recommendations and comments.

Established Name

The Agency finds your proposed established name, Levetiracetam Injection (b)(4) (b)(4), unacceptable. Delete the statement (b)(4) from all labels and labeling. We recommend the established name for each strength include the concentration of sodium chloride present, e.g. for the 500 mg/100 ml dosage strength - revise the established name to read "Levetiracetam in 0.82% Sodium Chloride Injection".

Please ensure that the established name is ½ the size of the proprietary name, and has prominence commensurate with the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

Proposed Container Label, Overwrap and Carton Labeling (All sizes and strengths)

1. Revise the route of administration from "I.V. Use Only" to read "For Intravenous Infusion Only."

1. The strength presentation is not prominently displayed. Increase the prominence of the strength presentation by increasing the font and using other means such as boxing or highlighting so that it is displayed prominently on the label.

1. The three strengths are not well differentiated from each other. The proposed labels employ the different color in the strength presentation; however, since the format and content of other information on the label is the same between the strengths, this is not adequate to differentiate the strengths. To avoid selection errors, revise the labels so that the strengths are adequately differentiated from each other. This can be achieved by increasing the prominence of the strength presentation and utilizing the strength presentation color in the presentation of the established names.

1. The container label is cluttered with unnecessary information. The clutter decreases the readability of the information on the labels. We request you make the following revisions to improve readability and prominence of information on the proposed labels:

1. Delete the statement (b)(4)
2. Delete the statement 'See USP controlled temperature'
3. Delete the statement (b)(4)
4. Revise the Usual dosage statement to read: Usual Dosage: See package insert.
5. Revise the "TO OPEN" statement to read as follows:

TO OPEN: TEAR AT NOTCH: Do not use if overwrap has been previously opened or damaged. Use unit promptly once overwrap is removed.

1. Move the statement (b)(4) to appear after the storage statement.

We ask that you respond to these issues promptly in order to continue our evaluation of your NDA. If you have any questions, please feel free to contact Jackie or me.

Sincerely,

Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4389
Silver Spring, MD 20993-0002
301-796-2899 phone
301-796-9842 fax
fannie.choy@fda.hhs.gov<mailto:fannie.choy@fda.hhs.gov>

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61 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

JACQUELINE H WARE
10/14/2011

Choy, Fannie

From: Choy, Fannie
Sent: Tuesday, September 27, 2011 4:22 PM
To: 'mscrofani@hqspecialtypharma.com'
Cc: 'jeanne squeglia hq'; Ware, Jacqueline H; Choy, Fannie
Subject: FDA Information: re: NDA202543 Levetiracetam

Dear Michele,

Please refer to your pending NDA 202543 for Levetiracetam in Sodium Chloride Injection. As part of our ongoing review of your application, the CDER Microbiology [group](#) has identified the following deficiencies:

Deficiency 1:

Drug Product Specification for Endotoxin

The drug product specification for the endotoxin limit at NMT (b) (4) which calculates at (b) (4) / 100 mL infused in 15 minutes for 5 mg/mL presentation or at (b) (4) / 100 mL for 15 mg/mL presentation, exceeds the maximum threshold for human safety at 350 EU/patient/hour (I.V. drugs, K=5 EU/Kg). Therefore, the endotoxin limit for the drug product should be lowered to NMT (b) (4) /mg.

Deficiency 2:

(b) (4)

In order to continue our evaluation of your NDA, we request that you please respond by COB October 7, 2011. If you have any questions, do not hesitate to contact Jackie or me.

Best Regards,
Fannie

Fannie Choy, RPh.
Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4389
Silver Spring, MD 20993-0002
301-796-2899 phone
301-796-9842 fax

fannie.choy@fda.hhs.gov

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Choy, Fannie

From: Choy, Fannie
Sent: Friday, September 30, 2011 10:58 AM
To: 'jeanne squeglia hq'; 'mscrofani@hqspecialtypharma.com'
Cc: Ware, Jacqueline H; Choy, Fannie
Subject: FDA Information Request: re: NDA 202543 Regulatory

Dear Jeanne:

Please refer to your pending NDA 202543 for Levetiracetam in Sodium Chloride Injection. In reviewing the Patent Certification for your application, we noted that the Paragraph II patent certification submitted cited an Abbreviated New Drug Application regulation. We ask that you promptly submit an amended patent certification citing the appropriate NDA patent certification regulation under 21 CFR 314.50(i)(1).

If you have any questions, please do not hesitate to contact Jackie or me.

Regards,

Fannie

Fannie Choy, RPh.

Regulatory Project Manager
Division of Neurology Products
Center for Drug Evaluation and Research
Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4389
Silver Spring, MD 20993-0002
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/s/

YUET L CHOY
09/30/2011



NDA 202543

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

H Q Specialty Pharma Corporation
Attention: Joseph M. Pizza
President
120 Route 17 North, Suite 130
Paramus, NJ 07653

Dear Mr. Pizza:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

- Levetiracetam in 0.82 % sodium chloride injection (500 mg/100 mL)
- Levetiracetam in 0.75 % sodium chloride injection (1000 mg/100 mL)
- Levetiracetam in 0.54% sodium chloride injection (1500 mg/100 mL)

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by Cetero Research in Houston, Texas (Cetero).¹ The pervasiveness and egregious nature of the violative practices by Cetero has led FDA to have significant concerns that the bioanalytical data generated at Cetero from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented Cetero and the Agency from determining the extent and impact of these violations.

Serious questions remain about the validity of any data generated in studies by Cetero Research in Houston, Texas during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability,

¹ These violations include studies conducted by Bioassay Laboratories and BA Research International specific to the Houston, Texas facility.

drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by Cetero Research in Houston, Texas during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have questions, contact your designated Regulatory Project Manager, at (301) 796-2250.

Sincerely,

{See appended electronic signature page}

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

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/s/

JACQUELINE H WARE

09/15/2011

Signed for Dr. Russell G. Katz

Choy, Fannie

From: Choy, Fannie
Sent: Wednesday, August 03, 2011 6:07 PM
To: 'jsqueglia@hqspecialtypharma.com'
Cc: Ware, Jacqueline H; Choy, Fannie
Subject: FDA advice: re: NDA 202543 Levetiracetam labeling comments

Dear Ms. Squeglia:

I am responding to your inquiry regarding our review of the proposed established name for your pending NDA 202543. We have finished the initial review of your proposed established name, and proposed container/carton labeling. The Agency is providing the following recommendations and comments.

Established Name

The Agency finds your proposed established name, Levetiracetam Injection (b) (4) unacceptable. Delete the statement (b) (4) from all labels and labeling. We recommend the established name for each strength include the concentration of sodium chloride present, e.g. for the 500 mg/100 ml dosage strength - revise the established name to read "**Levetiracetam in 0.82% Sodium Chloride Injection**".

Please ensure that the established name is ½ the size of the proprietary name, and has prominence commensurate with the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

Proposed Container Label, Overwrap and Carton Labeling (All sizes and strengths)

1. Revise the route of administration from "I.V. Use Only" to read "For Intravenous Infusion Only."
2. The strength presentation is not prominently displayed. Increase the prominence of the strength presentation by increasing the font and using other means such as boxing or highlighting so that it is displayed prominently on the label.
3. The three strengths are not well differentiated from each other. The proposed labels employ the different color in the strength presentation; however, since the format and content of other information on the label is the same between the strengths, this is not adequate to differentiate the strengths. To avoid selection errors, revise the labels so that the strengths are adequately differentiated from each other. This can be achieved by increasing the prominence of the strength presentation and utilizing the strength presentation color in the presentation of the established names.
4. The container label is cluttered with unnecessary information. The clutter decreases the readability of the information on the labels. We request you make the following revisions to improve readability and prominence of information on the proposed labels:
 - i) Delete the statement (b) (4)
 - ii) Delete the statement "See USP controlled temperature"
 - iii) Delete the statement (b) (4)
 - iv) Revise the Usual dosage statement to read: Usual Dosage: See package insert.
 - v) Revise the "TO OPEN" statement to read as follows:
TO OPEN: TEAR AT NOTCH: Do not use if overwrap has been previously opened or damaged.
Use unit promptly once overwrap is removed.
 - vi) Move the statement (b) (4) to appear after the storage statement.

We ask that you respond to these issues promptly in order to continue our evaluation of your NDA. If you have any questions, please feel free to contact Jackie or me.

Sincerely,

Fannie

Fannie Choy, RPh.

Regulatory Project Manager

Division of Neurology Products

Center for Drug Evaluation and Research

Food and Drug Administration

10903 New Hampshire Avenue, WO22 Rm. 4389

Silver Spring, MD 20993-0002

301-796-2899 phone

301-796-9842 fax

fannie.choy@fda.hhs.gov

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/s/

YUET L CHOY
08/05/2011



NDA 202-543

INFORMATION REQUEST

H Q Specialty Pharma Corporation
Attention: Joseph Pizza, President
120 Route 17 North
Suite 130
Paramus, NJ 07652

Dear Mr. Pizza:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Levetiracetam Injection.

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

1. Revise the drug product specification to include a single regulatory acceptance criterion for each test. A separate acceptance criterion at drug product release can be retained as an internal rather than regulatory limit.
2. Provide updated drug product stability data to include a minimum of 12-month long-term stability data.
3. Revise the drug product post-approval stability commitment to include annual testing of one lot of each strength.
4. Provide data to demonstrate the chemical compatibility of levetiracetam (assay, related substances etc) with the other antiepileptic drugs listed in 3.2.P.8 (lorazepam, diazepam, valproate sodium). Similarly, provide data to demonstrate that these drugs do not degrade in the presence of levetiracetam.
5. Humidity was not controlled during drug product stability studies as you have claimed that the drug product contains an "impermeable aluminum overwrap". Provide evidence of the moisture impermeability of the aluminum overwrap seal (e.g. USP <671>).
6. Remove the term (b) (4) from all labels and labeling. We recognize that none of the drug product components are manufactured from (b) (4) however no demonstration was provided nor was any monitoring proposed to ensure that the drug product does not contain (b) (4). Similarly, remove the term (b) (4) from labels and labeling.

If you have any questions, contact Teshara G. Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

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

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/s/

RAMESH K SOOD
07/11/2011



NDA 202543

FILING COMMUNICATION

H Q Specialty Pharma Corporation
Attention: Joseph M. Pizza
President
120 Route 17 North, Suite 130
Paramus, NJ 07653

Dear Mr. Pizza:

Please refer to your New Drug Application (NDA) dated January 13, 2011, received January 13, 2011, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Levetiracetam Injection, (b) (4) 500 mg/100 mL (5 mg/mL).

We also refer to your additional submission dated March 10, 2011.

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 November 13, 2011.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by October 14, 2011.

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

1. We remain concerned about the need for high infusion rates with high dosages (300 ml over 15 minutes). The references provided will be used in our review of the issues of local infiltration as well as potential fluid overload, particularly in hemodynamically compromised patients.

2. We continue to have concerns about the potential for medication errors with regard to your suggestion that (b) (4)

We note your request to amend this NDA with additional information regarding two additional dosage strengths (i.e., 1000 mg/100 ml bag and 1500 mg/100 ml bag), which may address the two issues described above. It is acceptable for you to submit this information, and we will do our best to review the additional information during this review cycle. However, we remind you, that, as stated in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*, “the applicant is responsible for submission of a complete marketing application to maximize the efficiency of the review process and reduce the need for multiple cycle reviews”.

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.

LABELING

During our preliminary review of your submitted labeling, we have not been able to view your proposed **Highlights (HL)** and **Table of Contents** sections. Therefore, we are unable to confirm that these sections are properly formatted and contain appropriate content. As such, we have the following labeling comments:

Highlights (HL)

1. General comments

- a. HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- b. HL is limited in length to one-half page. If it is longer than one-half page, you should request a waiver.
- c. There should be no redundancy of information.
- d. Section headings must be presented in the following order:

Highlights Limitation Statement (required statement)
Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
Initial U.S. Approval (required information)
Boxed Warning (if applicable)
Recent Major Changes (for a supplement)
Indications and Usage (required information)
Dosage and Administration (required information)
Dosage Forms and Strengths (required information)
Contraindications (required heading – if no contraindications are known, it must state “None”)
Warnings and Precautions (required information)
Adverse Reactions (required AR contact reporting statement)
Drug Interactions (optional heading)
Use in Specific Populations (optional heading)
Patient Counseling Information Statement (required statement)
Revision Date (required information)

2. **Highlights Limitation Statement** - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”
3. **Product Title** - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.
4. **Initial U.S. Approval** - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line.

We request that you resubmit, by April 30, 2011, labeling (as pdf and WORD files) that addresses these issues. The resubmitted labeling will be used for further labeling discussions.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

If you have any questions, call or email Jacqueline H. Ware, PharmD, Senior Regulatory Project Manager, at (301) 796-1160 or Jacqueline.Ware@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

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/s/

RUSSELL G KATZ
03/25/2011



NDA 202543

NDA ACKNOWLEDGMENT

H Q Specialty Pharma Corporation
Attention: Joseph M. Pizza
President
120 Route 17 North, Suite 130
Paramus, NJ 07653

Dear Mr. Pizza:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Levetiracetam Injection, Ready-to-Infuse Solution,
500 mg/100 mL (5 mg/mL)

Date of Application: January 13, 2011

Date of Receipt: January 13, 2011

Our Reference Number: NDA 202543

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 14, 2011, 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/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. 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). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. 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
Division of Neurology Products
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/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, please call me at 301-796-1160 or email me at Jacqueline.Ware@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jacqueline H. Ware, PharmD
Senior Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

JACQUELINE H H WARE
03/01/2011