

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202543Orig1s000

OTHER REVIEW(S)

SEALD SIGN-OFF REVIEW: U.S. PRESCRIBING INFORMATION

| | |
|--|---|
| Application Number | NDA 202543 |
| Type of Application | Original NDA |
| Applicant | HQ Speciality Pharma |
| Product Name | LEVETIRACETAM IN SODIUM CHLORIDE INJECTION |
| Indication | Partial Onset, Myoclonic, and Generalized Tonic-Clonic Seizures |
| Pharmacologic Class | Antiepileptic drug |
| Office/Division | ODEI/DNP |
| Division Project Manager | Jacqueline Ware |
| Submission Date | January 13, 2011 |
| PDUFA Goal Date | November 13, 2011 |
| SEALD Sign-Off Date | November 8, 2011 |
| OND ASSOCIATE DIRECTOR FOR STUDY ENDPOINTS AND LABELING | Laurie Burke |

This memo confirms that all Selected Requirements for Prescribing Information (SRPI) criteria are met in the final agreed-upon PI as noted in the SEALD Labeling Review filed 8 Nov 2011. SEALD has no objection to PI approval at this time.

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

/s/

LAURIE B BURKE
11/08/2011

SEALD LABELING REVIEW for LEVETIRACETAM for intravenous use

This SEALD Labeling Review evaluates whether there are major aspects of the prescription labeling (U.S. prescribing information) that do not meet the requirements of 21 CFR 201.56 and 201.57 or related CDER labeling guidances and policies.

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| Division Project Manager | Jacqueline Ware |
| Submission Date | January 13, 2011 |
| PDUFA Goal Date | November 13, 2011 |
| SEALD Review Date | November 7, 2011 |
| SEALD Labeling Reviewer | Eric Brodsky, M.D. |

The following checked Selected Requirements for Prescribing Information (SRPI) items have been reviewed for this efficacy supplement. These 46 specific SRPI items assess labeling format and content according to regulations and guidances. This reviewer actively engaged with the Division of Neurology Products on the content and the format of the LEVETIRACETAM IN SODIUM CHLORIDE INJECTION prescribing information. Based on this SRPI review, there are **NO** outstanding labeling issues that must be corrected before the final LEVETIRACETAM IN SODIUM CHLORIDE INJECTION prescribing information is approved.

SEALD LABELING REVIEW

Review of Selected Requirements for Prescribing Information (SRPI) for LEVETIRACETAM

Conclusion: No SRPI deficiencies based on review of 11/7/11 USPI

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. Only identified deficiencies are checked (no checks means no deficiencies).

Highlights (HL)

- **General comments**

- 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.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information.
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are 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) |

SEALD LABELING REVIEW

- **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) safely and effectively. See full prescribing information for (insert name of drug product).**”

- **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.

- **Initial U.S. Approval**

- The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**

- All text in the boxed warning is **bolded**.
- Summary of the warning must not exceed a length of 20 lines.
- Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
- Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**

- Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
- The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
- For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
- A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
- Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

SEALD LABELING REVIEW

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:
<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection is omitted from the FPI and TOC, the heading “**Full Prescribing Information: Contents**” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”

Full Prescribing Information (FPI)

• General Format

- A horizontal line must separate the TOC and FPI.
- The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

Labeling Reviewer Comment: The sponsor of this application will agree to change the title of Section 6.1 in the FPI from "Clinical Studies Experience" to "Clinical Trials Experience" to be consistent with 21 CFR 201.57 prior to the PDUFA goal date. The approved labeling will have the correct title.

• Boxed Warning

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

• Contraindications

SEALD LABELING REVIEW

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Labeling Review Comment: This section has a similar sentence that has the same meaning. Therefore, there is no SRPI deficiency.

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use (not needed for “peds only” indications) are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling ...

(insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
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/s/

ERIC R BRODSKY
11/08/2011

REGULATORY PROJECT MANAGER PLR FORMAT LABELING REVIEW

Application: NDA 202543

Name of Drug: Levetiracetam Injection, (b) (4) 500 mg/100 ml

Applicant: HQ Specialty Pharma

Labeling Reviewed

Submission Date: January 13, 2011

Receipt Date: January 13, 2011

Review

The submitted labeling was reviewed in accordance with 21 CFR 201.56 and 201.57 and relevant labeling guidance. Labeling issues are identified on the following pages with an “X.”

In addition, the following labeling issues were identified:

1. The format of the Highlights section is not viewable in either a pdf or a WORD file. The text of the Highlights and Table of Contents sections are not included in the submitted WORD file. Therefore, the applicant should resubmit labeling files which include these sections in the pdf and WORD formats.

Recommendations

All labeling issues identified on the following pages with an “X” will be conveyed to the applicant in the filing communication letter (i.e., the 74-day letter). The applicant will be asked to resubmit labeling that addresses all the identified labeling issues within three weeks of the date of letter issuance. The resubmitted labeling will be used for further labeling discussions.

Jackie Ware

Regulatory Project Manager

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

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- **Boxed Warning**
 - Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.

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- **Contraindications**

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- **Use in Specific Populations**

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- “See FDA-approved patient labeling (Patient Information)”
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/s/

JACQUELINE H WARE
11/07/2011

RPM FILING REVIEW
(Including Memo of Filing Meeting)

| Application Information | | |
|---|---|---|
| NDA # 202543 | NDA Supplement #:S- | Efficacy Supplement Type SE- |
| Proprietary Name: Established/Proper Name: Levetiracetam Dosage Form: Ready-to-Infusion Solution (injection) Strengths: 500 mg/ 100 mL | | |
| Applicant: HQ Specialty Pharma Agent for Applicant (if applicable): n/a | | |
| Date of Application: January 13, 2011 Date of Receipt: January 13, 2011 Date clock started after UN: | | |
| PDUFA Goal Date: November 13, 2011 | | Action Goal Date (if different): |
| Filing Date: March 14, 2011 | | Date of Filing Meeting: March 3, 2011 |
| Chemical Classification: (1,2,3 etc.) (original NDAs only) 5 | | |
| Proposed indication(s)/Proposed change(s): new presentation of levetiracetam injection; <ul style="list-style-type: none"> • Levetiracetam Injection, (b) (4) is an alternative for adult patients (16 years and older) when oral administration is temporarily not feasible. • Levetiracetam Injection (b) (4) is indicated as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy. • Levetiracetam Injection, (b) (4) is indicated as adjunctive therapy in the treatment of myoclonic seizures in adults with juvenile myoclonic epilepsy. • Levetiracetam Injection, (b) (4) is indicated as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults with idiopathic generalized epilepsy. | | |
| Type of Original NDA: AND (if applicable) Type of NDA Supplement: | <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) | |
| <i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i> | | |
| Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i> | <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted | |
| Resubmission after withdrawal? <input type="checkbox"/> | | Resubmission after refuse to file? <input type="checkbox"/> |
| Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i> | <input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product) | |

| | | | | |
|---|--|-----------|-----------|----------------|
| <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other: | <input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42) | | | |
| Collaborative Review Division (if OTC product): | | | | |
| List referenced IND Number(s): IND 108762 | | | | |
| Goal Dates/Product Names/Classification Properties | YES | NO | NA | Comment |
| PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i> | ✓ | | | |
| Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i> | ✓ | | | |
| Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i> | ✓ | | | |
| Application Integrity Policy | YES | NO | NA | Comment |
| Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i> | | ✓ | | |
| <i>If yes, explain in comment column.</i> | | | | |
| <i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified: ✓</i> | | | ✓ | |
| User Fees | YES | NO | NA | Comment |
| Is Form 3397 (User Fee Cover Sheet) included with authorized signature? | ✓ | | | |

| <p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p> | <p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p> | | | | | | | | | | | | | | | | | | | |
|---|--|------------------|------------------------|----------------------------------|--|--|--|--|--|--|--|--|--|--|--|--|--|----------|--|--|
| <p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p> | <p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p> | | | | | | | | | | | | | | | | | | | |
| <p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p> | <p>YES</p> | <p>NO</p> | <p>NA</p> | <p>Comment</p> | | | | | | | | | | | | | | | | |
| <p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p> | | <p>✓</p> | | | | | | | | | | | | | | | | | | |
| <p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p> | | <p>✓</p> | | | | | | | | | | | | | | | | | | |
| <p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p> | | <p>✓</p> | | | | | | | | | | | | | | | | | | |
| <p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table> | Application No. | Drug Name | Exclusivity Code | Exclusivity Expiration | | | | | | | | | | | | | | <p>✓</p> | | |
| Application No. | Drug Name | Exclusivity Code | Exclusivity Expiration | | | | | | | | | | | | | | | | | |
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| <p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p> | | | | | | | | | | | | | | | | | | | | |
| <p>Exclusivity</p> | <p>YES</p> | <p>NO</p> | <p>NA</p> | <p>Comment</p> | | | | | | | | | | | | | | | | |
| <p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p> | | <p>✓</p> | | <p>Indication is not orphan.</p> | | | | | | | | | | | | | | | | |

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| <p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p> | | | ✓ | |
| <p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p> | | ✓ | | |
| <p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p> | | ✓ | | |
| <p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p> | | | ✓ | |

| Format and Content | | | | |
|--|---|-----------|-----------|----------------|
| <p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p> | <input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD) | | | |
| <p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p> | | | | |
| Overall Format/Content | YES | NO | NA | Comment |
| <p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p> | ✓ | | | |
| <p>Index: Does the submission contain an accurate comprehensive index?</p> | ✓ | | | |
| <p>Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p> | ✓ | | | |

¹

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

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|---|------------|-----------|-----------|--|
| <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) | | | | |
| If no, explain. | | | | |
| BLAs only: Companion application received if a shared or divided manufacturing arrangement? | | | | |
| If yes, BLA # | | | | |
| Forms and Certifications | | | | |
| <i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i> | | | | |
| Application Form | YES | NO | NA | Comment |
| Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? | ✓ | | | |
| <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i> | | | | |
| Are all establishments and their registration numbers listed on the form/attached to the form? | ✓ | | | |
| Patent Information (NDAs/NDA efficacy supplements only) | YES | NO | NA | Comment |
| Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)? | | ✓ | | No patents claimed |
| Financial Disclosure | YES | NO | NA | Comment |
| Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? | | ✓ | | None submitted. No clinical studies conducted. |
| <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> | | | | |
| <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i> | | | | |
| Clinical Trials Database | YES | NO | NA | Comment |
| Is form FDA 3674 included with authorized signature? | ✓ | | | |
| <i>If yes, ensure that the application is also coded with the supporting document category, “Form 3674.”</i> | | | | |
| <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i> | | | | |
| Debarment Certification | YES | NO | NA | Comment |
| Is a correctly worded Debarment Certification included with authorized signature? | ✓ | | | |
| <i>Certification is not required for supplements if submitted in the</i> | | | | |

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| <p><i>original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p> | | | | |
| Field Copy Certification (NDAs/NDA efficacy supplements only) | YES | NO | NA | Comment |
| <p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p> | | | ✓ | |

| Controlled Substance/Product with Abuse Potential | YES | NO | NA | Comment |
|--|------------|-----------|-----------|----------------|
| <p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p> | | | ✓ | |

| Pediatrics | YES | NO | NA | Comment |
|---|------------|-----------|-----------|----------------|
| <p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p> | | ✓ | | |
| <p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p> | | | ✓ | |
| <p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver</p> | | | ✓ | |

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

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|---|--|-----------|-----------|----------------|
| and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i> | | | | |
| If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i> | | | ✓ | |
| <u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i> | | | | |
| Proprietary Name | YES | NO | NA | Comment |
| Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i> | | | ✓ | None proposed. |
| REMS | YES | NO | NA | Comment |
| Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i> | | ✓ | | |
| Prescription Labeling | <input type="checkbox"/> Not applicable | | | |
| Check all types of labeling submitted. | <input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify) | | | |
| | YES | NO | NA | Comment |
| Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i> | ✓ | | | |
| Is the PI submitted in PLR format? ⁴ | ✓ | | | |

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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| If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i> | | | ✓ | |
| All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC? | | ✓ | | |
| MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available) | | | ✓ | |
| Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)? | ✓ | | | |
| OTC Labeling | <input type="checkbox"/> Not Applicable | | | |
| Check all types of labeling submitted. | <input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify) | | | |
| | YES | NO | NA | Comment |
| Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i> | | | | |
| Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i> | | | | |
| If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i> | | | | |
| All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA? | | | | |
| Other Consults | YES | NO | NA | Comment |
| Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i> | ✓ | | | Biopharmaceutics |
| Meeting Minutes/SPAs | YES | NO | NA | Comment |
| End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i> | | ✓ | | |

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| Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): July 22, 2010 <i>If yes, distribute minutes before filing meeting</i> | ✓ | | | |
| Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i> | | ✓ | | |

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 3, 2011

BLA/NDA/Supp #: NDA 202543

PROPRIETARY NAME: none

ESTABLISHED/PROPER NAME: Levetiracetam (b)(4) for IV use

DOSAGE FORM/STRENGTH: 500 mg/100ml

APPLICANT: HQ Specialty

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): The applicant is proposing a new presentation of levetiracetam injection that is premixed in 100 ml of sodium chloride injection at a concentration of 5 mg/ml (500mg in 100ml). The proposed indications are the same as those currently approved for Keppra (levetiracetam) Injection 500mg/5ml.

- Levetiracetam Injection, (b)(4) is an alternative for adult patients (16 years and older) when oral administration is temporarily not feasible.
- Levetiracetam Injection, (b)(4) is indicated as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy.
- Levetiracetam Injection, (b)(4) is indicated as adjunctive therapy in the treatment of myoclonic seizures in adults with juvenile myoclonic epilepsy.
- Levetiracetam Injection, (b)(4) is indicated as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults with idiopathic generalized epilepsy.

REVIEW TEAM:

| Discipline/Organization | Names | | Present at filing meeting? (Y or N) |
|-------------------------------------|--------------------|--------------------|-------------------------------------|
| Regulatory Project Management | RPM: | Jackie Ware | Y |
| | CPMS/TL: | Robbin Nighswander | N |
| Cross-Discipline Team Leader (CDTL) | Norman Hershkowitz | | Y |
| Clinical | Reviewer: | Martin Rusinowitz | Y |
| | TL: | Norman Hershkowitz | Y |
| | TL: | | |

| | | | |
|--|-------------------------------------|----------------|---|
| Clinical Pharmacology | Reviewer: | | |
| | TL: | Angela Men | Y |
| Nonclinical (Pharmacology/Toxicology) | Reviewer: | Edward Fisher | Y |
| | TL: | Lois Freed | Y |
| Product Quality (CMC) | Reviewer: | David Claffey | Y |
| | TL: | Martha Heimann | Y |
| OSE/DMEPA (proprietary name) | Reviewer: | Lubna Merchant | N |
| | RPM: | Laurie Kelley | Y |
| Other reviewers | Angelica Dorantes, Biopharmaceutics | | Y |
| Other attendees | Millie Wright, PMHS | | Y |
| | Colleen Locicero, ODEI ADRA | | Y |
| | Kelly Summers, SRPM, DNP | | Y |

FILING MEETING DISCUSSION:

| | |
|---|---|
| <p>GENERAL</p> <ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p> | <input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |
| <ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p> | <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO |
| <ul style="list-style-type: none"> Electronic Submission comments <p>List comments: none</p> | <input type="checkbox"/> Not Applicable |
| <p>CLINICAL</p> <p>Comments: Concern about high infusion rates (300mg over 15min).</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p> | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |

| | |
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| <ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> | <input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: |
| <ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO |
| <p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p> | <input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| <ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? | <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO |
| <p>BIOSTATISTICS</p> <p>Comments:</p> | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |

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| <p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p> | <p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p> |
| <p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p> | <p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p> |
| <p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p> | <p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p> |
| <p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? <p>Comments:</p> | <p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> |
| <p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p> | <p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> |
| <p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p> | <p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> |

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|---|---|
| Facility/Microbiology Review (BLAs only) Comments: | <input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter |
| REGULATORY PROJECT MANAGEMENT | |
| Signatory Authority: Russell G. Katz | |
| REGULATORY CONCLUSIONS/DEFICIENCIES | |
| <input type="checkbox"/> | The application is unsuitable for filing. Explain why: |
| <input checked="" type="checkbox"/> | The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review |
| ACTIONS ITEMS | |
| <input checked="" type="checkbox"/> | Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug). |
| <input type="checkbox"/> | If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER). |
| <input type="checkbox"/> | If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review. |
| <input type="checkbox"/> | BLA/BLA supplements: If filed, send 60-day filing letter |
| <input type="checkbox"/> | If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier) |
| <input checked="" type="checkbox"/> | Send review issues/no review issues by day 74 |
| <input checked="" type="checkbox"/> | Conduct a PLR format labeling review and include labeling issues in the 74-day letter |

| | |
|--------------------------|--|
| <input type="checkbox"/> | BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822] |
| <input type="checkbox"/> | Other |

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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/s/

JACQUELINE H WARE
11/04/2011

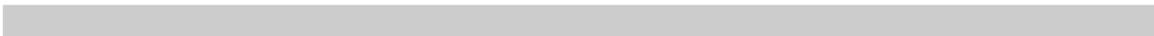
505(b)(2) ASSESSMENT

| Application Information | | |
|--|----------------------|----------------------------------|
| NDA # 202543 | NDA Supplement #: S- | Efficacy Supplement Type SE- |
| Proprietary Name: none proposed Established/Proper Name: 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) | | |
| Dosage Form: Injection Strengths: 500mg/100 ml; 1000 mg/100 ml; 1500 mg/ 100 ml | | |
| Applicant: H Q Specialty Pharma Corporation | | |
| Date of Receipt: January 13, 2011 | | |
| PDUFA Goal Date: November 13, 2011 | | Action Goal Date (if different): |
| Proposed Indication(s): Levetiracetam in Sodium Chloride Injection is an alternative for adult patients (16 years and older) when oral administration is temporarily not feasible. Levetiracetam in Sodium Chloride Injection is indicated as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy, as adjunctive therapy in the treatment of myoclonic seizures in adults with juvenile myoclonic epilepsy, and as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults with idiopathic generalized epilepsy. | | |

GENERAL INFORMATION

- 1) Is this application for a recombinant or biologically-derived product and/or protein or peptide product *OR* is the applicant relying on a recombinant or biologically-derived product and/or protein or peptide product to support approval of the proposed product?
YES NO

If "YES" contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.



**INFORMATION PROVIDED VIA RELIANCE
(LISTED DRUG OR LITERATURE)**

- 2) List the information essential to the approval of the proposed drug that is provided by reliance on our previous finding of safety and efficacy for a listed drug or by reliance on published literature. (*If not clearly identified by the applicant, this information can usually be derived from annotated labeling.*)

| Source of information* (e.g., published literature, name of referenced product) | Information provided (e.g., pharmacokinetic data, or specific sections of labeling) |
|---|---|
| NDA 21872/ Keppra (levetiracetam) Injection 500 mg/ 5 ml | Non-clinical information |
| NDA 21872/ Keppra (levetiracetam) Injection 500 mg/ 5 ml | Pharmacokinetic information |
| NDA 21872/ Keppra (levetiracetam) Injection 500 mg/ 5 ml | Clinical (efficacy and safety) information |

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

Biowaiver was requested by firm. The Office of New Drug Quality Assessment (ONDQA)-Biopharmaceutics has reviewed the information included in NDA 202-543 for Levetiracetam Injection (b)(4). Based on the evaluation of the provided information, Biopharmaceutics considers that the Applicant’s request for a waiver of the CFR’s requirement to provide in vivo BE data to support the approval of their product is acceptable and the biowaiver for the proposed Levetiracetam Injection (b)(4) (5 mg/mL, 10 mg/mL, and 15 mg/mL) is granted.

RELIANCE ON PUBLISHED LITERATURE

- 4) (a) Regardless of whether the applicant has explicitly stated a reliance on published literature to support their application, is reliance on published literature necessary to support the approval of the proposed drug product (i.e., the application *cannot* be approved without the published literature)?

YES NO
If “NO,” proceed to question #5.

(b) Does any of the published literature necessary to support approval identify a specific (e.g., brand name) *listed* drug product?

YES NO
*If “NO,” proceed to question #5.
If “YES”, list the listed drug(s) identified by name and answer question #4(c).*

(c) Are the drug product(s) listed in (b) identified by the applicant as the listed drug(s)?

YES NO

RELIANCE ON LISTED DRUG(S)

Reliance on published literature which identifies a specific approved (listed) drug constitutes reliance on that listed drug. Please answer questions #5-9 accordingly.

- 5) Regardless of whether the applicant has explicitly referenced the listed drug(s), does the application **rely** on the finding of safety and effectiveness for one or more listed drugs (approved drugs) to support the approval of the proposed drug product (i.e., the application cannot be approved without this reliance)?

YES NO

If "NO," proceed to question #10.

- 6) Name of listed drug(s) relied upon, and the NDA/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

| Name of Drug | NDA/ANDA # | Did applicant specify reliance on the product? (Y/N) |
|--|------------|--|
| Keppra (levetiracetam) Injection 500mg/ 5 mL | 021872 | Y |
| | | |

Applicants should specify reliance on the 356h, in the cover letter, and/or with their patent certification/statement. If you believe there is reliance on a listed product that has not been explicitly identified as such by the applicant, please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 7) If this is a (b)(2) supplement to an original (b)(2) application, does the supplement rely upon the same listed drug(s) as the original (b)(2) application?

N/A YES NO

If this application is a (b)(2) supplement to an original (b)(1) application or not a supplemental application, answer "N/A".

If "NO", please contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

- 8) Were any of the listed drug(s) relied upon for this application:

- a) Approved in a 505(b)(2) application?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved in a 505(b)(2) application:

- b) Approved by the DESI process?

YES NO

If "YES", please list which drug(s).

Name of drug(s) approved via the DESI process:

- c) Described in a monograph?

YES NO

If "YES", please list which drug(s).

Name of drug(s) described in a monograph:

d) Discontinued from marketing?

YES NO

If "YES", please list which drug(s) and answer question d) i. below.

If "NO", proceed to question #9.

Name of drug(s) discontinued from marketing:

i) Were the products discontinued for reasons related to safety or effectiveness?

YES NO

(Information regarding whether a drug has been discontinued from marketing for reasons of safety or effectiveness may be available in the Orange Book. Refer to section 1.11 for an explanation, and section 6.1 for the list of discontinued drugs. If a determination of the reason for discontinuation has not been published in the Federal Register (and noted in the Orange Book), you will need to research the archive file and/or consult with the review team. Do not rely solely on any statements made by the sponsor.)

9) Describe the change from the listed drug(s) relied upon to support this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsule to solution").

This application provides for a change in concentration from the RLD. The RLD is 500 mg/5ml, which must be further diluted prior to administration. This b2 product is proposed as 3 concentrations (500 mg/100ml, 1000 mg/100 ml, and 1500 mg/100ml), which does not require any further dilution prior to administration.

The purpose of the following two questions is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

The assessment of pharmaceutical equivalence for a recombinant or biologically-derived product and/or protein or peptide product is complex. If you answered YES to question #1, proceed to question #12; if you answered NO to question #1, proceed to question #10 below.

10) (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved (via an NDA or ANDA)?

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; **and** (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c)).*

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical equivalent must also be a combination of the same drugs.

YES NO

If "**NO**" to (a) proceed to question #11.
If "**YES**" to (a), answer (b) and (c) then proceed to question #12.

(b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the listed drug(s) referenced by the application a pharmaceutical equivalent?
YES NO

If "**YES**" to (c) and there are no additional pharmaceutical equivalents listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical equivalents that are not referenced by the application, list the NDA pharmaceutical equivalent(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved approved generics are listed in the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical equivalent(s):

11) (a) Is there a pharmaceutical alternative(s) already approved (via an NDA or ANDA)?

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

Note that for proposed combinations of one or more previously approved drugs, a pharmaceutical alternative must also be a combination of the same drugs.

YES NO
If "**NO**", proceed to question #12.

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval?
YES NO

(c) Is the approved pharmaceutical alternative(s) referenced as the listed drug(s)?
YES NO

If "**YES**" and there are no additional pharmaceutical alternatives listed, proceed to question #12.

If "**NO**" or if there are additional pharmaceutical alternatives that are not referenced by the application, list the NDA pharmaceutical alternative(s); you do not have to individually list all of the products approved as ANDAs, but please note below if approved generics are listed in

the Orange Book. Please also contact the (b)(2) review staff in the Immediate Office, Office of New Drugs.

Pharmaceutical alternative(s):

Keppra (levetiracetam) Tablets – NDA 021035

Keppra (levetiracetam) Solution – NDA 021505

Keppra (levetiracetam) Extended-Release Tablets – NDA 22285

There are also generic versions of the injection, tablet, solution, and extended-release formulations available.

PATENT CERTIFICATION/STATEMENTS

- 12) List the patent numbers of all unexpired patents listed in the Orange Book for the listed drug(s) for which our finding of safety and effectiveness is relied upon to support approval of the (b)(2) product.

Listed drug/Patent number(s):

No patents listed *proceed to question #14*

- 13) Did the applicant address (with an appropriate certification or statement) all of the unexpired patents listed in the Orange Book for the listed drug(s) relied upon to support approval of the (b)(2) product?

YES NO

If "NO", list which patents (and which listed drugs) were not addressed by the applicant.

Listed drug/Patent number(s):

- 14) Which of the following patent certifications does the application contain? (*Check all that apply and identify the patents to which each type of certification was made, as appropriate.*)

No patent certifications are required (e.g., because application is based solely on published literature that does not cite a specific innovator product)

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.

- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):
Method(s) of Use/Code(s):

15) Complete the following checklist **ONLY** for applications containing Paragraph IV certification and/or applications in which the applicant and patent holder have a licensing agreement:

- (a) Patent number(s):
- (b) Did the applicant submit a signed certification stating that the NDA holder and patent owner(s) were notified that this b(2) application was filed [21 CFR 314.52(b)]?
YES NO

If "NO", please contact the applicant and request the signed certification.

- (c) Did the applicant submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]? This is generally provided in the form of a registered mail receipt.
YES NO

If "NO", please contact the applicant and request the documentation.

- (d) What is/are the date(s) on the registered mail receipt(s) (i.e., the date(s) the NDA holder and patent owner(s) received notification):

Date(s):

- (e) Has the applicant been sued for patent infringement within 45-days of receipt of the notification listed above?

*Note that you may need to call the applicant (after 45 days of receipt of the notification) to verify this information **UNLESS** the applicant provided a written statement from the notified patent owner(s) that it consents to an immediate effective date of approval.*

YES NO Patent owner(s) consent(s) to an immediate effective date of approval

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/s/

JACQUELINE H WARE
11/04/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Date: June 27, 2011

Application Type/Number: NDA 202543

To: Russell Katz, Director
Division of Neurology Products

Through: Kellie Taylor, Pharm.D., MPH, Associate Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Lubna Merchant, M.S., Pharm.D, Team Leader
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Levetiracetam Injection Solution
500 mg/100 mL, 1000 mg/100 mL, and 1500 mg/100 mL

Applicant/sponsor: HQ Specialty Pharma Corporation

OSE RCM #: 2011-1300

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1. INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis evaluation of the proposed labels and labeling for Levetiracetam Injection Solution (NDA 202543) for areas of vulnerabilities that could lead to medication errors.

2. METHODS AND MATERIALS

Since Levetiracetam is currently marketed, the Division of Medication Error Prevention and Analysis (DMEPA) conducted a search of the FDA Adverse Event Reporting System (AERS) database to identify any medication errors relevant to the labels or labeling of Levetiracetam and reviewed proposed labels and labeling.

2.1. ADVERSE EVENT REPORTING SYSTEM (AERS)

An AERS search was conducted on April 28, 2011 using the search terms tradename “Keppra,” active ingredients “Levetiracetam” and verbatim terms “Levetiraceta%” and “Keppr%.” The reactions used were the HLG T term, “Medication Errors,” and the PT term, “Product Quality Issue.” The routes were limited to IV, IM, IV drip, and IV bolus. Dates were limited from July 31, 2006 to April 28, 2011.

Reports were manually reviewed to determine if a medication error occurred. Reports that did not describe a medication error or did not describe an error applicable to this review (e.g. adverse events related to Levetiracetam or concomitant medications, intentional or accidental overdose with no medication error, or not enough information to identify error) were excluded. If an error occurred, the reports were categorized by type of error and evaluated for contributing factors to the medication errors. Additionally the reports were reviewed to determine if the error could be applicable to the labels and labeling of Levetiracetam and thus pertinent to this review. Duplicate reports were combined into cases.

2.2 LABELS AND LABELING

Using Failure Mode and Effects Analysis (FMEA)¹, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the proposed labels and labeling submitted by the Applicant on April 26, 2011.

3. RESULTS

The following section describes the results of AERS and our label and labeling review.

3.1 AERS RESULTS

A total of 22 cases were retrieved in the AERS search, however after excluding cases as described in section 2.1, only 13 cases involved a medication error. These cases are categorized below:

- Wrong route error (n=4). These cases involved the Keppra oral solution being given via the intravenous route.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- Wrong frequency error (n=1), in which Keppra was prescribed as every 12 hours instead of every 24 hours.
- Wrong patient error (n=1), in this case the patient was given another patient's medications.
- Incorrect storage error (n=3). In all three cases, the product was stored in a refrigerator instead of room temperature.
- Wrong technique error (n=2). In both cases, intravenous injection of Keppra was administered without dilution.
- Wrong dose errors (n=2). In both cases, the patient received a five-fold overdose (2500 mg) instead of the prescribed amount (500 mg). One case listed the cause as the label attached to the vial may be misleading. No causality was listed in the second case.

3.2 LABELS AND LABELING

The label and labeling risk assessment identified the following deficiencies:

- (1) The use of the statement (b)(4) is misleading. The Dosage and administration section of the insert labeling does not list preparation technique prior to administration for renally impaired patients, (2) The strength presentation is not prominent, and (3) The three strengths are not well differentiated from each other, (4) The labels are cluttered which decreases the readability.

We provide label and labeling recommendations in section 5 to address these deficiencies.

4. DISCUSSION

The introduction of Levetiracetam in a ready-to-infuse 100 mL bag provides the opportunity for overdose medication errors in renally impaired patients treated with Levetiracetam. The statement (b)(4)

(b)(4) For safety reasons we recommend deleting the (b)(4) statement from the labeling.

We also note that the strength presentation is not prominently displayed on the labels and the proposed strengths need adequate differentiation 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. We recommend increased utilization of these colors throughout the labels to help differentiate the labels.

Additionally, the container label is too cluttered. This clutter decreases the readability of the label. The Agency, in conjunction with the U.S. Pharmacopeia (USP) and the Institute of Safe Medication Practices (ISMP), held a public meeting to discuss changes to the information on parenteral drug products to improve the safety of their use.² Following that meeting, DMEPA, USP and ISMP compiled a list of essential and non essential information that currently appears on infusion bags labels.

We provide recommendations to minimize some of the clutter to improve readability of the labels based on this list.

5. CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed labels and labeling identified areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations to the insert labeling in Section 5.1 Comments to the Division for discussion during the labeling meetings. Section 5.2 Comments to the Applicant for the container labels and carton labeling. We request the recommendations in Section 5.2 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Laurie Kelley at 301-796-5068.

5.1 COMMENTS TO THE DIVISION:

A. General Comments

1. The abbreviation I.V is used by the Applicant through out the insert labeling. The abbreviation, I.V can be misinterpreted to mean I.U or I.N. We recommend that IV be replaced with the text “intravenous.” In addition we recommend using the terms "greater than" or "less than" instead of the ">" and "<" symbols utilized in Table 2 of the insert labeling as these symbols have been mistaken as the opposite of their intended meaning. As part of a national campaign to decrease the use of error prone abbreviations, acronyms, dose designations, or symbols, FDA agreed to not use such error prone designations in the approved labeling of products.
2. Delete the statement (b) (4) from all insert labeling as this implies that (b) (4)
(b) (4)
(b) (4)
(b) (4) We recommend deleting this statement for all labels and labeling.
3. We defer to CMC for the acceptability of the (b) (4) statement in the established name.

B. Full Prescribing Information- Dosage and administration- Section 2

We propose changes to the insert labeling to improve the safety of the preparation technique prior to its administration to renally impaired patients. These changes are reflected in Appendix E.

5.2 COMMENTS TO THE APPLICANT:

A. Proposed Container Label (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 [REDACTED] (b) (4)
- ii) Delete the statement 'See USP controlled temperature'
- iii) Delete the statement [REDACTED] (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 [REDACTED] (b) (4) to appear after the storage statement.

B. Proposed Overwrap Labeling (All sizes and strengths)

See comments A1-A4

C. Proposed carton Labeling (All sizes and strengths)

1. See comments A1- A4

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

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/s/

LUBNA A MERCHANT
06/29/2011

KELLIE A TAYLOR
06/29/2011

KELLIE A TAYLOR on behalf of CAROL A HOLQUIST
06/29/2011