CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204417Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204417

COMPLETE RESPONSE

Sun Pharma Advanced Research Company Limited
c/o Salamandra, LLC
Attention: Karin A. Kook, PhD, Managing Director
One Bethesda Center, 4800 Hampden Lane, Ste. 900
Bethesda, Maryland 20814

Dear Dr. Kook:

Please refer to your New Drug Application (NDA) dated May 24, 2012, received May 29, 2012, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Elepsia XR (levetiracetam) extended-release tablets, 1000 mg and 1500 mg.

We acknowledge receipt of your amendment dated September 23, 2016, which constituted a complete response to our September 23, 2015, action letter. Specifically, this amendment included (1) information to address Agency comments regarding facility deficiencies, and (2) revised draft labeling, with proposed changes to dosing information for patients with renal impairment and additional labeling modifications to align with Keppra XR (innovator) labeling approved April 6, 2016.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS

The deficiencies associated with your manufacturing facilities remain unresolved. Specifically, during recent inspections of the Sun Pharmaceutical Industries, Limited (Sun Pharma) (FEI # 3002809586), facilities for this application, our field investigator conveyed deficiencies to the representative of the facilities. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRESCRIBING INFORMATION

We are unable to include in ELEPSIA XR labeling dosing information (b) (4)

(b) (4)

We reserve further comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms to format items in regulations and guidances. Your response must include updated 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.

REGULATORY INFORMATION

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf.

If you have any questions, please contact LaShawn Dianat, PharmD, Regulatory Project Manager, by phone at (240) 402-7713 or by email at lashawn.dianat@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

WILLIAM H Dunn
03/22/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204417

COMPLETE RESPONSE

Sun Pharma Advanced Research Company Limited
c/o Salamandra, LLC
Attention: Karin A. Kook, PhD, Managing Director
One Bethesda Center, 4800 Hampden Lane, Ste. 900
Bethesda, Maryland 20814

Dear Dr. Kook:

Please refer to your New Drug Application (NDA), dated May 24, 2012, received May 29, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), for Elepsia XR (levetiracetam) extended-release tablets, 1000 mg and 1500 mg.

We also refer to our September 23, 2015, letter informing you that we have rescinded our March 2, 2015, approval of NDA 204417.

We have completed our review of this application, as submitted, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS

During recent inspections of the Sun Pharmaceutical Industries, Limited (Sun Pharma) (FEI # 3002809586), facilities for this application, our field investigator conveyed deficiencies to the representative of the facilities. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRESCRIBING INFORMATION

We note that, on June 19, 2015, you submitted a prior approval (PA) labeling supplement (S-001) to this NDA, which proposes changes to Table 1 in the Dosage and Administration section of labeling. Given that the approval of this original NDA has been rescinded, we consider your pending supplement to be a minor labeling amendment to the original, now pending, NDA.

As such, we ask that, when you respond to this letter, you submit revised draft labeling that includes your proposed changes described in your June 19, 2015, submission.

In addition, submit updated 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.

To facilitate review of your submission, using the March 2, 2015, agreed upon labeling as the base document, please provide a highlighted or marked-up copy of labeling that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

REGULATORY INFORMATION

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

If you have any questions, please contact Jacqueline H. Ware, PharmD, Supervisory Regulatory Project Manager, by phone at (301) 796-1160 or by email at Jacqueline.ware@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Billy Dunn, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

WILLIAM H Dunn
09/23/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204417

COMPLETE RESPONSE

Sun Pharma Global FZE
c/o Salamandra, LLC
One Bethesda Center 4800
Hampden Lane, Suite 900
Bethesda, MD 20814-2998

Attention: Karin A. Kook, PhD
Managing Director

Dear Dr. Kook:

Please refer to your New Drug Application (NDA) dated May 24, 2012, received May 29, 2012, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Levetiracetam Extended-release Tablets, 1000mg and 1500mg.

We acknowledge receipt of your amendments dated September 7, 2012, September 27, 2012, October 11, 2012, October 25, 2012, November 29, 2012, December 17, 2012, December 28, 2012, January 17, 2013, February 25, 2013, March 4, 2013 and March 8, 2013 (2).

We also acknowledge receipt of your amendment dated March 19, 2013, which was not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL PHARMACOLOGY

We acknowledge that the data from your bioequivalence (BE) studies establish that your product is bioequivalent to Keppra XR in the fasted state. However, examination of the data from your two BE studies in the fed state (Studies 131 and 272) reveals that a substantial percent of patients have plasma concentration-time curves that differ significantly between your product and Keppra XR, despite the observation that in Study 272, your product meets bioequivalence criteria for Cmax and AUC. As you know, the Division considers similarity of the overall shapes of these curves to be an important factor in deciding that two products will have similar safety and effectiveness.

Although you provided simulations suggesting that the two products are likely to be bioequivalent at steady state (based on AUC and Cmax), the simulations provided did not

demonstrate that the individual plasma concentration-time profiles after administration of your drug at steady state would be similar in shape to that of Keppra XR.

Although you claim that, based on the Clinical Pharmacology and Biopharmaceutics Review for Keppra XR® (levetiracetam), "the range of trough concentrations resulting in subjects with prolonged pattern of release fall within the range of observed trough concentrations of 4.6-21 mg/mL in responders at 12-hour with Keppra," (b) (4) (b) (4) (b) (4). In addition, under Section 505(b)(2) of the FD&C Act, a sponsor may not reference the information contained in an FDA review of the Reference Listed Drug (RLD); the Agency can only rely on the specific information contained in the label of the RLD.

(b) (4) (b) (4). In conclusion, you have not provided evidence that the observed differences in the shape of the plasma concentration-time profiles in a substantial percent of patients after administration of your product with food will not affect the efficacy or safety of your product.

In addition, because we have found that the 1500 mg tablet does not perform similarly to Keppra XR, we cannot approve your 1000 mg tablet based on a waiver of the bioequivalence requirement for that strength.

In addition, the 1500 mg tablet showed dose dumping potential at the highest alcohol concentration (b) (4) in the *in vitro* studies. The labeling of the RLD does not have a statement limiting alcohol use. The Division is concerned that adding an alcohol use limitation to the label for your proposed ER formulation could lead to clinical consequences similar to those described above regarding fed/fasting administration. This issue, however, may potentially be resolved if you conduct an *in vivo* study to evaluate the impact of the observed effect *in vitro*.

LABELING

We reserve comment on the proposed labeling and container labels until the application is otherwise adequate. If you revise labeling, your response must include updated 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.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.
    - Present tabulations of the new safety data combined with the original NDA data.
    - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also

request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants," May 2009 at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Taura Holmes, PharmD, Regulatory Project Manager, at (301) 796-1932.

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
03/29/2013