CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208399Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208399

COMPLETE RESPONSE

TESARO, Inc.
Attention: Seth H. Miller
Director, Regulatory Affairs
1000 Winter Street, Suite 3300
Waltham, MA 02451

Dear Mr. Miller:

Please refer to your New Drug Application (NDA) dated March 11, 2016, received March 11, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for rolapitant injectable emulsion.

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.

PRODUCT QUALITY

1. You have not provided an adequate in vitro release method. As indicated in our correspondence dated May 24, 2016, for your drug product, which is an emulsion formulation, an in vitro release method needs to be developed for drug product quality control purposes (i.e., drug performance and drug quality tests) for assessing the in vitro release kinetics of rolapitant over time from the proposed drug product (performance) and for assessing any changes in composition/formulation, manufacturing site, the process, etc. of your drug product (quality).

   The following are deficiencies identified regarding your in vitro release method development and validation reports, and in vitro release data that need to be addressed and submitted for Agency review.

   A. In vitro release method development

(b) (4)

(b) (4)

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Submit the complete in vitro release method development report to the Agency for review.

B. Discriminatory capabilities of the in vitro release method

The proposed method shows discriminatory capabilities towards the changes in the composition of the formulation. However, you did not evaluate whether the proposed in vitro method can discriminate the changes in the manufacturing process.

C. Method validation

a. You stated that (b) (4)
(b) (4) eed to validate this statement and whether only released drug can permeate into the (b) (4)
b. You need to submit a method validation report for the in vitro release method in addition to a summary table for the validation of the analytical method.
c. You need to validate intermediate precision and robustness.

D. In vitro release data and specification

a. You did not report the complete in vitro release data (individual, mean, SD, RSD, mean profile) for other batches manufactured in (b) (4) (Batches 22903.002 and 22903.003) and (b) (4) (b) (4) (Batches D004007, D004065, and D004077).
b. Batch D003419 did not match any batch number reported in Module 3.2.P.5.4 batch analyses. You should provide detailed batch information.
c. You should compare the in vitro release profile of each batch manufactured in (b) (4) with that of each batch manufactured in (b) (4) and submit the complete comparative data to the Agency for review.
d. You should propose a specification for the in vitro release method.

E. Provide justification for the following statements you provided.

a. (b) (4)

b.

(b) (4)

F. You should provide rationale/justification as to why the release of free rolapitant reached only around (b) (4)% after 300 minutes and determine where the remaining (b) (4)% would be since the solution of API could reach more than (b) (4)% using the same in vitro release method.

CLINICAL PHARMACOLOGY

2. You have not provided an adequate bridge between the to-be-marketed formulation manufactured at your alternative manufacturing facility (i.e. (b) (4) (b) (4) and the formulation utilized in your clinical trial submitted to support your application, which was manufactured at a different site (i.e., (b) (4) (b) (4)

   You have not demonstrated the comparability between the products manufactured from the two sites (i.e. (b) (4) with adequate *in vitro* dissolution methods and comparable physicochemical properties.

   If you are not able to demonstrate the comparability with *in vitro* release data (see comments provided above under "Product Quality"), you need to conduct an *in vivo* BE study to support the alternative manufacturing facility.

FACILITY INSPECTIONS

3. During a recent inspection of (b) (4) (b) (4) manufacturing facility for this application our field investigators conveyed deficiencies to the representative of the facility. Satisfactory resolution of the deficiencies is required before this application may be approved.

PRESCRIBING INFORMATION

4. Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

   - The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
   - The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential

- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Submit draft labeling that addresses our proposed revisions in the attached labeling.

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. 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, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

PROPRIETARY NAME

5. Please refer to correspondence dated July 22, 2016, which addresses the proposed proprietary name, Varubi. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

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 in the original submission.
   - Present tabulations of the new safety data combined with the original application data.
   - Include tables that compare frequencies of adverse events in the original application 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 application 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 in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. 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.

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 Mary Chung, Regulatory Project Manager, at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Shari Targum, M.D., M.P.H.
Deputy Director, Acting
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):
Labeling

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

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

/s/

SHARI L TARGUM
01/11/2017