CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207963Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207963

TENTATIVE APPROVAL

Exela Pharma Sciences, LLC.
Attention: Jonathan E. Sterling
Vice President Quality and Regulatory Affairs
P.O. Box 818
1245 Blowing Rock Blvd.
Lenoir, NC 28645

Dear Mr. Sterling:

Please refer to your New Drug Application (NDA) dated August 7, 2014, received August 15, 2014, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Palonosetron Hydrochloride (HCl) Injection, 0.125 mg/mL.

We acknowledge receipt of your amendment dated September 22, 2015, which constituted a complete response to our June 15, 2015, action letter.

This NDA provides for the use of Palonosetron HCl Injection in adults for the prevention of chemotherapy-induced nausea and vomiting.

We have completed our review of this application, as amended. It is tentatively approved under 21 CFR 314.105 for use as recommended in the agreed-upon enclosed labeling (text for the package insert, text for the patient package insert) and submitted labeling (carton and immediate container labels submitted and received March 14, 2016 and March 17, 2016). This determination is based upon information available to the Agency at this time, [i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product]. This determination is subject to change on the basis of any new information that may come to our attention.

The listed drug upon which your application relies is subject to a period of patent protection and therefore final approval of your application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be made effective until the period has expired.

Your application contains certifications to each of the patents under section 505(b)(2)(A)(iv) of the Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of, this drug product under this application ("Paragraph IV certifications").

Section 505(c)(3)(C) of the Act provides that approval of a new drug application submitted pursuant to section 505(b)(2) of the Act shall be made effective immediately, unless an action is

brought for infringement of one or more of the patents that were the subject of the paragraph IV certifications. This action must be taken prior to the expiration of forty-five days from the date the notice provided under section 505(b)(3) is received by the patent owner/approved application holder. You notified us that you complied with the requirements of section 505(b)(3) of the Act.

In addition, you have notified the Agency that the patent owner and/or approved application holder has initiated a patent infringement suit against you with respect to patent 8,518,981 and 8,598,218 in the United States District Court, District of Delaware (Case 1:14-cv-01444-GMS). Therefore, final approval cannot be granted until:

1. a. expiration of the 30-month period provided for in Section 505(c)(3)(C) beginning on the date of receipt of the 45-day notice required under Section 505(b)(3), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or
   b. the date the court decides that the patents are invalid or not infringed as described in section 505(c)(3)(C)(i), (ii), (iii,) or (iv) of the Act, or,
   c. the listed patents have expired, and
2. we are assured there is no new information that would affect whether final approval should be granted.

To obtain final approval of this application, submit an amendment two or six months prior to the: 1.) expiration of the patent(s) or exclusivity protection or 2.) date you believe that your NDA will be eligible for final approval, as appropriate. In your cover letter, clearly identify your amendment as **"REQUEST FOR FINAL APPROVAL"**. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of any relevant court order or judgment settlement, or licensing agreement, as appropriate. In addition to a safety update, the amendment should also identify changes, if any, in the conditions under which your product was tentatively approved, i.e., updated labeling; chemistry, manufacturing, and controls data; and risk evaluation and mitigation strategy (REMS). If there are no changes, clearly state so in your cover letter. Any changes require our review before final approval and the goal date for our review will be set accordingly.

Until we issue a final approval letter, this NDA is not deemed approved.

Please note that this drug product may not be marketed in the United States without final agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d).

PROPRIETARY NAME

If you intend to have a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit a request for a proposed proprietary name review. See the guidance for industry titled, "Contents of a Complete Submission for the Evaluation of Proprietary Names", at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/u

cm075068.pdf and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".

If you have any questions, call Mary Chung, Regulatory Project Manager, at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

---

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

/s/

JOYCE A KORVICK
03/22/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207963

COMPLETE RESPONSE

Exela Pharma Sciences, LLC
Attention: Jonathan E. Sterling
Vice President of Quality, Regulatory and Product Development
1325 William White Place NE P.O. Box 818
Lenoir, NC 28645

Dear Mr. Sterling:

Please refer to your New Drug Application (NDA) dated August 7, 2014, received August 8, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for palonosetron hydrochloride injection, 0.125 mg/mL.

We acknowledge receipt of your amendments dated: November 20, 2014, December 31, 2014, January 8, 2015, February 27, 2015, March 4, 2015, March 6, 2015, March 9, 2015, March 24, 2015, March 25, 2015, March 31, 2015, March 31, 2015, April 24, 2015, May 13, 2015, and June 3, 2015.

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

1. You did not provide sufficient information to establish the safety of the proposed formulation of your drug product. You have not established that the hypotonicity of your drug product will not result in clinically relevant hemolysis.

   To address this deficiency, data can be provided from literature sources, nonclinical studies, or through review of intravenous products with comparable formulation characteristics. Particularly address the potential for hemolysis in patients with smaller blood volumes in whom the potential for hemolysis may be greater.

   In addition, provide justification that the design (including sample size and choice of comparator) and results of Study EPS-2014-001 support that the tonicity and pH will not pose a significant safety risk.

2. You have not provided adequate information to establish that your proposed concentration would not increase the potential for dosing errors with palonosetron. To address this deficiency, conduct a Human Factors study to characterize the risks of confusion and dosing errors between the currently marketed concentration of

palonosetron (0.05 mg/mL) and your proposed concentration ((0.125 mg/mL), and to demonstrate that your proposed strategies to address the identified risks mitigates the potential for error.

PRODUCT QUALITY

1. You have not provided an adequate description of the (b) (4) associated with the processing of the finished drug product. Provide the (b) (4) for the drug product (b) (4).

2. We cannot grant your request for a Biowaiver until the safety issues related to the hypotonicity of your product, as described above, are resolved.

REGULATORY

1. It appears that Helsinn and Roche received notice under 21 CFR 314.52. With respect to any other owner(s) of the patent(s) that are the subject of the certification or the representative designated by the owner to receive notice, please submit to FDA adequate documentation of receipt of notice, or re-notify the relevant recipients and submit to FDA adequate documentation of receipt of notice. You did not submit a return receipt or letter acknowledging receipt by the person(s) provided notice. See 21 CFR 314.52. We note that FDA did not agree to another form of documentation in advance.

PRESCRIBING INFORMATION

We reserve 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* website including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with 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

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.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

1. Consider the use of (b) (4)

(b) (4)

[redacted]

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.
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 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 LCDR James Carr, Senior Regulatory Project Manager, at (240) 402-6624.

Sincerely,

{See appended electronic signature page}

Joyce Korvick, M.D., M.P.H.
Deputy Director for Safety
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

JOYCE A KORVICK
06/15/2015