CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207155Orig1s000
207155Orig2s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207155 /Original 1
NDA 207155 /Original 2

COMPLETE RESPONSE

Spectrum Pharmaceuticals, Inc.
Attention: Anil K. Hiteshi, RAC
Vice President, Global Regulatory Affairs
157 Technology Drive
Irvine, CA 92618

Dear Mr. Hiteshi:

Please refer to your New Drug Application (NDA) dated December 23, 2014, received, December 23, 2014, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA)for EVOMELA™ (Captisol®-enabled melphalan HCl) for Injection; 50 mg (free base)/vial.

We acknowledge receipt of your amendments dated January 23; Feb 4 and 13; March 9, 17 and 23; April 20; May 8; July 27; August 25; September 2 and 30; and October 8 and 12, 2015.

NDA 207155 provides for the use of EVOMELA™ (melphalan HCl) for Injection; 50 mg (free base)/vial, for the following indications which, for administrative purposes, we have designated as follows:

- NDA 207155/Original 1 - High-dose conditioning treatment prior to hematopoietic progenitor (stem) cell transplantation in patients with multiple myeloma.

- NDA 207155/Original 2 – Palliative treatment of patients with multiple myeloma for whom oral therapy is not appropriate.

The subject of this action letter is NDA 207155/Original 1 and NDA 207155/Original 2.

All future submissions to NDA 207155/Original 1 and NDA 207155/Original 2 should specify the NDA number and the Original number to which each submission pertains.

We have completed our review of NDA 207155/Original 1 and NDA 207155/Original 2, as amended, and have determined that we cannot approve these applications in their present form.

We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. Your application referenced Drug Master File (DMF) [redacted]. This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on September 10, 2015. These deficiencies must be adequately addressed before this application can be approved. As part of your response to this letter, include the date the DMF holder amended their DMF to address the deficiencies.

2. Submit a toxicological risk assessment of [redacted] leachable from the [redacted].

LABELING

1. We reserve comment on the proposed labeling until NDA 207155/Original 1 and NDA 207155/Original 2 are 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.

FACILITY INSPECTIONS

During a recent inspection of the [redacted] manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

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

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 NDA 207155/Original 1 and NDA 207155/Original 2 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 for these indications until you have been notified in writing that NDA 207155/Original 1 and NDA 207155/Original 2 are approved.

If you have any questions, call Rachel McMullen, Regulatory Project Manager, at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
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/

EDVARDAS KAMINSKAS
10/22/2015