CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208400Orig1s000
208400Orig2s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208400, Original-1
NDA 208400, Original-2

COMPLETE RESPONSE

Silvergate Pharmaceuticals, Inc.
Attention: Michael C. Beckloff
Chief Development Officer
7300 West 110th Street, Suite 950
Overland Park, KS 66210

Dear Mr. Beckloff:

Please refer to your New Drug Application (NDA) dated August 31, 2015, received August 31, 2015, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xatmep (methotrexate) Oral Solution, 2.5 mg/mL.

We also acknowledge receipt of your amendment dated June 22, 2016, 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.

NDA 208400 provides for the use of Xatmep (methotrexate) Oral Solution, 2.5 mg/mL for the following indications which, for administrative purposes, we have designated as follows:

- NDA 208400/Original 1 – Treatment of pediatric patients with acute lymphoblastic leukemia (ALL) as part of a combination regimen.

- NDA 208400/Original 2 – Management of children with active polyarticular juvenile idiopathic arthritis (pJIA), who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full dose non-steroidal anti-inflammatory agents (NSAIDs).

The subject of this action letter is NDA 208400/Original-1 and NDA 208400/Original-2.

All future submissions to NDA 208400/Original-1 and NDA 208400/Original-2 should specify the NDA number and the Original number to which each submission pertains.

We have completed our review of NDA 208400/Original-1 and NDA 208400/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.

FACILITY INSPECTIONS

During a recent inspection of the (b) (4) 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.

LABELING

We reserve comment on the proposed labeling until NDA 208400/Original-1 and NDA 208400/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.

Your proposed prescribing information (PI) was not in compliance with PLLR (and PLR) labeling regulations (21 CFR 201.56(d) and 201.57) and not consistent with PLLR and PLR labeling guidances. Please refer to FDA's PLR Requirements for Prescribing Information website for additional information, including labeling resources (http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm).

In addition, the PI for a drug submitted under a 505(b)(2) application does not need to be identical to the PI for the reference drug. The PI for the 505(b)(2) application must meet all labeling regulatory requirements, should be consistent with labeling regulations and guidance recommendations, and should reflect currently available information for safe and effective use of the 505(b)(2) drug. When resubmitting the Prescribing Information in the future, please be sure to update labeling so that it will provide updated information on the safe and effective use of your product.

When you respond to the above facility inspections deficiencies, please submit draft labeling revised as follows.

The Pregnancy and Lactation Labeling Rule (PLLR) format required for this NDA should include a comprehensive, integrated review of the published literature sufficient to support the basis for the warnings related to methotrexate exposure during the periconceptional and prenatal periods, as well as the risk of infertility for females and males or reproductive potential following methotrexate exposure.

1. Provide a comprehensive, integrated review of the published literature to support the Warnings and Precautions related to:
   a. Embryo-fetal toxicity/fetal death/congenital anomalies
   b. Effects on fertility and its duration

2. Propose labeling language for the Human Data sub-heading under Section 8.1 Pregnancy of the full prescribing information. Refer to the PLLR guidance for additional information.

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 208400/Original-1 and NDA 208400/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 208400/Original-1 and NDA 208400/Original-2 are approved.

If you have any questions, please contact the regulatory project managers listed below.

NDA 208400/Original-1	Jessica Boehmer, Division of Hematology Products, 301 796-5357
NDA 208400/Original-2	Sadaf Nabavian, Division of Pulmonary, Allergy, and Rheumatology Products, 301-796-2777

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

Badrul A. Chowdhury, MD, PhD
Director
Division of Pulmonary, Allergy, and
Rheumatology Products
Office of Drug Evaluation II
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/

ANN T FARRELL
06/29/2016

SARAH K YIM
06/29/2016
Signing for Badrul Chowdhury, M.D., Ph.D.