NDA 011719/S-131

SUPPLEMENT APPROVAL

Hospira, Inc.
Attention: Maria Hinklin
Associate Director
275 North Field Drive, Building H1
Lake Forest, IL 60045

Dear Ms. Hinklin:

Please refer to your supplemental new drug application (sNDA) received May 29, 2020, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Methotrexate Injection USP, 50 mg/2 mL (Preserved) and 1 g/40 mL (Preservative-Free).

This Prior Approval sNDA provides for modifications to the approved indications and dosage regimens in the Prescribing Information (PI) for Methotrexate Injection, modifies product labeling to comply with the Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) format, and removes obsolete and inaccurate information based on information in current published literature.

Key changes provided by this supplement include:

- Removal of the lung cancer and hydatidiform mole indications.
- Removal of the intra-arterial route of administration.
- Substitution of the currently accepted clinical term “gestational trophoblastic neoplasia” for the previously approved indications of “gestational choriocarcinoma” and “chorioadenoma destruens”.
- Modifications to broaden the lymphoma indication to non-Hodgkin lymphoma (NHL) to include all histologic subsets (previous indications were for the treatment of advanced non-Hodgkin lymphoma, Burkitt lymphoma, and mycosis fungoides).
- Revisions to the Dosage and Administration section.
- Removal of outdated and unnecessary recommendations for liver biopsy in patients with psoriasis and subsets of patients with rheumatoid arthritis.
- Revision of the Boxed Warning to enhance readability, eliminate redundant or outdated information, and include information about neurotoxicity.
- Revision or removal of contraindications that were no longer supported by evidence.
- Addition of a Patient Package Insert (PPI).

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 011719 S-131**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are granting a partial waiver for the conduct of an assessment of the safety and effectiveness of Methotrexate Injection in pediatric patients less than 2 years of age with polyarticular juvenile idiopathic arthritis and a full waiver for the conduct of pediatric assessments for lung cancer, breast cancer, and squamous cell cancer of the head and neck because necessary studies are impossible or highly impracticable to conduct in the pediatric population since the indications rarely, if ever, exists in children and an adequate study population does not exist.

The literature-based assessments submitted to support changes to the indications or dosage regimens for acute lymphoblastic leukemia, non-Hodgkin lymphoma, osteosarcoma, pediatric patients with polyarticular juvenile idiopathic arthritis 2 years of age and older, and rheumatoid arthritis fulfil the requirements for a pediatric assessment for these indications.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jacqueline Glen, M.S., Regulatory Health Project Manager, at (240) 402-9558.

Sincerely,

{See appended electronic signature page}

Martha Donoghue, M.D.
Deputy Director
Division of Oncology 2
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARTHA B DONOGHUE
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