DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 11719/S-122

SUPPLEMENT APPROVAL

Hospira, Inc.
Attention: Douglas Hoffman, M.S., R.Ph.
Senior Associate – Global Regulatory Affairs
275 North Field Drive, Dept. 0390, Building H2-2
Lake Forest, IL 60045

Dear Mr. Hoffman:

Please refer to your Supplemental New Drug Application (sNDA) dated May 20, 2015, received May 20, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Methotrexate Injection, 25 mg/mL (Preservative) and Methotrexate Injection, 1 g/40 mL (Preservative-Free).

This "Prior Approval" supplemental new drug application provides for the following;

Methotrexate Injection, 25 mg/mL (Preservative)

- To revise the Indications and Usage and Dosage and Administration sections to eliminate references to treatment and prophylaxis of meningeal leukemia.

- To revise the Boxed Warnings, Warnings, Description, Precautions, and Dosage and Administration sections of the package insert to clearly communicate that the preserved formulation contains benzyl alcohol and instruct healthcare providers not to use the preserved formulation for intrathecal or high dose therapy.

- To revise the Clinical Pharmacology, Excretion subsection of the package insert to add "decreased" to the sentence, "Methotrexate clearance rates vary widely and are generally decreased at higher doses."

- To revise the Overdosage section to include information regarding the use of glucarpidase for the treatment of toxic methotrexate concentrations in patients with delayed methotrexate clearance to impaired renal function.

Methotrexate Injection, USP 1 g/40 mL (Preservative-Free)

- To revise the Boxed Warnings, Warnings, Description, Precautions, and Dosage and Administration sections of the package insert to clearly communicate that the preserved

formulation contains benzyl alcohol and instruct healthcare providers not to use the preserved formulation for intrathecal or high dose therapy.

Methotrexate Injection, USP 1 g/40 mL (Preservative-Free)

- To revise the Boxed Warnings, Warnings, Description, Precautions, and Dosage and Administration sections of the package insert to clearly communicate that the preserved formulation contains benzyl alcohol and instruct healthcare providers not to use the preserved formulation for intrathecal or high dose therapy.

- To revise the Clinical Pharmacology, Excretion subsection of the package insert to add "decreased" to the sentence, "Methotrexate clearance rates vary widely and are generally decreased at higher doses."

- To revise the Overdosage section to include information regarding the use of glucarpidase for the treatment of toxic methotrexate concentrations in patients with delayed methotrexate clearance to impaired renal function.

- To update the Description and How Supplied sections to reflect the discontinuation of all preservative-free presentations except the 25 mg/mL 40 mL (1 g) vial.

APPROVAL & LABELING

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

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 http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the 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 titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes 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 MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, 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).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels, excluding the phrase "multi-dose vial" from the container labels, submitted on November 20, 2015, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 11719/S-122**." Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

OPDP Regulatory Project Manager
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Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must submit final promotional materials and package insert(s), accompanied 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 http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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 Gina M. Davis, Senior Regulatory Health Project Manager, at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Jeffery Summers, M.D.
Deputy Director for Safety
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container

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

/s/

JEFFERY L SUMMERS
11/20/2015