CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214121Orig1s000

SUMMARY REVIEW

NDA 214121– Clinical and CDTL Review

Application Type (NDA/BLA)	NDA
Application Number(s)/ supplement number	214121
Received Date	October 24, 2019
PDUFA Goal Date	August 24, 2020
Review Completion Date	August 24, 2020
Division/Office	OOD/DO2
Medical Officer	Amy Barone
Team Leader	Amy Barone
Signatory	Harpreet Singh
Product: Established Name (Trade name)	Methotrexate
Formulation	100 mg/mL clear orange-yellow sterile solution in single-dose vial
Established Pharmacologic Class (EPC)	Antimetabolite
Applicant	Accord Healthcare Inc.
Recommended Regulatory Action	Approval

1. Executive Summary:

The applicant submitted a 505 (b)(2) new drug application for methotrexate (100 mg/mL) where the Listed Drug (LD) was Methotrexate Injection, USP 25 mg/mL (Preservative Free) [NDA# 011719]. Per FDA request, the label was resubmitted on January 27, 2020 in accordance with the Physician Labeling Rule (PLR) and the Pregnancy and Location Labeling Rule (PLLR) format. Upon submission of the supplement, FDA proposed changes based on literature and extensive internal consultants who were experts in the disease areas for which methotrexate injection has historically been indicated or is currently indicated. The final product labeling is the result of these internal consultations, literature review, and collaborations with the Sponsor.

Based on the high risk of potentially fatal medical errors due to the higher concentration of this product, the indications have been limited to those treated with high-dose methotrexate regimens only. This is in line with Accord's rationale for the proposed higher concentration product- that this product will provide practitioners with a convenient alternative to reduce hazardous waste disposal and cost for course of therapy. Please see the review from Division of Medication Error Prevention and Analysis (DMEPA) for detailed risk assessment. In addition, a post-marketing commitment will be issued stating that Accord must, "monitor medication errors and submit a summary of all reports associated with Methotrexate Injection 100 mg/mL concentration (e.g., dosing errors, selection errors, etc.) for 3 years. Include a review of medication error reports, (preferable in a PDF file) and a line by line detail of case narratives (preferable in an Excel file) to the Agency every 6 months."

Regarding the Pediatric Research Equity Act (PREA) requirement, (b) (4) . FDA determined PREA was triggered due to different dosing regimens and proposed routes of administration compared to the reference product; however, given the extensive clinical experience with methotrexate, additional studies are not practicable and there is an abundance of information available in the literature to support the proposed indications. In order to fulfill the PREA requirement, Accord conducted a brief assessment based on available literature of the safety and effectiveness of methotrexate injection in pediatric patients with acute lymphoblastic leukemia, Burkitt's lymphoma, non-Hodgkin lymphoma and osteosarcoma treated with methotrexate injection as part of a combination chemotherapy regimen and submit the final report to the NDA. This submission was reviewed and fulfills the PREA requirement; no further action necessary.

2. Regulatory Background

- This NDA refers to the Reference Listed Drug (RLD), Methotrexate Injection, USP 25 mg/mL (Preservative Free), a product of Hospira, Inc., USA (NDA 011719).
- A pre-IND/pre-NDA Type B meeting was granted on October 25, 2017 and FDA provided written response on November 20, 2017. Accord requested further guidance and clarification on December 5, 2017 for which FDA provided a written response on December 10, 2017. Responses were largely CMC related. FDA recommended that Accord not seek non-oncology indications as it is not routine to dilute methotrexate for non-oncology indications; Accord agreed.

3. Background and Review of Clinical Data

The information used to support the changes in the product label were described in published literature, including review of U.S. medical practice guidelines describing current treatment regimens for methotrexates for the treatment of oncologic diseases and taking into consideration the recommendations of consultation with disease-specific clinical subject matter experts within the FDA. This review is largely adapted from the clinical review of methotrexate tablets (Dava) which was revised to PLR format and approved May 4, 2020.

No new clinical data were submitted by the Applicant in support of this application.

4. Labeling changes

Substantive changes to the approved product labeling are outlined below. Please see the Labeling Review for full detail and rationale to support changes.

The approved labeling includes the dosing information for methotrexate tablets. Because oral dosing is not pertinent to the methotrexate injection labeling, this information is revised to include only dosing for methotrexate injection.

4.1 BOXED WARNING

The boxed warning was revised to summarize risks; details about each risk were removed and added to the WARNINGS AND PRECAUTIONS section instead. Information that is not pertinent to a boxed warning was omitted (e.g., (b) (4)).

4.2 INDICATIONS AND USAGE

Based on the high risk of potentially fatal medical errors, the indications have been limited those treated with high-dose methotrexate regimens only. Indications treated with high-dose methotrexate regimens include acute lymphoblastic leukemia, non-Hodgkin lymphoma, Burkitt lymphoma, and osteosarcoma.

A Limitations of Use statement was added to ensure safe and effective use of this product, because other methotrexate products that have non-oncology indications have a boxed warning and a contraindication for embryo-fetal toxicity.

> Limitations of Use: Methotrexate Injection is not indicated for non-oncology diseases.

4.3 DOSAGE AND ADMINISTRATION

Given the concern for medication error leading to overdose because of concentration, the following line was added to Section 2.1:

> For intravenous use only. Methotrexate Injection is available as a preservative-free solution at a concentration of 100 mg/mL. Verify the concentration prior to preparation and administration to avoid overdosage.

Recommendations regarding monitoring and concomitant therapies to promote methotrexate elimination were clarified.

The following summarizes proposed changes in the context of current U.S. medical practice and the adequacy of the published literature to support the updates to the DOSAGE AND ADMINISTRATION sections:

> Acute lymphoblastic leukemia
>
> (b) (4) All of the other dosing regimens are based on the literature, which hasn't been reviewed by the Agency for safety (or efficacy). The range based on the literature would be 30-5000 mg/m^2 IV.
>
> Burkitt's lymphoma and (b) (4) non-Hodgkin Lymphoma
>
> The currently approved labeling did not include adequate IV doses for lymphoma. Based on the literature, the dose range of 1000-3000 mg/m^2 is supported. Of note, (b) (4)
>
> Osteosarcoma

Revised the indication based on current labeling practice. Revised dosing and administration based on the protocol used to provide the foundation for this treatment.

Dosage modifications for adverse reactions were grouped by the recommended action (i.e., discontinue, withhold, dose reduce) in section 2.7. The original product label lacked a comparable section; actions to be taken were addressed in the relevant warnings and precautions.

4.4 DOSAGE FORMS AND STRENGTHS

There were no substantive changes to this section.

4.5 CONTRAINDICATIONS

(b) (4)

4.6 WARNINGS AND PRECAUTIONS

Created a separate subsection for each W&P listed as recommended in W&P guidance and listed in order to reflect the relative clinical significant of the adverse reactions. Considered seriousness of the adverse reaction, the ability to prevent or mitigate the adverse reaction and the likelihood of its occurrence. Consistent with 21CFR 201.57(c)(6) risk mitigation or management strategies were revised or added.

4.7 ADVERSE REACTIONS

This section was reorganized to align with PLR format and to be consistent with Warnings and Precautions. (b) (4) was removed since it is a risk, not an adverse reaction. (b) (4)

4.8 DRUG INTERACTIONS

The drug interactions section was extensively reorganized and updated to provide a more useful resource to providers. The section now includes a list of drugs that increase methotrexate exposure, as well as separate sections on nitrous oxide (which has a unique mechanism of action) and folic acid. Please refer to clinical pharmacology review for specific evidence to support these changes.

4.9 USE IN SPECIFIC POPULATIONS

Information in this section is derived from “Carcinogenicity, Mutagenesis and Impairment of Fertility.” The information has been reformatted in accordance with current labeling guidelines. Instructions regarding the recommended window to avoid breastfeeding after receipt of the last dose of methotrexate has been included based on the terminal half-life for high-dose therapy. Advice regarding duration of contraception for female patients of reproductive potential was revised on the basis of a published draft guidance for genotoxic drugs (Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations: Guidance for Industry).

References to [redacted] (b) (4) were removed as this product [redacted] (b) (4) .

Section 8.4, pediatrics, was written in accordance with current labeling practices. [redacted] (b) (4) cautionary language regarding comorbidities (renal impairment, hepatic impairment). [redacted] (b) (4) these comorbidities are addressed in separate sections (sections 8.6 and 8.7), and the increase in the incidence of organ impairment with age is generally understood.

4.10 OVERDOSAGE

Extensive reorganization and modifications to provide clarification to providers. As noted previously, information regarding glucarpidase has been incorporated into the label.

4.11 DESCRIPTION

Standard information regarding the molecular formula, quantity in standard packaging, inactive and active ingredients is included in this section. Refer to CMC review for full details.

4.12 CLINICAL PHARMACOLOGY

Information in this section has been revised and reorganized in accordance with current labeling practice. Extensive editing for brevity and references to [redacted] (b) (4) were removed. Refer to the clinical pharmacology review for full details.

4.13 NONCLINICAL TOXICOLOGY

Information in this section has been revised and reorganized in accordance with current labeling practice. Refer to the nonclinical review for full details.

4.14 HOW SUPPLIED/STORAGE AND HANDLING

Refer to CMC review.

4.15 PATIENT COUNSELING INFORMATION

Information in this section has been revised and reorganized in accordance with current labeling practice, and to align with changes made in other sections of the product label.

5. Recommended Regulatory Action

The clinical review team recommends approval of this 505(b)(2) application as summarized in this review.

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/

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