CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214121Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	214121
Submission Dates	10/24/2019 (SDN 1) and 1/27/2020 (SDN 3)
Submission Type	New Drug Application (NDA) – 505(b)(2)
	NDA Location: \\CDSESUB1\evsprod\NDA214121\0001 (SDN 1) Label Location: \\CDSESUB1\evsprod\NDA214121\0003 (SDN 3)
Brand Name	Methotrexate Injection
Generic Name	Methotrexate
Dosage Form and Strength	100 mg/mL in 50-mL single dose glass vials
Route of Administration	Intravenous (IV)
Indication(s)	(b) (4) Methotrexate Injection, USP 25 mg/mL (Preservative Free) (NDA 011719) by Hospira, Inc.
Related IND(s)/NDAs	IND 137010 NDA 011719
Applicant	Accord Healthcare, Inc. (Accord)
OCP Review Team	Safaa Burns (Reviewer) Jeanne Fourie Zirkelbach (Team Leader)

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1. EXECUTIVE SUMMARY

Accord submitted an original New Drug Application (NDA) for Methotrexate Injection USP 100 mg/mL pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Methotrexate Injection USP 100 mg/mL will be supplied as a 50-mL single dose glass vial. (b) (4)

There is **no** new clinical pharmacology information included in the current 505(b)(2) NDA submission; however, the Drug Interactions, Specific Populations and Clinical Pharmacology sections of the Applicant's proposed package insert were updated based on literature data.

1.1 Recommendation

The Office of Clinical Pharmacology considers the original NDA 214121 approvable from a clinical pharmacology perspective. The Applicant and the Agency came to a mutually satisfactory agreement regarding the labeling language.

1.2 Post-Marketing Requirements and Commitments

[None]

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

2.2 General Dosing and Therapeutic Individualization

2.2.2 Therapeutic Individualization

Refer to the clinical pharmacology review performed for NDA 011719 dated 4/26/2017 (SDN 339) in DARRTS (Reference ID: 4152043). See also **APPENDIX 4.1** for the currently approved Hospira's package insert for Methotrexate Injection.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling revisions to the final package insert for Methotrexate Injection sent to the Applicant:

Labeling Section	Applicant's Proposed Labeling	Clinical Pharmacology Labeling Recommendations
HIGHLIGHTS OF PRESCRIBING INFORMATION **7 Drug Interactions**	**---------DRUG INTERACTIONS--------** (b) (4)	**---------DRUG INTERACTIONS--------** Refer to the full prescribing information for drug interactions with methotrexate. (7) - - **7.1 Effects of Other Drugs on Methotrexate** Drugs that Increase Methotrexate Exposure Coadministration of methotrexate with the following products may increase methotrexate plasma concentrations, which may increase the risk of methotrexate severe adverse reactions. In some cases, the coadministration of methotrexate with these products may also subsequently reduce active metabolite formation, which may decrease the clinical effectiveness of methotrexate. Increased organ specific adverse reactions may also occur when methotrexate is coadministered with hepatotoxic or nephrotoxic products. If coadministration cannot be avoided, monitor closely for methotrexate adverse reactions when coadministered with: • Penicillin or sulfonamide antibiotics • Highly protein-bound drugs (e.g., oral anticoagulants, phenytoin, salicylates, sulfonamides, sulfonylureas, and tetracyclines) —Proton pump inhibitors • Weak acids (e.g., salicylates) • Nephrotoxic products • Probenecid • Antifolate drugs (e.g., dapsone, pemetrexed, pyrimethamine and sulfonamides) • Aspirin and other nonsteroidal anti-inflammatory drugs • Hepatotoxic products Nitrous Oxide Coadministration of methotrexate with nitrous oxide anesthesia potentiates the effect of methotrexate on folate-dependent metabolic pathways, which may increase the risk of severe methotrexate adverse reactions. Avoid nitrous oxide anesthesia in patients receiving methotrexate. Consider alternative therapies in patients who have received prior nitrous oxide anesthesia. Folic Acid Coadministration of methotrexate with folic acid or its derivatives decreases the clinical effectiveness of methotrexate. Methotrexate competes with reduced folates for active transport across cell membranes. Instruct patients to take folic or folinic acid only as directed by their

Labeling Section	Applicant's Proposed Labeling	Clinical Pharmacology Labeling Recommendations
	(b) (4)	healthcare provider *[see Warnings and Precautions (5.16)]*. **8.6 Renal Impairment** Methotrexate elimination is reduced in patients with renal impairment *[see Clinical Pharmacology (12.3)]*. Patients with renal impairment are at increased risk for methotrexate adverse reactions. Closely monitor patients with renal impairment [creatinine clearance (CLcr) less than 90 mL/min, Cockcroft-Gault] for adverse reactions. Reduce the dosage or discontinue methotrexate Injection as appropriate *[see Warnings and Precautions (5.7)]*. **8.7 Hepatic Impairment** The pharmacokinetics and safety of methotrexate in patients with hepatic impairment is unknown. Patients with hepatic impairment may be at increased risk for methotrexate adverse reactions based on the elimination characteristics of methotrexate *[see Clinical Pharmacology (12.3)]*. Closely monitor patients with hepatic impairment for adverse reactions. Reduce the dosage or discontinue Methotrexate Injection as appropriate *[see Warnings and Precautions (5.4)]*. *Distribution* After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4 to 0.8 L/kg (40 to 80% of body weight). Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. Methotrexate in serum is approximately 50% protein bound.

Labeling Section	Applicant's Proposed Labeling	Clinical Pharmacology Labeling Recommendations
	(b) (4)	Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given intravenously. <u>Elimination</u> For patients receiving high doses of methotrexate, the terminal half-life is eight to 15 hours. *Metabolism* Methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumors. Methotrexate undergoes minor metabolism to 7-hydroxymethotrexate and accumulation may become significant at the high dosages. The aqueous solubility of 7-hydroxymethotrexate is 3- to 5-fold lower than the solubility of methotrexate. *Excretion* Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. With intravenous administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed. Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed at doses between 7.5 and 30 mg. <u>Specific Populations</u> *Pediatric Patients* In pediatric patients receiving methotrexate for acute lymphoblastic leukemia (5000

Labeling Section	Applicant's Proposed Labeling	Clinical Pharmacology Labeling Recommendations
	(b) (4)	mg/m^2 intravenous over 24 hours), serum methotrexate level decreased from a median level of 66 µmol/L during the first 12 hours post infusion, with a median half-life of 1.8 hours (range: 1.7 to 2.3 h). *Patients with Renal impairment* The elimination half-life of methotrexate increases with the severity of renal impairment, with high inter-individual variability *[see Use in Specific Populations (8.6)]*.

Labeling Section	Applicant's Proposed Labeling	Clinical Pharmacology Labeling Recommendations
8 USE IN SPECIFIC POPULATIONS	**8.6 Renal Impairment** Methotrexate elimination is reduced in patients with impaired renal function. (b) (4) (b) (4)	
12.3 Clinical Pharmacology	(b) (4)	

Labeling Section	Applicant's Proposed Labeling	Clinical Pharmacology Labeling Recommendations
	(b) (4) [redacted]	
	Distribution After intravenous administration, the initial volume of distribution is approximately 0.18 L/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4 to 0.8 L/kg (40 to 80% of body weight). Methotrexate competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 micromolar, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. Methotrexate in serum is approximately 50% protein bound. (b) (4) [redacted]	

Labeling Section	Applicant's Proposed Labeling	Clinical Pharmacology Labeling Recommendations
	(b) (4) Methotrexate does not penetrate the blood-cerebrospinal fluid barrier in therapeutic amounts when given (b) (4). (b) (4) (b) (4) *Metabolism* (b) (4) methotrexate undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to methotrexate by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of methotrexate polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues and tumors. (b) (4) metabolism to 7-hydroxymethotrexate (b) (4) (b) (4)	

Labeling Section	Applicant's Proposed Labeling	Clinical Pharmacology Labeling Recommendations
	(b) (4) [redacted]	
	Excretion Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. With IV administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of methotrexate has been proposed. Renal excretion occurs by glomerular filtration and active tubular secretion. Nonlinear elimination due to saturation of renal tubular reabsorption has been observed in psoriatic patients at doses between 7.5 and 30 mg.	
	(b) (4) [redacted]	

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Methotrexate, an antimetabolite and an analogue of folic acid, was initially approved on 12/7/1953 (as methotrexate or methotrexate sodium). Methotrexate is commercially available in 32 countries, while methotrexate sodium is commercially available in 39 countries.

Methotrexate is commercially available as follows:

- Preserved (benzyl alcohol as preservative) solution for intravenous (IV) injection containing 25-mg/mL (50 mg/2 mL) of methotrexate in single-use vials.
- Preservative free solution for IV injection containing 10 mg/mL (20 mg/2 mL) and 25 mg/mL (500 mg/20 mL, 1 g/40 mL or 2.5 g/100 mL) of methotrexate in single-use vials.
- Solution for subcutaneous (SC) injection containing 7.5 mg/0.4, 10 mg/0.4 mL, 12.5 mg/0.4 mL, 15 mg/0.4 mL, 17.5 mg/0.4 mL, 20 mg/0.4 mL, 22.5 mg/0.4 mL and 25 mg/0.4 mL of methotrexate in single-use vials.
- Oral tablet containing 2.5 mg of methotrexate sodium.

- Oral solution containing 2.5 mg/mL of methotrexate sodium.

Methotrexate is indicated for the treatment of solid tumors and hematologic malignancies like choriocarcinoma (gestational trophoblastic neoplasm), chorioadenoma destruens, hydatidiform mole, acute lymphoblastic leukemia, breast cancer, cervical cancer, ovarian carcinoma, testicular carcinoma, bladder cancer (locally advanced/metastatic), epidermoid cancers (squamous cell carcinoma) of head and neck, mycosis fungoides (cutaneous T cell lymphoma), lung cancer, non-Hodgkin's lymphoma, meningeal lymphoma, histiocytic and lymphatic lymphoma, Burkitt's lymphoma, osteosarcoma, and meningeal leukemia. Other diseases include psoriasis and rheumatoid arthritis.

Regulatory History:

- On 4/26/2017, Hospira submitted a prior approval supplement (PAS) in accordance with the CDER Guidance for Industry: Changes to an Approved NDA, Section X.B.5 (Labeling) and 21 CFR 314.7 for Methotrexate Injection in the conventional format (Suppl-125). The FDA recommended Hospira during a teleconference on 4/19/2017 to submit Hospira's *Methotrexate Injection* labeling in the PLR format. Hospira's *Methotrexate Injection* PAS supplement-125 was approved on 5/7/2018.
- Accord has submitted a Type B/pre-NDA meeting package on 10/25/2017 for Methotrexate Injection USP 100 mg/mL under IND 137010. The FDA has provided preliminary written response to meeting questions on 11/20/2017 (Meeting Minutes in DARRTS, Reference ID: 4183743).
- To seek FDA's guidance/response on additional questions related to proposed 505(b)(2) application, Accord has submitted an amendment requesting further guidance and clarification on the preliminary comments on 12/5/2017 for Methotrexate Injection USP 100 mg/mL (PIND 137010). FDA has provided written response to the amendment for guidance and clarification of the preliminary comments on 12/10/2017 (Meeting Minutes in DARRTS, Reference ID: 4193095).
- On 10/24/2019, Accord submitted their proposed original NDA 214121 as a 505(b)(2) submission for Methotrexate Injection USP 100 mg/mL (50 mL/vial).

3.2 General Pharmacological and Pharmacokinetic Characteristics

Pharmacokinetics

Refer to the clinical pharmacology review of the labeling Supplement-125 for NDA 011719 dated 4/26/2017 (SDN 339) (Reference ID: 4152043).

3.3 Clinical Pharmacology Questions

3.3.2 Is the proposed general dosing regimen appropriate for the general patient population for which the indication is being sought?

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

In response to the above questions, refer to the clinical pharmacology review of the labeling Supplement-125 for **NDA 011719** dated 4/26/2017 (SDN 339) (Reference ID: 4152043). Minor

edits were made in **Section 12.3** in the proposed Accord's labeling based on the information from this review.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

In response to the above question, the FDA's DDIs recommendations were included in **Section 7** in the proposed Accord's labeling based on DDIs information cited in the most recently appoved DAVA's PLR labeling for oral methotrexate based on **published data**. Refer to the clinical pharmacology review for **NDA 008085** supplemtnt-071 dated 7/9/2019, SDN 317) (Reference ID: 4591034) for detailed information in support of these DDIs.

4. APPENDICES

4.1 Approved package insert

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/

SAFAA BURNS
06/11/2020 03:58:22 PM

JEANNE FOURIE ZIRKELBACH
06/15/2020 12:05:39 PM