CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214121Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 214121
Assessment #1

Drug Product Name	METHOTREXATE
Dosage Form	Injection
Strength	5 g/50 mL (100 mg/mL)
Route of Administration	for intravenous (b) (4) use
Rx/OTC Dispensed	Rx
Applicant	ACCORD HEALTHCARE INC
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original NDA	10/24/2019	CMC
Labeling Amendment	11/26/2019	DP
Labeling Amendment	01/27/2020	DP
Quality Amendment	02/19/2020	DP
Quality Amendment	03/06/2020	DP
Quality Amendment	03/20/2020	OPMA
Quality Amendment	04/16/2020	OPMA, Microbiology
Quality Amendment	06/05/2020	Microbiology
Labeling Amendment	07/21/2020	DP

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Raymond Frankewich	Ali Al Hakim
Drug Product	Amit Mitra	Anamitro Banerjee
Biopharm	Qi Zhang	Banu Zolnik
Manufacturing	Yifang Wang	Bogdan Kurtyka
Microbiology	Alifiya Ghadiali	Samata Tiwari
Regulatory Business Process Manager	Kristine Leahy	
Application Technical Lead	Xing Wang	

Xing Wang

Digitally signed by Xing Wang
Date: 8/04/2020 12:09:35PM
GUID: 525daca300039122a4daaad45e49c6fb

U.S. FOOD & DRUG ADMINISTRATION

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Complete CMC information has been submitted to NDA 214121 and found to be adequate upon completion of the review. All facilities are approvable based on acceptable compliance history.

OPQ recommends **APPROVAL** of NDA 214121 for METHOTREXATE injection, 5 g/50 mL (100 mg/mL). OPQ grants a 24-month expiration period when store at controlled room temperature, 20 to 25°C (68 to 77°F) [see USP Controlled Room Temperature]; excursions permitted to 15 to 30°C (59 to 86°F). Protect from light.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Methotrexate is a dihydrofolate reductase inhibitor indicated for neoplastic diseases. The listed drug (NDA #11719) is a solution at a concentration of 25 mg/ml of methotrexate with the following inactive ingredients: sodium chloride and sodium hydroxide and water for injection.

Methotrexate is practically insoluble in water. Therefore, the pH of the methotrexate solution is adjusted to approximately 8.5 with sodium hydroxide in water for injection to produce methotrexate injection. Methotrexate Injection is supplied as clear orange-yellow sterile solution in clear glass single-dose vial sealed with gray rubber stopper and yellow aluminum flip-off seal for intravenous (b) (4) use. Each 100 mg/mL, 50 mL vial contains 5 g methotrexate and the following inactive ingredient: sodium hydroxide to adjust the pH to approximately 8.5.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. PROTECT FROM LIGHT.

Proposed Indication(s) including Intended Patient Population	Methotrexate is a dihydrofolate reductase inhibitor indicated for neoplastic diseases: • Acute Lymphoblastic Leukemia. • Non-Hodgkin Lymphoma. • Burkitt Lymphoma. • Osteosarcoma.
Duration of Treatment	Until disease progression or unacceptable toxicity
Maximum Daily Dose	(b) (4)

Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

Reference is provided to DMF# (b) (4) held by (b) (4) for Methotrexate. DMF (b) (4) was evaluated recently in two reviews finalized May 30, 2017 (for an Injectable dosage form) and November 10, 2018 (for an oral tablet dosage form). Both reviews found that Adequate information was provided in the DMF to support approval of the application for which they were being reviewed. Updates that have been submitted to DMF (b) (4) since the review finalized November 10, 2018 have consisted of revisions to administrative information only.

The applicant acknowledges the Agency's comment on 02/05/2020 and confirms that the Methotrexate USP (drug substance, batch numbers 1802563 and 1701905) used in the exhibit batches of Methotrexate Injection USP 100 mg/mL, 50 mL (drug product, batch numbers PX03910, PX04066, and PX04073) may contain (b) (4) The applicant also acknowledges that the drug product is intended to (b) (4) (b) (4) (b) (4) Based on above facts and as recommended by the Agency, the applicant commits not to commercially distribute the exhibit batches of Methotrexate Injection USP 100 mg/mL, 50 mL (drug product, batch numbers PX03910, PX04066, and PX04073) which may contain (b) (4) The applicant also commits that the drug substance Methotrexate USP that contains (b) (4) will not be used in the manufacture of Methotrexate Injection USP 100 mg/mL, 50 mL in future.

Drug Product: Adequate

The listed drug (LD) is a solution at a concentration of 25 mg/ml of methotrexate with the following inactive ingredients: sodium chloride and sodium hydroxide and water for injection. Accord chose the 505 (b)2 path since the active ingredient for the proposed drug product is different quantitatively from that of the listed drug product. Methotrexate Injection is supplied as clear orange-yellow sterile solution in clear glass single-dose vial sealed with gray rubber stopper and yellow aluminum flip-off seal for intravenous (b) (4) use. Each 100 mg/mL, 50 mL vial contains 5 g methotrexate and the following inactive ingredient: sodium hydroxide to adjust the pH to approximately 8.5. The proposed commercial primary container closure is 50 ml USP type (b) (4) clear vial with 20 mm grey (b) (4) stopper and a flip off plain yellow seal. The drug product quality control is conducted with the following quality attributes: Appearance, Description including color, ID (IR and HPLC by retention time), Assay

(HPLC), Volume in containers, Related compounds (HPLC), Sub-visible particles (USP <788>), Bacterial endotoxin (USP<85>), Sterility (USP<71>) and pH (USP <791>).
The applicant has provided satisfactory stability data for a maximum of 12 months under long term storage conditions (25°C/60% RH). The sponsor is requesting a shelf life of 24 months. Therefore, the sponsor was requested to justify the shelf life of 24 months since under accelerated conditions (40°C/75% RH) the drug product failed to meet the related substances specification. In an amendment, dated, 06-MAR-2020 the applicant provided statistical extrapolation data to cover the tentative shelf life for up to 24 months. The sponsor was requested to add a statement on the label to keep the drug product in original carton until use since it is light sensitive.

Labeling: Adequate

All CMC comments/edits have been conveyed to OND and the applicant.

Biopharmaceutics: Adequate

This 505(b)(2) application, for Methotrexate Injection, USP, 5 g/50 mL in a single-dose vial, relies for approval on FDA's findings of safety and effectiveness of the Listed Drug (LD), Methotrexate Injection, USP, 1 g/ 40 mL vials [NDA 011719, Hospira Inc.]. Since the proposed drug product (DP) is formulated with different strength as compared to the LD (5 g/50 mL vs 1 g/40 mL), and the formulation is not qualitatively and quantitatively (Q1/Q2) the same as that of the LD [the absence of two inactive ingredients (sodium chloride and hydrochloric acid)], a biowaiver under 21 CFR 320.22(b)(1) does not apply. However, bridging under 21 CFR 320.24(b)(6) is feasible. The Biopharmaceutics review focuses on the data supporting the bridging between the proposed DP and the LD. Based on the totality of the information provided (e.g., side-by-side comparison of the formulation and physiochemical data, as well as information available in the labeling), the proposed DP and the LD will (b) (4) (b) (4). The proposed DP and the LD are both (b) (4) isotonic, sterile, perseverative free solutions, and have comparable pH (approximately 6-8) and osmolarities (approximately 270-320 mOsm/kg) after further dilution with 5% dextrose or with 0.9% sodium chloride solution. The removal of sodium chloride as (b) (4) and hydrochloric acid as a pH adjusting agent is not anticipated to alter the pharmacokinetics, efficacy and safety of the proposed DP, relative to the LD in subjects. Overall, from a Biopharmaceutics perspective, the bridging between the proposed Methotrexate Injection, USP (5 g/50 mL) and the LD (1 g/40 mL) is adequately established under 21 CFR 320.24(b)(6), therefore, an

in-vivo bioavailability study, comparing the LD to the proposed DP, is not needed.

Manufacturing: Adequate

The drug product manufacturing process involves (b) (4) (b) (4) scale-up is proposed. In-process results of the exhibit batches are acceptable. No PAI is triggered. The OMIR is deemed adequate based on facilities' current cGMP compliance status and past inspectional history.

Microbiology: Adequate

The submission is recommended for approval on the basis of sterility assurance. The Applicant has met regulatory expectations for the drug product release specifications.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipments • Site	H	(b) (4)	Acceptable	
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipments • Site	M		Acceptable	
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M		Acceptable	

			(b) (4)		
Uniformity of Dose (Fill Volume/deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L		Acceptable	
Appearance (Color/turbidity)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	
Particulate matter	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M		Acceptable	
Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	
pH- (High)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		Acceptable	

Application Technical Lead Name and Date:

Xing Wang

Xing Wang

Digitally signed by Xing Wang
Date: 8/04/2020 12:10:11PM
GUID: 525daca300039122a4daaad45e49c6fb

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III	(b) (4)		Adequate	07/05/2020	MAPP 5015.5 (Rev.1)
	III			Adequate	07/05/2020	
	V			Adequate	07/05/2020	

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
NDA	11719	Listed Drug

2. CONSULTS None

52 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

LABELING

{For NDA only}

R Regional Information (NDA 214121)

1.14 Labeling

1. Package Insert: Is being conducted with the labeling review. ***

(a) "Highlights" Section (21CFR 201.57(a))

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Established name: Methotrexate injection	Satisfactory
Dosage form, route of administration	Injection, Intravenous and intrathecal	Satisfactory
Controlled drug substance symbol (if applicable)	N/A	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Injection: 5 g/50 ml (100 mg/ml) in a single-dose vial	Satisfactory

Reviewer's Assessment: The highlight is satisfactory with respect to established name, dosage form and strengths. The PI is yet to be finalized.

(b) "Full Prescribing Information" Section

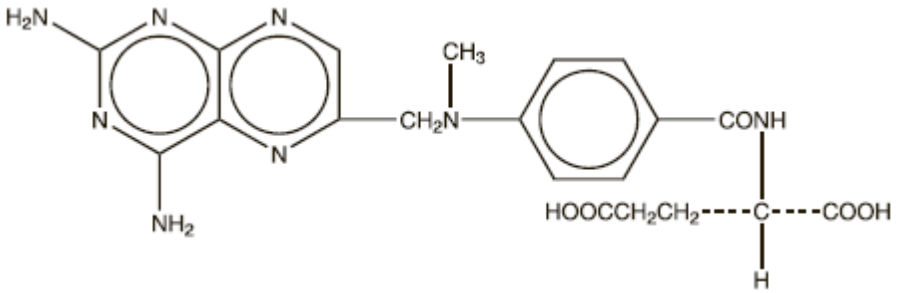
 # 3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Injection	Satisfactory
Strengths: in metric system	5 g/50 ml (100 mg/ml)	Satisfactory
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Clear, orange-yellow, isotonic, sterile, preservative-free solution in a single-dose vial	Satisfactory

Reviewer's Assessment: The PI may be revised, as necessary. The PI is yet to be finalized.

#11: Description (21CFR 201.57(c)(12))

Methotrexate is a (b) (4) inhibitor with the chemical name of N-[4-[[(2,4-diamino-6-pteridinyl) methyl]methylamino]benzoyl]-L-glutamic acid. The molecular weight is 454.45 and the molecular formula is $C_{20}H_{22}N_8O_5$. The structural formula is:



Methotrexate is practically insoluble in water. Therefore, the pH of the methotrexate solution is adjusted to approximately 8.5 with sodium hydroxide in water for injection to produce methotrexate injection. Methotrexate Injection is supplied as a clear orange-yellow sterile solution in clear single-dose vial sealed

with gray rubber stopper and yellow aluminum flip-off seal (b) (4) . Each 100 mg/ml, 50 ml vial contains 5 g methotrexate and the following ingredient: sodium hydroxide to adjust the pH to approximately 8.5.

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	Established name: Methotrexate injection	Satisfactory
Dosage form and route of administration	Injection, intravenous (b) (4)	Satisfactory
Active moiety expression of strength with equivalence statement for salt (if applicable)	Methotrexate is not a salt but forms a salt in combination with sodium hydroxide	Satisfactory
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.	See the text above under "Description" section	Satisfactory
Statement of being sterile (if applicable)	Satisfactory	Satisfactory
Pharmacological/ therapeutic class	Satisfactory	Satisfactory
Chemical name, structural formula, molecular weight	Yes	Satisfactory
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa, solubility, or pH)	Practically insoluble	Satisfactory

Reviewer's Assessment: The Description section is satisfactory.

16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

Methotrexate Injection is a clear, orange-yellow, isotonic sterile, preservative-free solution supplied in a carton containing 1 single-dose vial: 5 g/50 ml (100 mg/ml) 5 g, 50 mL Vial NDC 16729-516-11.

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	5 g/50 ml (100 mg/ml)	Satisfactory
Available units (e.g., bottles of 100 tablets)	1	Satisfactory
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	clear, orange-yellow, isotonic sterile, preservative-free solution. NDC 16729-516-11	Satisfactory
Special handling (e.g., protect from light, do not freeze)	None	Satisfactory
Storage conditions	Store at controlled room temperature, 20°C to 25°C (68°F to 77°F) *[see USP Controlled Room Temperature];* excursion permitted to 15°C to 30°C (59°F to 86°F). Protect from light	Satisfactory

Manufacturer/distributor name listed at the end of PI, following Section #17

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Manufactured For: Accord Healthcare, Inc., 1009, Slater Road, Suite 210-B, Durham, NC 27703, USA. Manufactured By: Intas Pharmaceuticals Limited, Plot No. 5 to 14, Pharmez, Nr. Village Matoda, Bavla Road, Ta.-Sanand, Dist. Ahmedabad-382 213, INDIA.	Satisfactory

Reviewer's comment: The "How Supplied" section is satisfactory.

Immediate Container Label ***

5 g/50 ml (100 mg/ml)

(b) (4)

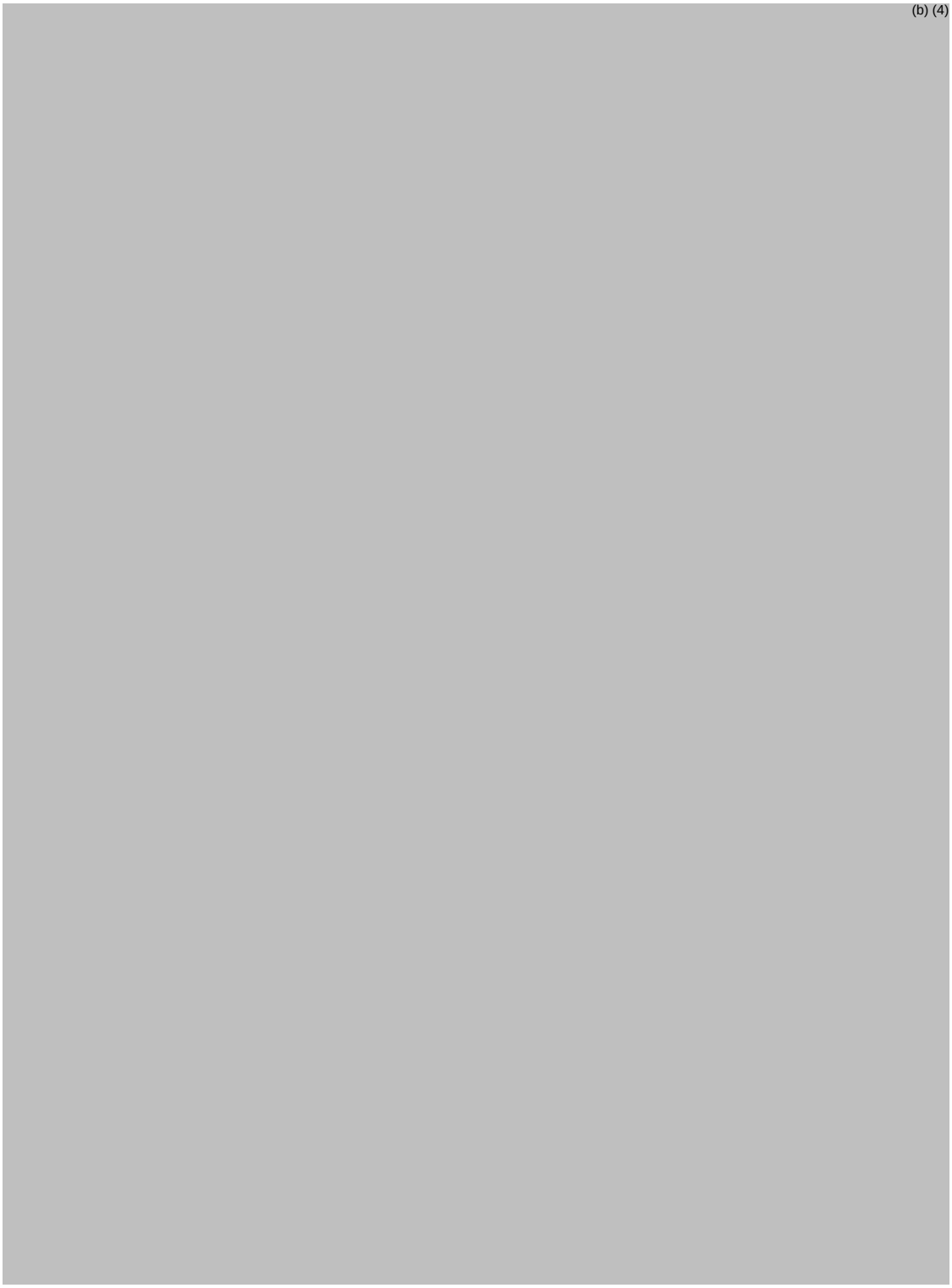
Reviewer's Assessment:
The applicant provided the following required items: Established dose strength, prescription only, lot #, bar code, and expiration date. DMEPA may have additional comments.

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Established name: Methotrexate injection	Satisfactory
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	5 g/50 ml (100 mg/ml)	Satisfactory
Net contents (21 CFR 201.51(a))	One vial	Satisfactory
Lot number per 21 CFR 201.18	None	Satisfactory
Expiration date per 21 CFR 201.17	None	Satisfactory
"Rx only" statement per 21 CFR 201.100(b)(1)	None	Satisfactory
Storage (not required)	None	Satisfactory
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	Included	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	None	Satisfactory
Name of manufacturer/distributor	None	Satisfactory
Others		

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled ''sample'', ''physician's sample'', or a substantially similar statement and the contents of the package do not exceed 8 grams.
**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

5 g/50ml

(b) (4)



Item	Comments on the Information Provided in NDA	Conclusions
"Keep out of reach of children" (optional for Rx, required for OTC)	None	Satisfactory
"Rx only" statement per 21 CFR 201.100(b)(1)	None	Satisfactory
"See package insert for dosage information" (21 CFR 201.55)	Referenced	Satisfactory
Bar Code per 21 CFR 201.25(c)(2)**	None	Satisfactory
Expiration date per 21 CFR 201.17	None	Satisfactory
Lot number per 21 CFR 201.18	None	Satisfactory
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables)[201.10(a), 21CFR201.100(b)(5)(iii)]	None	Satisfactory
Name of manufacturer/distributor	None	Satisfactory
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	None	Satisfactory
Net contents (21 CFR 201.51(a))	None	Satisfactory
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))	None	Satisfactory

Route of Administration (not required for oral, 21 CFR 201.100(b)(3))	Refers to PI for multiple routes of administration	Satisfactory
Sterility Information (if applicable)	None	Satisfactory
Storage Conditions	None	Satisfactory
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	None	Satisfactory

Reviewer's Assessment: The labels are satisfactory.

List of Deficiencies: **None**

Primary Labeling Reviewer Name and Date: See electronic signature

Secondary Reviewer Name and Date (and Secondary Summary, as needed): See electronic signature

Amit Mitra

Digitally signed by Amit Mitra
Date: 7/05/2020 01:39:20PM
GUID: 502d1ab500002af97e86c5f6f3951edc
Comments: Approved

Anamitro Banerjee

Digitally signed by Anamitro Banerjee
Date: 7/05/2020 06:30:46PM
GUID: 5075764700003844b7bc89632228509f

15 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VI: BIOPHARMACEUTICS

NDA Number	214121; 505(b)(2) Type 5-New Formulation
Assessment Cycle Number	1
Drug Product Name/ Strength	Methotrexate Injection, USP, 100 mg/mL
Route of Administration	Intravenous (IV)
Applicant Name	Accord Healthcare Inc.
Therapeutic Classification/ OND Division	Oncology OND/OOD/DHM2
Associated INDs	IND 137010
Listed Drug	NDA 011719; Methotrexate Injection, USP, 25 mg/mL (preservative free); Hospira Inc.
Proposed Indication	Treatment of solid tumors and hematologic malignancies
Primary Assessor's Name:	Qi Zhang, Ph.D.
Secondary Assessor's Name:	Banu S. Zolnik, Ph.D.
Assessment Recommendation:	**Adequate**

ASSESSMENT SUMMARY:

This 505(b)(2) application, for Methotrexate Injection, USP, 5 g/50 mL in a single-dose vial, relies for approval on FDA's findings of safety and effectiveness of the Listed Drug (LD), Methotrexate Injection, USP, 1 g/ 40 mL vials [NDA 011719, Hospira Inc.]. Since the proposed drug product (DP) is formulated with different strength as compared to the LD (5 g/50 mL vs 1 g/40 mL), and the formulation is not qualitatively and quantitatively (Q1/Q2) the same as that of the LD [the absence of two inactive ingredients (sodium chloride and hydrochloric acid)], a biowaiver under 21 CFR 320.22(b)(1) does not apply. However, bridging under 21 CFR 320.24(b)(6) is feasible. The Biopharmaceutics review focuses on the data supporting the bridging between the proposed DP and the LD.

Based on the totality of the information provided (e.g., side-by-side comparison of the formulation and physiochemical data, as well as information available in the labeling), the proposed DP and the LD will have (b) (4) (b) (4) (b) (4). The proposed DP and the LD are both (b) (4) isotonic, sterile, perseverative free solutions, and have comparable pH (approximately 6-8) and osmolarities (approximately 270-320 mOsm/kg) after further dilution with 5% dextrose or with 0.9% sodium chloride solution. The removal of sodium chloride as (b) (4) and hydrochloric acid as a pH adjusting agent is not anticipated to alter the pharmacokinetics, efficacy and safety of the proposed DP, relative to the LD in subjects.

Overall, from a Biopharmaceutics perspective, the bridging between the proposed Methotrexate Injection, USP (5 g/50 mL) and the LD (1 g/40 mL) is adequately

established under 21 CFR 320.24(b)(6), therefore, an in-vivo bioavailability study, comparing the LD to the proposed DP, is not needed. Refer to the FDA's labeling review by Drs. Janine Stewart and Chi-Ming (Alice) Tu for the recommended labeling to ensure safe and effective use of the proposed Methotrexate Injection, USP (5 g/50 mL).

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Original Submission	10/24/2019

Concise Description of Outstanding Issues (List bullet points with key information and update as needed):
None.

B.1 BCS DESIGNATION

Assessment: *Not Applicable*

Solubility: Per the proposed labeling (revised by the FDA 06/26/2020), methotrexate is practically insoluble in water. Therefore, the pH of the methotrexate solution is adjusted to approximately 8.5 with sodium hydroxide in water for injection to produce methotrexate injection.

Permeability: Not provided in the submission, and it is not needed.

Dissolution: Not applicable for parenteral drug products.

B.12 BIOWAIVER REQUEST

Assessment: *Not Applicable*

The LD, Methotrexate Injection USP (NDA 011719) in a single use 40 mL vial (25 mg/mL) approved for intramuscular, intravenous or intra-arterial route administration is a preservative free solution of methotrexate. [Noted that the LD is also available in 25 mg/mL, 2 mL (50 mg) vials but contains preservative (benzyl alcohol) and does not use for intrathecal administration]. The current labeling for the LD (revised 05/07/2018; https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/011719s125lbl.pdf) states that "Each 25 mg/mL, 40 mL vial contains methotrexate sodium equivalent to 1 g methotrexate and the following inactive ingredients: Sodium Chloride 0.490% w/v. Sodium Hydroxide and, if necessary, Hydrochloric Acid are added to adjust the pH to approximately 8.5.".

Unlike the LD, the proposed Methotrexate Injection USP is seeking approval only for IV administration, and the dosage form is "5 g/50 mL (100 mg/mL), clear, orange-yellow, isotonic, sterile, preservative-free solution in a single-dose vial", and "contains 5 g methotrexate and sodium hydroxide to adjust the pH to approximately 8.5" (refer to the proposed labelling revised by the FDA 06/26/2020).

Since the proposed DP is formulated with different strength as compared to the LD (5 g/50 mL vs 1 g/40 mL), and the formulation is not Q1/Q2 the same as that of the LD, due to the absence of two inactive ingredients (sodium chloride and hydrochloric acid), a biowaiver under 21 CFR 320.22(b)(1) does not apply. However, bridging under 21 CFR 320.24(b)(6) is feasible, which is discussed under the Section B13.

B.13 BRIDGING

Assessment: *Adequate*

The Applicant had previously discussed with FDA regarding the bioequivalence approach for the proposed Methotrexate Injection (5 g/50 mL) relative to the LD (1 g/ 40 mL) (refer to IND 137010 meeting minutes in DARRTS dated 11/20/2017). FDA provided feedback that for the IV administration (refer to the FDA Response to Question 3), bioequivalence could be established through the bridging studies as outlined in the meeting, i.e., the Applicant must characterize the differences in formation and physiochemical properties (the measurements should be done after dilution), and provide information demonstrating the differences do not affect safety and efficacy of the proposed DP relative to the LD. (b) (4) (b) (4) (b) (4) In the current NDA submission, the Applicant provided a side-by-side comparison including formulation composition (Appendix-Tables 1 and 2) and physicochemical data (Appendix-Tables 3 and 4) between the proposed DP and the LD for intravenous administration.

Strength

(b) (4)

Since the proposed DP has higher drug concentration and larger volume presentation (5 g/ 50 mL) than the LD (1 g/40 mL), the proposed DP permits administration of a reduced number of units of the injectable solution, while delivering the same amount of methotrexate as the LD. However, due to drug concentration differences and high drug dose in the proposed DP, FDA is concerned about possible overdose of the proposed DP. Refer to the FDA's labeling review by Drs. Janine Stewart and Chi-Ming (Alice) Tu. Defer to OND review team for the final recommendation with respect to assessment and labeling for the risk of possible overdose.

Absence of NaCl and HCl

Per the Applicant, Methotrexate Injection 100 mg/mL is reported (b) (4) and hence, NaCl presented (b) (4) in the LD formulation is not added and only NaOH is used in the proposed formulation as (b) (4) and pH adjusting agent is used to reach the desired pH.

Collectively, the following information support that the changes in inactive ingredients i.e. removal of NaCl and HCl and adjusting content with sodium hydroxide are not expected to affect distribution/ disposition kinetics of methotrexate: (1) The provided comparative physiochemical data demonstrate that the proposed formulation resulted in similar pH and osmolarity as compared to the LD after appropriate dilution prior to administration (refer to "comparative physicochemical properties" below). (2) NaCl, HCl and NaOH are listed in FDA's IIG Database for IV use. The amount of NaOH that will be used is low as it is only used for pH adjustment. (3) NaCl does not induce interference with methotrexate in the solution. (4) The proposed (b) (4) route of administration (IV) are the same as those approved for the LD.

Comparative Physicochemical Properties

The pH data confirmed that there is no difference in pH; the pH for both products is 8.3 or 8.4 before dilution. After dilution, the pH of the proposed DP (Registration Batch PX04073) and the LD (Batch E034457AA) is consistently similar (approximately 6-8) at final concentration levels of 0.4, 1 and 20 mg/mL with dilution of 5% dextrose or 0.9% sodium chloride solution (refer to Appendix-Table 4).

The osmolality data showed that the proposed DP and the LD have similar osmolality at final concentrations of 0.4 and 1 mg/mL with dilution of 5% dextrose or 0.9% sodium chloride solution (refer to Appendix-Table 4). After dilution at 20 mg/mL the osmolality for the proposed DP is approximately 322 vs. 271 mOsm/Kg for the LD, but such difference is not a concern when considering the safety of the proposed DP.

In addition, the in-use stability studies demonstrate the diluted solution of the proposed DP (3 registration lots at 1 mg/mL and 20 mg/mL concentration with dilution of 5% dextrose and 0.9% sodium chloride solution) is physically and chemically stable during the in-use period (stored for a period of 48 hours at 20-25°C). Refer to the Drug Product Review.

In conclusion, the bridging between the proposed Methotrexate Injection USP and the LD is adequately established for IV administration, based on the side-by-side comparison of the formulation, physicochemical properties between the proposed DP and the LD, as well as information available in the labeling; therefore, an in-vivo bioavailability study, comparing the LD to the proposed DP, is not needed.

Refer to the Drug Substance and Drug Product Reviews for additional CMC information. Refer to the FDA recommended labeling to ensure safe and effective use of the proposed DP.

BIOPHARMACEUTICS LIST OF DEFICIENCIES CONVEYED TO THE APPLICANT DURING THE REVIEW

None.

APPENDIX

Table 1: Comparison of Drug Product Formulation between Accord's Methotrexate injection USP 100 mg/mL, 50 mL and RLD's (& RS) Methotrexate Injection, USP 25 mg/mL, NDA # 011719.

Sr. No.	Ingredients	Accord's formulation: Methotrexate injection USP, 100 mg/mL, 50 mL		RLD and RS formulation's: Methotrexate Injection, USP 25 mg/mL, 40 mL	
		Concentration per mL	Concentration per vial (50 mL)	Concentration per mL	Concentration per vial (40 mL)
1	Methotrexate	100.0 mg	5.0 g	25.0 mg	1.0 g
2	Sodium Hydroxide	q.s. to pH adjustment	q.s. to pH adjustment	q.s. to pH adjustment	q.s. to pH adjustment
3	Sodium Chloride	Not used	Not used	0.490% w/v	0.196 mg
4	Hydrochloric Acid	Not used	Not used	q.s. to pH adjustment	q.s. to pH adjustment
5	Water for injection	q.s. to 1.0 mL	q.s. to 50.0 mL	q.s. to 1.0 mL	q.s. to 40.0 mL

Table 2: Side-By-Side Comparison on Formulation, Dosage Form and Administered Volume of Accord's Proposed Drug Product and Reference Listed Drug Product

Sr. No.	Parameter		Accord's formulation: Methotrexate injection USP, 100 mg/mL, 50 mL		RLD and RS formulation's: Methotrexate Injection, USP 25 mg/mL, 40 mL	
1	**Qualitative and quantitative composition – Before dilution and after dilution to get 10 mg/mL concentration**					
	Ingredients	**Comp. Ref.**	**Before Dilution**	**After Dilution (10 mg/mL)**	**Before Dilution**	**After Dilution (10 mg/mL)**
	Methotrexate	USP	100.0 mg/mL	10.0 mg/mL	25.0 mg/mL	10.0 mg/mL
	Sodium Hydroxide	NF	q.s. to pH adjustment	q.s. to pH adjustment	q.s. to pH adjustment	q.s. to pH adjustment
	Water for injection	USP	q.s. to 1.0 mL	q.s. to 100 mL	q.s. to 1.0 mL	q.s. to 400 mL
	Diluent (1 L of 5% Dextrose Solution or 0.9% Sodium Chloride Injection)	USP	Not present	q.s. to 900 mL	Not present	q.s. to 600 mL
2	**Administered Volume* for 10 g methotrexate dose**		100 mL of undiluted product	1000 mL of diluted product (10 g of Methotrexate)	400 mL of undiluted product	1000 mL of diluted product (10 g of Methotrexate)
3	**Dosage Form**		Intravenous Infusion		Intravenous Infusion	

(b) (4)

Table 3: Chemical Evaluation of US RLD Methotrexate Injection (Preservative Free) (NDA # 011719) And Its Comparison With Accord's Methotrexate Injection

Product	**Methotrexate Injection, USP 25 mg/mL, 40 mL (preservative free) (NDA # 011719)**	**Methotrexate Injection, USP 100 mg/mL, 50 mL (Accord Healthcare)**		
Presentation	25 mg/mL, 40 mL [1 g/40 mL]	100 mg/mL, 50 mL [5 g/50 mL]		
Batch number	E034457AA	PX03910	PX04066	PX04073
Manufacturing date	--	August 2018	August 2018	August 2018
Expiry date	April 2019	July 2020	July 2020	July 2020
Date of analysis	November 23, 2017	September 15, 2019	September 15, 2019	September 18, 2019
AR. No.	(b) (4)			
Storage condition	Long term (20°-25°C (68°-77°F)			
Tests				
Description	(b) (4) solution	Clear orange-yellow solution filled in clear glass vial. When examined under suitable conditions of visibility it is practically free from particles.	Clear orange-yellow solution filled in clear glass vial. When examined under suitable conditions of visibility it is practically free from particles.	Clear orange-yellow solution filled in clear glass vial. When examined under suitable conditions of visibility it is practically free from particles.
pH	8.30	8.3	8.4	8.3
Assay of Methotrexate (%)	103.2%	102.0%	102.0%	101.9%
Related substances (%)	(b) (4)			

Table 4: Comparative pH And Osmolality Data for Accord's Proposed Drug Product and Reference Listed Drug Product

Results of pH									
Concentration of Diluted product	Diluent	Methotrexate Injection, USP 100 mg/mL, 50 mL (Accord) Batch No: PX04073				Methotrexate Injection, USP 25 mg/mL, 40 mL (preservative free) (NDA # 011719) Batch No:E034457AA			
		1	2	3	Avg pH	1	2	3	Avg pH
0.4 mg/ml	0.9% NS	6.78	6.81	6.82	**6.80**	7.01	7.00	7.01	**7.01**
	5D	6.26	6.25	6.25	**6.25**	6.24	6.25	6.25	**6.25**
1 mg/ml	0.9% NS	6.99	7.00	7.00	**7.00**	7.52	7.50	7.53	**7.52**
	5D	6.59	6.60	6.61	**6.60**	6.75	6.76	6.75	**6.75**
20 mg/ml	0.9% NS	7.72	7.70	7.72	**7.71**	8.57	8.56	8.57	**8.57**
	5D	7.69	7.70	7.69	**7.69**	8.53	8.54	8.54	**8.54**
Results of Osmolality (mOsm/kg)									
Concentration of Diluted product	Diluent	Methotrexate Injection, USP 100 mg/mL, 50 mL (Accord) Batch No: PX04073				Methotrexate Injection, USP 25 mg/mL, 40 mL (preservative free) (NDA # 011719) Batch No:E034457AA			
		1	2	3	Avg	1	2	3	Avg
0.4 mg/ml	0.9% NS	292	286	287	**288**	290	292	291	**291**
	5D	298	298	298	**298**	296	297	294	**296**
1 mg/ml	0.9% NS	292	292	292	**292**	291	291	288	**290**
	5D	298	296	297	**297**	296	296	295	**296**
20 mg/ml	0.9% NS	318	318	319	**318**	272	271	270	**271**
	5D	322	322	321	**322**	272	272	270	**271**

0.9% NS - 0.9% Sodium Chloride Injection; 5D - 5% Dextrose Solution

Qi Zhang

Digitally signed by Qi Zhang
Date: 7/07/2020 12:43:20PM
GUID: 547e178000007695c91eb10380b07939

Banu Zolnik

Digitally signed by Banu Zolnik
Date: 7/07/2020 01:19:44PM
GUID: 508da7270002a568e175a2c0dd90f334

U.S. FOOD & DRUG ADMINISTRATION

MICROBIOLOGY

Product Information	(b) (4) RLD is Methotrexate Injection, USP (NDA 011719)
NDA Number	214121
Assessment Cycle Number	01
Drug Product Name / Strength	Methotrexate Injection USP, 100 mg/mL (50mL fill)
Route of Administration	Intravenous (b) (4)
Applicant Name	Accord Healthcare Inc.
Therapeutic Classification/ OND Division	CDER/OGD
Manufacturing Site	Intas Pharmaceuticals Limited Plot No. 5 to 14, Pharmez, Near Village Matoda Sarkhej-Bavla Highway, No. 8-A, Taluka: Sanand Ahmedabad, Gujarat 382213
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: The submission is **recommended** for approval on the basis of sterility assurance.

List Submissions Being Assessed

Document(s)	Date Received
NDA-214121-ORIG-1	10/24/2019
NDA-214121-ORIG-1-AMEND-2	11/26/2019
NDA-214121-ORIG-1-AMEND-4	02/19/2020
NDA-214121-ORIG-1-AMEND-7	04/16/2020
NDA-214121-ORIG-1-AMEND-8	06/05/2020

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: N/A

Concise Description of Outstanding Issues: The Division of Microbiology Assessment has no deficiencies or additional comments.

Supporting Documents:
Type V DMF (b) (4) and associated microbiology review D(b) (4)M18R01 dated 05/03/2018 was referenced for (b) (4) validation of the proposed rubber stopper.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of drug product

The subject drug product is a clear, orange-yellow solution filled in a clear 50mL glass vial with 20mm rubber stopper and seal.

Drug product composition

Ingredients	Content (mg/mL)	Content (mg/vial)	Function
Methotrexate, USP	100.00 mg	5.0 g	API
Sodium hydroxide, NF	Q.S.	Q.S.	pH adjustment
Water for Injection, USP	Q.S. to 1mL	Q.S. to 50mL	Solvent
(b) (4)			

Description of container closure system

Configuration	Component	Description	DMF	Manufacturer
100 mg/mL (50 mL fill)	Container	50 mL USP Type (b) (4) clear glass vial	N/A	(b) (4)
	Closure	20 mm (b) (4) rubber stopper (b) (4)	(b) (4)	
	Seal	20 mm flip off plain yellow seal	N/A	

Assessment: ***Adequate***

The Applicant has provided an adequate description of the drug product composition and the container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

Container/Closure and Package Integrity

(3.2.P.2. pharmaceutical-development, p 59/402)

(b) (4)

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/

XING WANG
08/04/2020 12:44:16 PM