CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214408Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

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

NDA 214408
Review #3

Drug Product Name	Pemetrexed Injection
Dosage Form	Solution for Intravenous Injection
Strength(s)	25 mg/mL (100 mg/4 mL, 500 mg/20 mL, 850 mg/34 mL and 1000 mg/40 mL)
Route of Administration	Intravenous Injection
Rx/OTC Dispensed	Rx
Applicant	Accord Healthcare Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SN-17 NDA Class 1 Resubmission	05/19/2022	All

QUALITY ASSESSMENT TEAM

DISCIPLINE	PRIMARY REVIEWER/ SECONDARY REVIEWER	BRANCH/DIVISION
Drug Substance	Paresma Patel	OPQ/ONDP/DNDAPI
Drug Product	Tefsit Bekele/Xing Wang	OPQ/ONDP/DNDPI
Facility/Process	Jin Lee/James Norman	OPQ/OPMA/DMAIV
Microbiology	Jason God/Julie Nemecek	OPQ/OPF/DMA
Biopharmaceutics	Gerlie Gieser	OPQ/ONDP/DB
Regulatory Business Process Manager	Rabiya Haider	OPQ/OPRO/RBPMI
Application Technical Lead	Mei Ou	OPQ/ONDP/DBPI
Laboratory (OTR)	NA	NA
ORA Lead	NA	NA

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	Reviewed by Katherine Windsor 09/25/2020 Adequate (b) (4) NAI Adequate by Katherine Windsor 03/11/2021	MAPP 5015.5 (Rev.1)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
ALIMTA	NDA 021462	Listed Drug Product

2. CONSULTS

None

Executive Summary

Recommendations and Conclusion on Approvability:

From a Pharmaceutical Quality perspective, NDA 214408-ORIG-1-RESUB-17 is recommended for APPROVAL.

Summary of Quality Assessments

A. Product Overview

Accord Healthcare Inc. submitted the original NDA 214408 on January 27, 2020, for Pemetrexed Injection solution (25 mg/mL). This 505(b)(2) NDA relies for approval on the FDA's previous findings of safety and efficacy for the Listed Drug (LD) product, ALIMTA® (pemetrexed) lyophilized powder for injection (NDA 021462). ALIMTA was approved on February 04, 2004, for the treatment of patients with locally advanced or metastatic non-squamous non-small cell lung cancer as well as mesothelioma and is available as a lyophilized powder (containing 100 mg and 500 mg pemetrexed per vial).

The proposed Pemetrexed Injection is a clear, colorless to pale yellow, ready-to-dilute (RTD) solution supplied in pemetrexed concentrations of 100 mg/4 mL, 500 mg/20 mL, 850 mg/34 mL, and 1000 mg/40 mL packaged in 7 mL, 20 mL 50 mL and 50 mL (b) (4) clear glass vials, respectively. The proposed drug product differs from LD product in terms of dosage form (i.e., RTD solution formulation vs. lyophilized powder formulation for reconstitution and further dilution) and excipients (i.e., absence of mannitol, and addition of citric acid, L-methionine and monothioglycerol).

The original NDA received a Complete Response (CR) Letter on November 23, 2020. The resubmission dated November 17, 2021 received a Tentative Approval on May 17, 2022. The Applicant resubmitted this NDA 214408 on May 19, 2022, requesting for final approval upon the expiration of the patent protection. The Applicant certifies that there are no changes made to the chemistry, manufacturing, and controls; carton/container labeling; and prescribing information/patient package insert labeling sections of the application after the issuance of the tentative approval letter.

Proposed Indication(s) including Intended Patient Population	• in combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations. • in combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous, NSCLC. • as a single agent for the maintenance treatment of patients with locally advanced or metastatic,

	non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. • as a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy. • initial treatment, in combination with cisplatin, of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.
Duration of Treatment	The recommended dose of Pemetrexed Injection administered with pembrolizumab and platinum chemotherapy in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater is 500 mg/m^2 as an intravenous infusion over 10 minutes, administered after pembrolizumab and prior to platinum chemotherapy, on Day 1 of each 21-day cycle.
Maximum Daily Dose	500 mg/m^2
Alternative Methods of Administration	NA

B. Quality Assessment Overview

DRUG SUBSTANCE: No Action Indicated (NAI)
*The Drug Substance remains **Approval**.*
DRUG PRODUCT: NAI
*The Drug Product remains **Approval**.*
PROCESS and FACILITIES: NAI
*The Process and Facilities remains **Approval**.*
MICROBIOLOGY: NAI
*The Microbiology remains **Approval.***
BIOPHARMACEUTICS: NAI
*The Biopharmaceutics remains **Approval**.*

C. Special Product Quality Labeling Recommendations

None

D. Risk Assessment

FROM INITIAL RISK IDENTIFICATION			REVIEW ASSESSMENT		
Attribute	**Factors that can impact the CQA**	**Initial risk ranking**	**Risk mitigation approach**	**Final risk evaluation**	**Lifecyle consideration**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		L	
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		L	
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		L	
Assay ((b) (4)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		L	
Uniformity of Dose (Fill Volume/ deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		L	
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		L	
pH	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		L	

Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		L	
Appearance (Color /turbidity)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		L	

E. List of Deficiencies for Complete Response
None

Application Technical Lead Name and Date for NDA-214408-ORIG-1-RESUB-17: Mei Ou, Ph.D. 06/28/2022

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/s/

MEI OU
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RECOMMENDATION

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

NDA 214408
Review #2

Drug Product Name	Pemetrexed Injection
Dosage Form	Solution for Intravenous Injection
Strength(s)	25 mg/mL (100 mg/4 mL, 500 mg/20 mL, 850 mg/34 mL and 1000 mg/40 mL)
Route of Administration	Intravenous Injection
Rx/OTC Dispensed	Rx
Applicant	Accord Healthcare Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SN-10 Resubmission NDA Class 2	11/17/2021	All
SN-11 Response to Information Request	03/02/2022	Drug Product
SN-12 Labeling Amendment	03/24/2022	All

QUALITY ASSESSMENT TEAM

DISCIPLINE	PRIMARY REVIEWER/ SECONDARY REVIEWER	BRANCH/DIVISION
Drug Substance	Paresma Patel	OPQ/ONDP/DNDAPI
Drug Product	Tefsit Bekele/Xing Wang	OPQ/ONDP/DNDPI
Facility/Process	Jin Lee/James Norman	OPQ/OPMA/DMAIV
Microbiology	Jason God/Julie Nemecek	OPQ/OPF/DMA
Biopharmaceutics	Gerlie Gieser	OPQ/ONDP/DB
Regulatory Business Process Manager	Rabiya Haider	OPQ/OPRO/RBPMI
Application Technical Lead	Mei Ou	OPQ/ONDP/DBI
Laboratory (OTR)	NA	NA
ORA Lead	NA	NA

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)		Adequate	Reviewed by Katherine Windsor 09/25/2020 Adequate (b) (4) NAI Adequate by Katherine Windsor 03/11/2021	MAPP 5015.5 (Rev.1)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
ALIMTA	NDA 021462	Listed Drug Product

2. CONSULTS

None

Executive Summary

Recommendations and Conclusion on Approvability:

From a Pharmaceutical Quality perspective, NDA 214408-ORIG-1-RESUB-10 is recommended for APPROVAL.

Summary of Quality Assessments

A. Product Overview

Accord Healthcare Inc. submitted the original NDA 214408 on January 27, 2020, for Pemetrexed injection solution (25 mg/mL). This 505(b)(2) NDA relies for approval on the FDA's prior findings of safety and efficacy for the Listed Drug (LD) product, ALIMTA® (pemetrexed) lyophilized powder for injection (NDA 021462). ALIMTA was approved on February 04, 2004, for the treatment of patients with locally advanced or metastatic non-squamous non-small cell lung cancer as well as mesothelioma and is available as a lyophilized powder (containing 100 mg and 500 mg pemetrexed per vial).

The proposed Pemetrexed injection is a clear, colorless to pale yellow, ready-to-dilute (RTD) solution supplied in pemetrexed concentrations of 100 mg/4 mL, 500 mg/20 mL, 850 mg/34 mL, and 1000 mg/40 mL packaged in 7 mL, 20 mL 50 mL and 50 mL (b) (4) clear glass vials, respectively. The proposed drug product differs from LD product in terms of dosage form (i.e., RTD solution formulation vs. lyophilized powder formulation for reconstitution and further dilution) and excipients (i.e., absence of mannitol, and addition of citric acid, L-methionine and monothioglycerol).

The original NDA received a Complete Response (CR) Letter on November 23, 2020, due to insufficient information provided to support the safety of the amount of the citric acid excipient in the proposed formulation. The Applicant resubmitted the NDA 214408 on November 17, 2021 and included new nonclinical data to address deficiencies regarding the use of citric acid as an excipient in the proposed formulation.

Quality review cycle #2 addresses the product quality and biopharmaceutics comments cited by FDA in the CR letter issued on November 23, 2020.

Proposed Indication(s) including Intended Patient Population	• in combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations. • in combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous, non-small cell lung cancer (NSCLC). • as a single agent for the maintenance treatment of

	patients with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. • as a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy. Limitations of Use: Pemetrexed injection is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer. • in combination with cisplatin, for the initial treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.
Duration of Treatment	The recommended dose of Pemetrexed injection (b) (4) administered with pembrolizumab and platinum chemotherapy (b) (4) (b) (4) in patients with a creatinine clearance (calculated by Cockcroft-Gault equation) of 45 mL/min or greater is 500 mg/m^2 as an intravenous infusion over 10 minutes administered after pembrolizumab and prior to (b) (4) on Day 1 of each 21-day cycle (b) (4).
Maximum Daily Dose	500 mg/m^2
Alternative Methods of Administration	NA

B. Quality Assessment Overview

DRUG SUBSTANCE: No Action Indicated (NAI)
This NDA was adequate during review of the original submission by Katherine Windsor on 25-Sept-2020 and remains adequate. The cross referenced DMF (b) (4) was last NAI reviewed by Katherine Windsor on 11-Mar-2021 and remains adequate with no unreviewed amendments. *The Drug Substance remains **Approval**.*
DRUG PRODUCT: ADEQUATE
The acceptance criterion for monothioglycerol is revised from ≤ (b) (4)% to ≤ (b) (4)% on stability and it is adequately justified by the stability data submitted. Pemetrexed is prone to (b) (4)

(b) (4)

(b) (4). Based on available stability data it is acceptable for the applicant to update the specification limit of monothioglycerol to ≤ (b) (4)% on stability.

As part of the resubmission, a revised labeling was submitted on March 24, 2022. CMC has no additional comments to provide as DMEPA sent comments to the applicant during this review cycle (April 22, 2022) which included request to replace "package insert" with "prescribing information". The labels comply with all regulatory requirements, and it is recommended for approval from a CMC perspective pending revision of what were noted in the original CMC labeling and current DMEPA reviews.

*The Drug Product recommends for **Approval**.*

PROCESS and FACILITIES: NAI

No changes noted in manufacturing process since original submission (was adequate). No changes or alerts noted in facility since original submission (was acceptable). The overall manufacturing inspection recommendation (OMIR) has been closed with approve.

*The Process and Facilities remains **Approval**.*

MICROBIOLOGY: NAI

*The Microbiology remains **Approval.***

BIOPHARMACEUTICS: ADEQUATE

From the Biopharmaceutics perspective, the comparative *in vitro* (protein binding, and physico-chemical characterization) data and the comparative nonclinical (acute animal toxicity) data between the proposed and the LD products (as well as the CMC data/information including the stability data provided for the proposed solution drug product) provided in the original NDA and the current NDA resubmission are adequate to support the scientific bridge between the proposed to-be-marketed drug product and the relied upon Listed Drug product, in accordance with 21 CFR 320.24(b)(6).

*The Biopharmaceutics Reviewer recommends **Approval**.*

C. Special Product Quality Labeling Recommendations
None

D. Risk Assessment

FROM INITIAL RISK IDENTIFICATION			REVIEW ASSESSMENT		
Attribute	**Factors that can impact the CQA**	**Initial risk ranking**	**Risk mitigation approach**	**Final risk evaluation**	**Lifecyle consideration**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		L	
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipment • Site	M		L	The non-clinical team confirmed that the level of citric acid in the formulation is not a concern anymore.
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		L	
Assay (b) (4) (b) (4)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		L	There were no meaningful changes for citric acid and L-methionine contents through the available 30-month timepoints. The 30 months stability batches support the acceptance criterion for monothioglycerol is revised from ≤ (b) (4)% to ≤ (b) (4)%.

Uniformity of Dose (Fill Volume/ deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		L	
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		L	
pH	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		L	
Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		L	
Appearance (Color /turbidity)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		L	The 30 months batches are within specification for color and achromicity of solution.

E. List of Deficiencies for Complete Response
None

Application Technical Lead Name and Date for NDA-214408-ORIG-1-RESUB-10:
Mei Ou, Ph.D. 04/26/2022

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U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM
NDA 214408
Pemetrexed Injection

Accord Healthcare Inc. submitted a 505(b)(2) for Pemetrexed injection on January 27, 2020. A complete response (CR) was issued on November 23, 2020, due to insufficient information provided to support the safety of the amount of the citric acid excipient in the formulation. The original CMC labeling review for pemetrexed injection 100 mg/4 mL, 500 mg/20 mL, 850 mg/34 mL, and 1000 mg/40 mL was uploaded in panorama on October 20, 2020. CMC recommended approval pending revision of the prescribing information, container labels and carton labeling as advised in the review. The applicant accepted the recommendation and revised the container labels and carton labeling accordingly except replacing “package insert” with “prescribing information” on the container and carton labeling. Internal labeling review of the prescribing information was ongoing at the time a CR was issued.

The applicant submitted a class 2-resubmission on November 17, 2021, to provide a non-clinical safety data to support the amount of citric acid present in the proposed pemetrexed formulation. As part of the resubmission, a revised labeling was submitted on March 24, 2022. CMC has no additional comments to provide as DMEPA sent comments to the applicant during this review cycle (April 22, 2022) which included request to replace “package insert” with “prescribing information”. The labels comply with all regulatory requirements, and it is recommended for approval from a CMC perspective pending revision of what were noted in the original CMC labeling and current DMEPA reviews.

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TEFSIT BEKELE

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Xing Wang

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BIOPHARMACEUTICS MEMO

Product Information	
NDA Number	NDA-214408-ORIG-1-RESUB-10 NDA214408 - (0010)
Assessment Cycle Number	Class 2 Resubmission After Complete Response
Drug Product Name/ Strength	Pemetrexed Injection 25 mg/mL (presented as 100 mg/4 mL, 500 mg/20 mL, 850 mg/34 mL,1000 mg/40 mL Ready-To-Dilute (RTD) solution in single-dose vials)
Route of Administration	For Intravenous Infusion
Applicant Name	ACCORD HEALTHCARE INC
Therapeutic Classification/ OND Division	Anticancer: Folate analog metabolic inhibitor Division of Oncology 2
Listed Drug Product Relied Upon	ALIMTA® lyophilized powder for reconstitution and further dilution [NDA 21462]
Proposed Indication	Treatment of non-squamous, non-small cell lung cancer

Assessment Recommendation: APPROVAL

Background

On 11/23/2020, the original NDA of the proposed Ready-To-Dilute Pemetrexed solution injectable drug product received an FDA Complete Response (CR) Letter[1] citing mainly the inadequacy of nonclinical safety data related to the amount and infusion rate of the citric acid excipient present in the proposed formulation; refer to the Pharmacology/Toxicology Memo[2] for details. Consequently, due to this safety concern, the scientific bridge between the proposed and the relied upon Listed Drug (LD) product could not be established; for more information, refer to the Biopharmaceutics Review[3] of the original NDA. Also, as stated in the CR Letter, comments on the proposed labeling were deferred until the NDA is otherwise deemed adequate.

Biopharmaceutics Assessment of the NDA Resubmission:

Per this Class 2 NDA Resubmission's Pharmacology/Toxicology Review[4], the submitted toxicology study[5] results are adequate to support the safety of the specific amount of citric acid excipient in the proposed RTD solution formulation.

Note that this NDA Resubmission also provides for a revision of the finished product QC specifications with respect to the (b) (4) content in the solution drug product during

[1] https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af805b26e3
[2] https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af805ab506&showAsPdf=true
[3] https://panorama.fda.gov/document/view?ID=5f80883b0001ffcc84c313e5058e7ca9
[4] https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af8064d3c1
[5] \\CDSESUB1\evsprod\nda214408\0010\m4\42-stud-rep\423-tox\4231-single-dose-tox\vll0721gt113\study-report.pdf

shelf-life. Per the Drug Product Reviewer (Dr. Tefsit Bekele), based on the provided supporting stability data, the Applicant's proposal to revise the acceptance criterion for monothioglycerol content during shelf-life from "NLT (b) (4)% of input ((b) (4)mg/mL) to "NLT (b) (4)% of input" is acceptable. Dr. Bekele and the Process Reviewer (Dr. Jin Lee) confirmed that in this NDA Resubmission there are no proposed changes to the drug product formulation and manufacturing process. Additionally, Dr. Lee noted that there are no changes to the facility status since the original NDA submission.

Thus, from the Biopharmaceutics perspective, the comparative *in vitro* (protein binding, and physico-chemical characterization) data and the comparative nonclinical (acute animal toxicity) data between the proposed and the LD products (as well as the CMC data/information including the stability data provided for the proposed solution drug product) provided in the original NDA and the current NDA resubmission are adequate to support the scientific bridge between the proposed to-be-marketed drug product and the relied upon Listed Drug product, in accordance with 21 CFR 320.24(b)(6).

Biopharmaceutics Reviewer and Date: Gerlie Gieser, Ph.D. (3/23/2022)

Gerlie Gieser

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Mei Ou

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/s/

MEI OU
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Recommendation: COMPLETE RESPONSE

NDA 204408
Review #1

Drug Name/Dosage Form	Pemetrexed Injection/Injection, Solution, (b) (4)
Strength(s)	25 mg/mL (100 mg/4 mL, 500 mg/20 mL, 850 mg/34 mL and 1000 mg/40 mL)
Route of Administration	Intravenous Injection (infusion)
Rx/OTC Dispensed	Rx
Applicant	Accord Healthcare Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	01/27/2020	ONDP-All
Quality Amendment	03/31/2020	Process and Facilities, Biopharmaceutics
Quality Amendment	04/27/2020	Microbiology
Quality Amendment	04/28/2020	Biopharmaceutics
Quality Amendment	06/01/2020	Biopharmaceutics
Quality Amendment	06/26/2020	Biopharmaceutics
Quality Amendment	07/06/2020	Drug Product, Biopharmaceutics
Labeling Amendment	09/17/2020	Drug Product
Pharmacology Toxicology Amendment	09/29/2020	Biopharmaceutics

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER/ SECONDARY REVIEWER	BRANCH/DIVISION
Drug Substance	Katherine Windsor/ Ali Al Hakim	OPQ/ONDP/DNDPAPI
Drug Product	Tefsit Bekele/ Anamitro Banerjee	OPQ/ONDP/DNDPI
OPMA/Facility	David Anderson/Ying Zhang	OPQ/OPF/DPAI
Microbiology	Jason God/Denise Miller	OPQ/OPF/DMA
Biopharmaceutics	Gerlie Gieser/Banu Zolnik	OPQ/ONDP/DB/
Regulatory Business Process Manager	Kristine Leahy	OPQ/OPRO/RBPMI
Application Technical Lead	Banu Zolnik	OPQ/ONDP/DB
Laboratory (OTR)	NA	NA
ORA Lead	Caryn McNabb	ORA

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	9/25/2020	MAPP 5015.5 (Rev.1)
	Type III			Adequate	9/29/2020	
	Type III			Adequate	9/29/2020	
	Type III			Adequate	9/29/2020	
	Type III			Adequate	8/28/2019	

B. Other Documents: *IND or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
Alimta Label	NDA 021462	Listed Drug, Alimta

2. CONSULTS

None

Executive Summary

I. Recommendations and Conclusion on Approvability

***COMPLETE RESPONSE** is recommended for this NDA from a Pharmaceutical Quality perspective.*

Overall, the submitted data/information were deemed inadequate to support the scientific bridge between the proposed to-be-marketed drug product and the relied upon Listed Drug (LD) product. Specifically, the Pharm/Tox review team concluded that the submitted data/information are not sufficient to justify the level of added citric acid in the proposed solution injectable drug product, i.e., from a safety perspective.

Summary of Quality Assessments

A. Product Overview

Accord Healthcare Inc. has submitted a new NDA 214408 505(b)(2) for Pemetrexed Injection. Pemetrexed Injection is a sterile, ready-to-dilute (RTD) solution supplied as 100 mg/4 mL, 500 mg/20 mL, 850 mg/34 mL, and 1000 mg/40 mL in 7 mL, 20 mL, 50 mL, and 50 mL clear (b) (4) glass vials respectively. The vials are closed with 20 mm dark grey (b) (4) rubber stopper and 20 mm flip-off seal with different colors for different presentations.

Pemetrexed Injection is a sterile, clear, colorless to pale yellow solution supplied in single-dose vials. Each vial is stoppered with (b) (4) rubber closures and aluminum seals with plastic flip-off tops. Four presentations are available as 25 mg/mL concentration; 4 mL, 20 mL, 34 mL, and 40 mL fill volumes. The proposed RTD solution drug product was mainly developed to eliminate the reconstitution step required for the ALIMTA® lyophilized powder, i.e., prior to the final dilution step. In addition to dosage form, the proposed drug product differs mainly from the LD in terms of added excipients, i.e., absence of mannitol ((b) (4) and addition of citric acid, L-methionine, and monothioglycerol (b) (4)

Pemetrexed Injection contains pemetrexed disodium drug substance (hemipentahydrate) together with citric acid, L-methionine, monothioglycerol, sodium hydroxide, hydrochloric acid, and water for injection.

Proposed Indication(s) including Intended Patient Population	• in combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations. (1.1) • in combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous,

	non-small cell lung cancer (NSCLC). (1.1) • as a single agent for the maintenance treatment of patients with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. (1.1) • as a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy. (1.1) Limitations of Use: Pemetrexed injection is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer. (1.1) • initial treatment, in combination with cisplatin, of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery. (1.2)
Duration of Treatment	The highest recommended duration of treatment in the label for Non-Squamous NSCLC: Day 1 of each 21-day cycle until disease progression or unacceptable toxicity after four cycles of platinum-based first-line chemotherapy
Maximum Daily Dose	500 mg/m^2
Alternative Methods of Administration	NA

B. Quality Assessment Overview

DRUG SUBSTANCE: ADEQUATE
Pemetrexed disodium is a folate analog metabolic inhibitor. The drug substance is isolated as the hemipentahydrate, which is soluble in water. There is a USP monograph for pemetrexed disodium (listing heptahydrate, anhydrous, and free acid forms, but not the hemipentahydrate form). The Applicant cross-referenced the CMC information for pemetrexed disodium hemipentahydrate drug substance to DMF (b) (4) DMF (b) (4) was reviewed by Katherine Windsor Ph.D. (final signature 25-SEP-2020) and was found adequate to support NDA 214408. Specified and unspecified impurity controls are sufficient. Stability data in the referenced DMF support the drug product manufacturer's proposed retest period of (b) (4) year for pemetrexed disodium (hemipentahydrate) drug substance stored at (b) (4) The Drug Substance Reviewer recommended for Approval.

DRUG PRODUCT: ADEQUATE

Pemetrexed Injection is a sterile solution containing no antimicrobial preservatives. It is supplied as clear colorless to pale yellow solution in 100 mg/4 mL, 500 mg/20 mL, 850 mg/34 mL and 1000 mg/40 mL (single-dose) strengths. It is a ready-to-dilute solution intended for IV infusion administration over 10 minutes. The overall formulation development indicates that the quality and chemical stability of the proposed product is equivalent to the listed drug. Three registration batches of each strength were manufactured that conform to the proposed specifications. Pemetrexed is prone to (b) (4) (b) (4) (b) (4) Agency has asked the applicant to add "store in original carton" statement as part of the storage conditions for the product in the US Prescribing Information (USPI). The product is required to be diluted in 0.9% NaCl infusion solution. The in-use stability data provided in the NDA supports storage of the final admixture up to 24 hours at 2–8 °C. Pemetrexed Injection is stable up to 18 months at 2–8 °C and 25 °C/60% RH. Based on the available 18 months stability data at 25 °C/60% RH, the requested 24 months expiration date may be granted. This determination is based on ICH Q1A (R2) and ICH Q1E. The applicant provided satisfactory drug product information including stability of the product. The Drug Product reviewer recommended for approval.

PROCESS and FACILITIES: ADEQUATE

The drug product manufacturing process involves (b) (4) (b) (4) The drug substance is (b) (4) (b) (4) In addition, the manufacturing process is performed (b) (4)

All facilities used to support commercial manufacturing facilities appear to have a favorable cGMP status. The process and facilities are recommended for approval.

MICROBIOLOGY: ADEQUATE

Microbiology review covers sterility assurance and microbiological quality of the drug product. The applicant has met regulatory expectations with regard to the information related to issues of product quality microbiology that is provided in the product labeling. Post-dilution storage conditions are sufficient to mitigate the risk of adventitious microbial growth. The Microbiology reviewer recommended for approval.

BIOPHARMACEUTICS: INADEQUATE

To justify that the formulation, dosage form and other product quality differences would not impact efficacy and safety of the proposed drug product (and thus, enable scientific bridging to the relied upon LD product), the Applicant conducted physico-chemical and *in vitro* protein binding characterization studies to compare the proposed and the LD products, as well as stability testing of the proposed drug product, and a

survey of the Inactive Ingredients Database and package inserts of CDER approved drug products.

Overall, the submitted data/information and associated justifications for the observed differences between products were not determined to be sufficient to establish the scientific bridge between the proposed drug product and the relied upon Listed Drug product. Based on the Biopharmaceutics Reviewer's assessment, the data/information provided by the Applicant to justify that each of these cross-product differences would not impact the PK (disposition), quality attributes during shelf-life, and efficacy (but NOT safety/tolerability) of the proposed drug product were deemed adequate. Specifically, based on the input of the Pharmacology/Toxicology and Medical Reviewers, it was determined that the data provided in the NDA were not sufficient to justify the (safety of the) level of added citric acid in the proposed drug product.

C. Special Product Quality Labeling Recommendations

NA

D. Final Risk Assessment

FROM INITIAL RISK IDENTIFICATION			REVIEW ASSESSMENT		
Attribute	**Factors that can impact the CQA**	**Initial risk ranking**	**Risk mitigation approach**	**Final risk evaluation**	**Lifecyle consideration**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipments • Site	H	(b) (4)	L	
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipments • Site	M		L	
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		L	
Physical stability (solid state) lyophilized small molecule products molecule products	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L		L	
Uniformity of Dose (Fill Volume/deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L		L	
Assay ((b) (4)	Formulation • Raw materials • Process parameters • Scale/equipments • Site	L		**M**	The level of citric acid pose safety concerns per Pharm/Tox reviewer. The Applicant was asked to either reformulate or conduct a toxicology study to address he safety concern in resubmission
Osmolality	• Formulation • Raw materials • Process	L		L	

Banu S. Zolnik, Ph.D.
Application Technical Lead, NDA 214408

Banu Zolnik

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U.S. FOOD & DRUG ADMINISTRATION

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CHAPTER III: ENVIRONMENTAL

IQA NDA Assessment Guide Reference

R REGIONAL INFORMATION

EA assessment is covered under Chapter 2 Drug Product review

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

Refer to Chapter 2: DP review

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	214408
Assessment Cycle Number	Original 505(b)(2) NDA
Drug Product Name/ Strength	Pemetrexed Injection 25 mg/mL (presented as 100 mg/4 mL, 500 mg/20 mL, 850 mg/34 mL,1000 mg/40 mL Ready-To-Dilute (RTD) solution in single-dose vials)
Route of Administration	For Intravenous Infusion
Applicant Name	ACCORD HEALTHCARE INC
Therapeutic Classification/ OND Division	Anticancer: Folate analog metabolic inhibitor DO2
Listed Drug Product Relied Upon	ALIMTA® lyophilized powder for reconstitution and further dilution [NDA 21462]
Proposed Indication	Treatment of non-squamous, non-small cell lung cancer

Assessment Recommendation: ***COMPLETE RESPONSE***

Assessment Summary:
This 505(b)(2) NDA for Pemetrexed (Ready-To-Dilute/RTD solution for) Injection, 25 mg/mL, relies for approval on the FDA's findings of efficacy and safety for the Listed Drug (LD) product, ALIMTA® (pemetrexed disodium) [powder] for Injection, as well as (at least in part) on the nonclinical and clinical pharmacology information in the LD's approved labeling.

The proposed RTD solution drug product was mainly developed to eliminate the reconstitution step required for the ALIMTA® lyophilized powder, i.e., prior to the final dilution step. In addition to dosage form, the proposed drug product differs mainly from the LD in terms of added excipients, i.e., absence of mannitol ((b) (4) and addition of citric acid, L-methionine, and monothioglycerol ((b) (4)

Overall, the submitted data/information were deemed inadequate to support the scientific bridge between the proposed to-be-marketed drug product and the relied upon Listed Drug product. Specifically, the FDA Review team concluded that the submitted data/information are not sufficient to justify the level of added citric acid in the proposed solution injectable drug product, i.e., from a safety perspective.

Supporting documents assessed:

	Date Received
SDN-1 (Original)	1/27/2020
SDN-2 (Response to Biopharmaceutics Information Request)	3/31/2020
SDN-4 (Response to Biopharmaceutics Information Request)	4/28/2020

SDN-6 (Response to Biopharmaceutics Information Request)	6/26/2020
SDN-7 (Response to Drug Product) Information Request)	7/6/2020
SDN-9 (Response to Pharmacology/Toxicology Information Request)	9/29/2020

Concise Description of Outstanding Issues:
Sufficient justification for the safety of the level of added citric acid in the proposed formulation

B.12 BRIDGING OF DEVELOPMENTAL FORMULATIONS OF THE PROPOSED DRUG PRODUCT

Assessment: *WITHIN PRODUCT BRIDGING – Not Needed*

The proposed commercial formulation, process and batch scale/size(s) were used for the manufacture of the drug product batches evaluated in stability, comparative physico-chemical and comparative *in vitro* protein binding studies. Additionally, the proposed commercial drug product manufacturer (Intas Pharmaceuticals Limited/Pharmez, India) produced the exhibit batches and the lots tested in comparative *in vitro* studies, i.e., using the drug substance (pemetrexed disodium *hemipentahydrate*) manufactured by the proposed commercial API supplier ((b) (4) (b) (4)).

Note that the proposed drug product was not tested in any *in vivo* animal or human studies/trials.

B. 13 BIOWAIVER REQUEST OR CROSS-PRODUCT BRIDGING

Assessment: *BRIDGING OF PROPOSED & LISTED DRUG PRODUCTS* - ***Inadequate***

Note that during the early stage of NDA review, the Applicant acknowledged the FDA's comment that their biowaiver request (pursuant to 21 CFR 320.22) would not be feasible because the formulation of the proposed injectable solution drug product is not qualitatively and quantitatively (Q1/Q2) the same as that of the Listed Drug/LD (ALIMTA®) being relied upon. As stated in the FDA WRO Pre-IND/Pre-NDA meeting minutes and reiterated by FDA in the recent communication, bridging of the proposed and the LD products can be established, via 21 CFR 320.24, provided the comparative *in vitro* data and additional submitted supporting data/information are considered adequate during NDA review.

The noted similarities and differences between the proposed drug product and the relied upon Listed Drug are summarized in Table 1. In addition to differences in excipients, the proposed and the LD drug products do not have the same (shelf-life) dosage forms (RTD solution versus i.e.. powder for reconstitution and further dilution). To justify that the

formulation, dosage form and other product quality differences would not impact efficacy and safety of the proposed drug product (and thus, enable scientific bridging to the relied upon LD product), the Applicant conducted physico-chemical and *in vitro* protein binding characterization studies to compare the proposed and the LD products, as well as stability testing of the proposed drug product, and a survey of the Inactive Ingredients Database and package inserts of CDER approved drug products.

Overall, the submitted data/information and associated justifications for the observed differences between products were not determined to be sufficient to establish the scientific bridge between the proposed drug product and the relied upon Listed Drug product. For details, refer to the Reviewer's assessment of the data/information provided by the Applicant to justify that each of these cross-product differences would not impact the PK (disposition), quality attributes during shelf-life, efficacy and safety/tolerability of the proposed drug product.

Table 1. Comparison of the Proposed Drug Product and the Relied Upon Listed Drug Product

	Proposed Drug Product[a] Pemetrexed (Ready-To-Dilute Solution for) Injection, Accord Healthcare, Inc.	**Listed Drug Product Being Relied Upon** ALIMTA® (pemetrexed for injection); NDA 021462, Eli Lilly & Company
Dosage Form; Strength(s)/Presentation	Ready-To-Dilute (RTD) Solution; 25 mg pemetrexed free acid/mL (single-dose vials containing 100 mg/4 mL, 500 mg/20 mL, 850 mg/34 mL and 1000 mg/40 mL RTD solution)[#]	Lyophilized Powder for Reconstitution and Further Dilution with preservative-free NSS (single dose 100 mg, and 500 mg free acid/vial)
Formulation Composition	Each glass vial of 100 mg/4 mL RTD solution contains (in addition to 110 (b) (4) mg pemetrexed disodium hemipentahydrate) anhydrous citric acid (60 mg)[b], L-methionine (2 mg)[b], Monothioglycerol (17.6 mg)[b] Water for Injection (q.s. ad 4 mL) HCl or NaOH to adjust pH	Each glass vial of 100 mg pemetrexed (eq. to 139.8 mg pemetrexed disodium heptahydrate) contains Mannitol (106 mg) HCl or NaOH to adjust pH
Final Concentration at the point of patient contact	<u>For BSA = 1.8 m^2:</u> 9 mg/mL upon dilution with NSS to 100 mL	(25 mg/mL upon reconstitution) <u>For BSA = 1.8 m^2:</u> 9 mg/mL upon dilution with NSS to 100 mL
Proposed Indications/Route of Administration/Dosing Regimen	Indications, Administration Routes, and Dosing Regimens the same as LD; Final dilution administered as 10-min IV infusion	
Physico-chemical properties of the final dilution for IV infusion		
Appearance	Clear, colorless (to pale yellow) solution; free from visible particulates	
Assay	-	Before Reconstitution: 101.9%, 107.4%;

	Before dilution: 103% *After dilution (9 mg/mL): 103.7%, 99.7%* [Proposed ranges: (b) (4)% of label claim/LC (release); (b) (4)% (shelf-life)]	Reconstituted/Before dilution: 99.6%; *After dilution (9 mg/mL): 102.6%* [Approved range: (b) (4)% of LC]
pH	Before dilution: 7.7; *After dilution (9 mg/mL): 7.46, 7.37* [Proposed ranges: (b) (4) (release); (b) (4) (shelf-life)]	Reconstituted/Before dilution: 7.07; *After dilution (9 mg/mL): 6.83* [Approved range: (b) (4)
Osmolality (mOsm/kg)	Before dilution: 369 *After dilution (9 mg/mL): 328, 324*	Reconstituted/Before dilution: 530, 524 *After dilution (9 mg/mL): 387*
Viscosity (mPa.s)	Before dilution: 1.2543 *After dilution (9 mg/mL): 1.0973, 1.0924*	Reconstituted/Before dilution: 1.246 *After dilution (9 mg/mL): 0.962*
Specific gravity	Before dilution: 1.0270 *After dilution (9 mg/mL): 1.0133, 1.0088*	Reconstituted/Before dilution:1.025,1.023 *After dilution (9 mg/mL): 1.0123*
Surface Tension (mN/m)	Before dilution: 74	Before dilution: 74.5
In Vitro Protein Binding (%, mean) 0.5 mcg/mL 200 mcg/mL 9 mg/mL pemetrexed	 90.8 87.5 29.4	 91 87 27.5
Recommended storage during product shelf-life and upon preparation	RTD – Refrigerated or a (b) (4) (b) (4) **Protect from Light (use diluted solution within 24 hours of preparation under refrigeration)	Powder – USP Controlled Room Temperature (use both reconstituted and diluted solution within 24 hours of preparation under refrigeration)
Container-closure	USP (b) (4) glass vial with (b) (4) rubber stopper with aluminium seal	
Physico-chemical & microbiological stability		
Total Impurities/ Degradants	(b) (4)% (batch release) NMT (b) (4)% (6 months at 40°C/75%RH)	Below quantification limit
Sterility	via (b) (4) maintained during 6 months accelerated and 12 months of long-term stability testing of the RTD solution, and after dilution within 24 hours under refrigeration	-
Bacterial Endotoxins (NMT 0.17 EU/mg of Pemetrexed)	Conforms during initial and later stability time points	
Special QC specifications (tests and acceptance ranges) proposed/approved	1. Minimum Fill Volume[c]/Container Content: NLT nominal (e.g., during manufacture (b) (4) mL for 100 mg/4mL)	Reconstitution time = NMT (b) (4) sec[d]
	2. Assay of three (b) (4) — At Release — During Shelf-Life	-
	Monothioglycerol — (b) (4)% of input — NMT (b) (4)% of input	
	Citric acid — (b) (4)% of input — (b) (4)% of input	
	L- Methionine — (b) (4)% of input — (b) (4)% of input	
	3. Impurities — At Release — During Shelf-Life	

	(b) (4)

[a] The majority of the comparative physicochemical data tabulated above were measured using the proposed drug product's 100 mg/4 mL and the LD's 500 mg/vial presentations. Wherever a 2nd value is presented for each parameter, such was obtained using the proposed product's 850 mg/34 mL or the LD's 100 mg/vial presentation.
[b] The proposed drug product contains three excipients which serve as (b) (4) and (b) (4) (b) (4). Mannitol was excluded because the drug product (b) (4) (b) (4)
[c] fill volumes (overfill): (b) (4)
[d] information from NDA of ALIMTA
***Tentative expiration dating period = 24 months (Refrigerated or RT)
ND – Not Determined

The Reviewer's assessment of the Applicant's justifications for the differences between the proposed drug product and the Listed Drug product are discussed in detail below.

Justification for

1. *Difference in crystalline hydrates of the API salt (hemipentahydrate vs heptahydrate), and the potential slight difference in the strengths of the proposed product's 100 mg/4 mL presentation versus the Listed Drug product's 100 mg/vial upon reconstitution with (b) (4) mL vehicle, notwithstanding the contribution of overage/overfill – Impact on quality*

   Per the Applicant, pemetrexed disodium exists in either of two crystalline API polymorphic forms, hemipentahydrate and heptahydrate. The proposed drug product uses hemipentahydrate whereas the LD uses heptahydrate. In the Applicant's Response (SDN-2, 3/31/2020) to the FDA's Quality Information Request, the comparative pH-solubility profiles of the two API polymorphic forms cannot be provided because the Applicant does not have the heptahydrate form. Nevertheless, the Applicant provided the solubility data of the hemipentahydrate form of pemetrexed disodium in various aqueous media (which confirmed high solubility in water, 0.9% NaCl solution, 0.5% Dextrose Solution, pH 4.5 and pH 6.8 buffers, but low solubility in pH 1.2 medium), as well as information that both the proposed drug product (prior to and after dilution) and the reconstituted LD and its final dilution (prepared according to the approved/proposed labeling instructions) yielded clear, colorless solutions that are free from particulates, thereby providing evidence of the proposed drug product's in-use physical stability potential by demonstratring visually complete solubility). Additionally, the Applicant reported that even though the LD's 100 mg/vial is reconstituted with (b) (4) mL (instead of 4 mL) vehicle, the proposed drug product's 100 mg/4 mL vial's measured Assay values (prior to and after dilution) were not exceedingly high but were close to 100% (i.e., (b) (4) %) of label claim. Also in SDN-2, the Applicant stated that during manufacture, the vial for the 100 mg/4 mL presentation is filled with a minimum RTD solution volume of (b) (4) mL, which should be sufficient to withdraw NLT the nominal fill volume of 4 mL. *Per the Process Reviewer (Dr. Ying Zhang), the proposed target fill volume acceptance ranges for all four presentations of the proposed drug product (e.g., (b) (4) mL for 100 mg/4 mL) are adequate to allow withdrawal and administration of the labeled amount of drug product.*

Of note, based on the ALIMTA NDA database, both hemipentahydrate and heptahydrate forms of pemetrexed disodium are highly soluble in water; however, the heptahydrate form is (b) (4)
dosage form], and was also found to have (b) (4) of impurities.

2. *Difference in Formulations/Excipients – Impact on pemetrexed PK*

The Applicant reported that based on the results of an *in vitro* human plasma protein binding study, the amounts of total and free pemetrexed were almost similar (and the percentage of protein binding were comparable) between the test/proposed product (Exhibit Batch PX05234) and reference product (ALIMTA, Batch C994605A & Batch D066851A) at the studied drug concentration range (0.5 to 200 mcg/mL, post-addition of the pemetrexed infusion solution into plasma), and therefore, no significant difference in drug distribution profiles between the proposed and the reference drug products is expected. Additional data provided showed that the *in vitro* protein binding data at the final dilution concentration of 9 mg/mL was substantially lower for both proposed and reference drug products, i.e., 27.5% and 29.4%, respectively, as compared to at the 0.5 to 200 mcg/mL range (~87% to 91%). Per the Applicant, the *in vitro* protein binding study results indicate that no significant difference in renal elimination of pemetrexed is expected between the proposed and the LD products because theoretically, drug distribution is followed by renal elimination of the drug.

Furthermore, this Reviewer believes that the removal of mannitol and the addition of the three (b) (4) in the proposed drug product would not be anticipated to result in a difference in pemetrexed PK (disposition) between the proposed and the reference drug products, for the following reasons: (***i***) The maximum dose of mannitol in ALIMTA (1.06 grams in 1000 mg) is approximately 14-fold lower than the mannitol dose required to induce diuresis in a 70 kg patient given a maintenance (mannitol) dose of 200 mg/kg via IV infusion (3 – 5 min). Thus, this Reviewer assumes that the mannitol (added as a (b) (4) excipient) in ALIMTA does not significantly influence the drug's renal elimination. (***ii***) Additionally, based on this Reviewer's literature survey, it appears that none of the three added (b) (4) possess diuretic or anti-diuretic activity. (***iii***) Furthermore, the similarity of the proposed and LD products in terms of *in vitro* protein binding data suggests anticipated similarity with respect to drug interaction potential where protein binding displacement/competition is the mechanism involved.

3. *Difference in Formulations/Excipients – Impact on drug product safety/tolerabillity and quality*

Per the Applicant, the excipients (three (b) (4) and pH-adjusting agents) in the proposed drug product's formulation are commonly used in parenteral formulations, and are very well within the Inactive Ingredients Database (IIG) limits for intravenous route of administration, per the following table (Table 3 of the Pharmaceutical Development Report 1/PDR-1). Additionally, per the Applicant, the maximum daily intake of the three excipients from the proposed drug product will not exceed the total daily intake (TDI) from the cited approved drug products (refer to Tables 4 and 5 of the PDR-1). *Note that the Drug Product*

Reviewer confirmed that the proposed levels of monothioglycerol and other added (b) (4) *in the proposed drug product formulation are acceptable from a product quality (stability) perspective.* ***However, based on the evaluation of the submitted literature justification by the Pharmacology/Toxicology Review Team led by Dr. Whitney Helms, there appears to be some residual uncertainty regarding the systemic safety of the citric acid excipient. Specifically, for a 70 kg patient, the rate of citric acid administered over 10 minutes as part of the proposed Pemetrexed Injection is approximately*** (b) (4) ***mg/kg/min whereas the cited medical literature (Bunker et al, 1955) reported that a citrate infusion rate of 1 mg/kg/min resulted in hypocalcemia in a significant number of citrated blood recipients with normal or abnormal liver function. In some cases, such were prevented or corrected by intravenous administration of calcium (usually chloride salt). For additional details regarding the citric acid issue, refer to the Pharmacology/Toxicology Memo. Based on the outcome of FDA internal discussions, approval of this NDA in this review cycle cannot be recommended. At the time of NDA resubmission, the Applicant will have to satisfactorily address the safety concern regarding the level of added citric acid in the proposed injectable solution either either by (1) reformulating, or (2) submitting additional preclinical data in order to demonstrate the safety of the proposed drug product/formulation.***

Table 03: IIG limits of excipients

Ingredients	Quantity (%w/v)	IIG limits (%w/v)
Citric Acid Anhydrous	1.5%	(b) (4)%
L-Methionine	0.05%	0.16%
Monothioglycerol	0.44%	(b) (4)%
Sodium hydroxide	q.s. to pH	ADJ PH
Hydrochloric acid	q.s. to pH	ADJ PH

Table 04: Maximum daily intake of excipients (considering (b) (4) **mg maximum daily dose of drug substance (pemetrexed)**

Excipients	Per mL quantity of excipients in Pemetrexed Injection 25 mg/mL	Max. daily intake of excipients as per drug substance maximum daily dose (b) (4) mg
Anhydrous Citric Acid	15 mg/mL	(b) (4)
L-Methionine	0.50 mg/mL	
Monothioglycerol	4.40 mg/mL	

Total Daily Intake (TDI) of excipient from dosing the cited Listed Drug product (source: adapted from Table 5 of Pharmaceutical Development Report-1 for a 70 kg patient):

Anhydrous Citric Acid: (b) (4) *mg from* (b) (4)

Methionine: (b) (4) *mg from* (b) (4)

(b) (4)

Monothioglycerol: (b) (4) *mg from* (b) (4)

4. Difference in Dosage Form and Presentation - Impact on Clinical Outcomes

Per the Applicant, all presentations of the proposed and Listed drug products will have the same pharmaceutical form (solution) at the point of patient contact, the same drug product concentrations prior to final dilution (25 mg/mL) and after final dilution (e.g., 9 mg/mL for a

patient with BSA 1.8 m^2), as well as the same administration route and dosing regimens. Additionally, the Applicant stated that both proposed drug product and LD are presented as single dose vials.

The proposal to market presentations containing higher total drug content, i.e., the 850 mg/34 mL and 1000 mg/40 mL (in addition to the 100 mg/4 mL and 500 mg/20 mL) single dose vial presentations of the 25 mg/mL pemetrexed RTD solution is reasonable when considering that the recommended drug dosage is 500 mg/m^2. Thus, for a typical adult patient with a BSA of 1.8 m^2, the required 900 mg dose can be derived using the content of the just one vial of 1000 mg/40 mL of the proposed drug product. [Also, it is noted that the Clinical Pharmacology Review for ALIMTA® includes 1000 mg/40 mL solution.]

5. *Difference in Dosage Form and Presentation - Impact on product quality*

At the time of comparative *in vitro* testing, the LD did not have detectable levels of impurities/degradants in the reconstituted/diluted solution prepared from the lyophilized powder. On the other hand, the exhibit batches of the proposed Ready-To-Dilute injectable solution drug product, during 6 months of accelerated (40 ± 2 °C/75 ±5 RH) and 18 months of long-term (5 ± 3 °C, and 25°C± 2°C; RH: 60%±5%) stability testing, exhibited NMT (b) (4)% total impurities. *Per Dr. Tefsite Bekele (Drug Product Reviewer), the proposed tolerance limits for total impurities (NMT (b) (4)% during shelf-life, even though numerically higher than that approved for the LD) is acceptable. Additionally, Dr. Bekele confirmed that the stability of the proposed drug product during extreme conditions of shipping was demonstrated based on the comparable Assay values of the drug product with and without filtration following three freeze-thaw cycles.*

The Applicant stated that one of the impurities in the proposed and relied upon LD products, i.e., (b) (4) is an *in vivo* pemetrexed metabolite forming up to (b) (4)% *in vivo*. Based on the ICH guidance for qualification of impurities that are metabolites, the Applicant considers the proposed (b) (4) limit of NMT (b) (4)% (during shelf-life) to be justified in terms of safety, efficacy and test formulation stability data in final finished formulation. *Thus, that the proposed (b) (4) limit of NMT (b) (4)% exceeds that approved for the LD was deemed acceptable by the Pharm/Tox and CMC Reviewers.* Additionally, the Applicant stated that the proposed drug product complies with the requirements of USP <1> Injections and Implanted Drug Products.

As is the case for Total Impurities, the proposed acceptance ranges for finished drug product pH, Assay, and Individual Impurities are wider or more permissive during shelf-life/stability testing than at batch release of the proposed RTD solution drug product. Per Dr. Bekele, the proposed finished product QC specifications at batch release and during shelf-life, as well as the proposed expiration dating period (24 months under refrigeration of at controlled room temperature) are acceptable. Additionally, as indicated above, the proposed target fill volumes for all presentations during manufacture of the proposed drug product are acceptable to the Process Reviewer.

Per the Applicant, the primary packaging of the drug product (glass vial and rubber stoppers) are in compliance with the requirements in USP<660> (Containers – Glass), and USP <381> Elastomeric Closures for Injections, and were confirmed to be suitable for use with the proposed solution drug product based on the results of compatibility, container-closure integrity (e.g., leakage), and glass delamination studies. Per the Applicant, the Scanning Electron Microscope (SEM) study did not reveal minor scratches or chemical based surface contamination in control vial samples and in drug product samples exposed to 6 months of accelerated storage (40 °C/75% RH) conditions. *The Drug Product Reviewer confirmed that the results of the conducted glass delamination, extractables and leachables studies are satisfactory, and pose no safety concerns.* Note that like the LD, a (b) (4) coated rubber stopper is used for the packaging of the proposed RTD solution drug product.

6. *Difference in Recommended Storage Conditions - Protect from Light (mandatory), and Refrigeration (as alternative to Room Temperature Storage during drug product shelf-life)*

   The provided 12-months of long-term stability data for the exhibit batches indicate that the potency and the levels of specific and total impurities in the proposed solution drug product conform to the proposed acceptance criteria when stored either in the refrigerator or at room temperature. The Applicant concluded (and the Drug Product Reviewer confirmed) that the proposed drug product remains stable when diluted and stored as recommended in the approved ALIMTA labeling (i.e., up to 24 hours under refrigeration). Additionally, per the Applicant, three freeze/thaw treatment cycles did not alter the proposed drug product's quality.

   The Applicant also reported that based on the results of the photostability study, the proposed solution drug product in a clear glass vial, but without a secondary (opaque carton) packaging, was (b) (4) per ICH conditions (but not to day light for up to 7 days). Thus, the proposed labels of the cartons and vials, as well as the proposed package insert state: "Protect from Light", *which is acceptable to the Drug Product Reviewer; however, the Applicant was requested to include a labeling recommendation to "keep the drug product (vial) in the original container until time of use".*

BIOPHARMACEUTICS LIST OF DEFICIENCIES

Data to support the safety of the added level of citric acid in the proposed drug product (refer to the Pharmacology/Toxicology Reviewer Memo)

Primary Biopharmaceutics Assessor's Name and Date:

Gerlie Gieser, Ph.D. (11/10/2020)

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Banu Zolnik, Ph.D. (11/12/2020)

Gerlie Gieser

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Banu Zolnik

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	(b) (4) solution for injection
NDA Number	214408
Assessment Cycle Number	1
Drug Product Name/ Strength	Pemetrexed / 25 mg/mL
Route of Administration	IV
Applicant Name	Accord Healthcare Inc.
Therapeutic Classification/ OND Division	OND/ODD/DO2
Manufacturing Site	Intas Pharmaceuticals Limited Plot No. 5 to 14, Pharmez Near Village Matoda, Sarkhej-Bavla Highway No. 8-A, Taluka : Sanand Ahmedabad, Gujarat, India 382213
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: This review covers sterility assurance and microbiological quality of the drug product.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0001	**01/27/2020**
0003	**04/27/2020**

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

Remarks: An information request was issued by the Agency, dated 21 April 2020. The applicant's response, received 27 April 202, is addressed in the appropriate section of this review.

Concise Description of Outstanding Issues
(None)

Supporting Documents:
DMA review (b) (4) dated 5/21/2019 (adequate), is referenced for review of floor plans showing pressure differentials, environmental monitoring procedures and alert/action limits, media fill

procedures and specification, media fill data and actions taken concerning the product following media fill failure.

DMF (b) (4) Rubber Compounds, was reviewed by DMA in (b) (4), dated 28 August 2019 (adequate), for the (b) (4) (b) (4) DMF LOA dated 6 November 2019.

S DRUG SUBSTANCE

Drug substance is supplied (b) (4)

Assessment: NA, drug substance is not sterile.

P. Drug Product

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** Clear, colorless to pale yellow solution.

- **Drug product composition –** Drug product is manufactured at 25 mg/mL in the following presentations: 4 mL, 20 mL, 34 mL and 40 mL. The proposed batch size for all presentations is (b) (4) L. Table 1, below, shows the batch formula for the 4 mL presentation. Quantity/mL and quantity/batch are the same for all formulations.

Table 1: Batch formula for 25 mg/mL Pemetrexed, 4 mL

Ingredients	Reference to quality standards	Quantity per mL	Quantity per vial (4 mL fill volume)	Quantity/batch Batch size: (b) (4)
Pemetrexed Disodium (Hemipentahydrate)#	In house	27.5 (b) (4) mg	110 (b) (4) mg	(b) (4)
Citric Acid Anhydrous	USP	15.00 mg	60 mg	
L-Methionine (b) (4)	USP	0.50 mg	2 mg	
Monothioglycerol	USP	4.40** mg	17.6** mg	
Sodium Hydroxide##	NF	q.s. for pH adjustment	q.s.	
Hydrochloric Acid, (b) (4)	NF	q.s. for pH adjustment	q.s.	
Water for Injection	USP	q.s. to 1 mL	q.s. to 4 mL	
(b) (4)				

Table 1 was reproduced from Table 2 in "batch-formula," located in Module 3.2.P.1

- **Container Closure System –** Container closure system details are summarized in Table 2, below.

Table 2: Summary of container closure systems for Pemetrexed 25 mg/mL

Presentation/ Fill volume	25 mg/mL, 4 mL	25 mg/mL, 20 mL	25 mg/mL, 34 mL	25 mg/mL, 40 mL
Container (Glass Vial)	7 mL (b) (4) clear glass vial (b) (4)	20 mL clear (b) (4) glass vial (b) (4)	50 mL clear (b) (4) glass vial (b) (4)	50 mL clear (b) (4) glass vial (b) (4)
Closure (Rubber Stopper)	20 mm (b) (4) (b) (4) rubber stoppers (20 MM (b) (4) (b) (4)			
Seal	20 mm Flip off (b) (4) (b) (4) seal (b) (4) (b) (4)	20 mm flip off (b) (4) (b) (4) seal (b) (4) (b) (4)	20 mm flip off (b) (4) (b) (4) seals (b) (4) (b) (4)	20 mm flip off (b) (4) (b) (4) seals (b) (4) (b) (4)

Table 2 was reproduced from Table 1 in "container-closure-system," located in Module 3.2.P.7

Assessment: *Adequate*

(b) (4)

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