CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214408Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 18, 2022
From	Mei Ou, Ph.D. OPQ/ONDP/Division of Biopharmaceutics
Subject	Cross-Discipline Team Leader Review
NDA	NDA 214408-ORIG-1-RESUB-17
Type of Submission	505(b)(2)
Applicant	Accord Healthcare Inc.
Date of Submission	May 19, 2022
PDUFA Goal Date	July 19, 2022
Established or Proper names	Pemetrexed Injection
Dosage forms / Strength	Solution for Intravenous Injection 25 mg/mL (100 mg/4 mL, 500 mg/20 mL, 850 mg/34 mL and 1000 mg/40 mL)
Proposed Indications	• 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.
Recommendation:	**APPROVAL**

This CDTL review is based on the primary reviews/memos of:

DICIPLINE	PRIMARY REVIEWER/TL	FINAL REVIEW DATE
Quality IQA	Mei Ou (Application Technical Lead)	06/28/2022
Clinical	Satinder (Mona) Choudhary	N/A
Non-Clinical (Pharmacology/Toxicology)	Melissa Pegues/Claudia Miller	N/A
Clinical Pharmacology	Suryatheja Ananthula/ Jeanne Fourie Zirkelbach	N/A
Division of Medication Error Prevention and Analysis	Tingting Gao	N/A
505(b)(2) Committee	Mary Ann Holovac	N/A

Cross Discipline Team Leader Review

1. Background

This NDA for Pemetrexed Injection (25 mg/mL) 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), approved on February 4, 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 has the same indications as described for ALIMTA, as:

- 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.

The proposed drug product also has the same route of administration and contains the same active moiety (pemetrexed) as the approved LD. There is no difference in dosing regimen (500 mg/m^2 as an intravenous infusion over 10 minutes).

The proposed drug product differs from LD product in terms of dosage form (i.e., ready-to-dilute (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).

No clinical pharmacology, safety or efficacy data were submitted in this NDA application.

The original 505(b)(2) application by Accord Healthcare Inc. submitted on January 27, 2020 but received a Complete Response (CR) letter on November 23, 2020. The first-time resubmission, a class 2 resubmission, dated November 17, 2021 received a Tentative Approval on May 17, 2022. The Applicant resubmitted this NDA 214408, a class 1 resubmission, on May 19, 2022, requesting for final approval upon the expiration of the patent protection. There are no changes made to the chemistry, manufacturing, and controls; and carton/container labeling. The Applicant accepted the recommended changes in U.S. prescribing information (USPI) and the patient package insert (PPI) labeling sections of the application.

2. Product Information

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.

To deliver the required pemetrexed dose (calculated based on the patient's body surface area (BSA), 500 mg/m^2), the appropriate volume of the RTD Pemetrexed 25 mg/mL solution is to be withdrawn from the vial(s) and then diluted with 0.9% Sodium Chloride Injection to achieve a total volume of 100 mL for intravenous infusion for over 10 minutes.

The amount of citric acid excipient in the proposed formulation is up to (b) (4) citric acid at the clinical dose of 500 mg/m^2 pemetrexed. Additionally, the Applicant proposed intravenous administration over a 10 minute infusion period, resulting in an infusion rate of approximately (b) (4) mg/kg/minute citric acid, so that potential safety risks at this infusion rate include citric acid intoxication and metabolic alkalosis.

3. Pharmaceutical Quality- ADEQUATE

The OPQ review team recommended APPROVAL for the current class 1 resubmission.

4. Nonclinical Pharmacology/Toxicology – No Action Indicated (NAI)

5. Clinical Pharmacology – NAI

6. Clinical – NAI

7. Pediatric Research Equity Act Waiver – NAI

8. Advisory Committee Meeting – NAI

9. Other Relevant Regulatory Issues – NAI

10. Labeling

There are no further changes made to the carton/container labeling after the tentative approval letter. The Applicant accepted all the recommended changes in U.S. prescribing information (USPI) and the patient package insert (PPI) labeling sections of the application.

11. Risk Benefit Assessment

Please refer to NDA 021462 (Alimta)

12. Recommendations

The cross disciplinary team lead recommendation for NDA-214408-ORIG-1-RESUB-17 is **APPROVAL**.

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/

MEI OU
07/18/2022 05:24:25 PM

ERIN A LARKINS
07/18/2022 05:33:03 PM

Cross-Discipline Team Leader Review

Date	April 26, 2022
From	Mei Ou, Ph.D. OPQ/ONDP/Division of Biopharmaceutics
Subject	Cross-Discipline Team Leader Review
NDA	NDA 214408-ORIG-1-RESUB-10
Type of Submission	505(b)(2)
Applicant	Accord Healthcare Inc.
Date of Submission	November 17, 2021
PDUFA Goal Date	May 17, 2022
Established or Proper names	Pemetrexed Injection Solution
Dosage forms / Strength	Solution for Intravenous Injection 25 mg/mL (100 mg/4 mL, 500 mg/20 mL, 850 mg/34 mL and 1000 mg/40 mL)
Proposed Indications	The same as Alimta®: • In combination with pembrolizumab and platinum chemotherapy, in 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. Limitations of Use: Pemetrexed injection is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer. • 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.
Recommendation:	**TENTATIVE APPROVAL**

This CDTL review is based on the primary reviews/memos of:

DICIPLINE	PRIMARY REVIEWER/TL	FINAL REVIEW DATE
Quality IQA	Mei Ou (Application Technical Lead)	04/26/2022
Drug Substance	Paresma Patel	02/17/2022
Drug Product	Tefsit Bekele/Xing Wang	03/09/2022
Process/Facility	Jin Lee/James Norman	02/17/2022
Quality Microbiology	Jason God/Julie Nemecek	02/17/2022
Biopharmaceutics	Gerlie Gieser	03/10/2022
Clinical	Satinder (Mona) Choudhary	N/A
Non-Clinical (Pharmacology/Toxicology)	Melissa Pegues/Claudia Miller	03/10/2022
Clinical Pharmacology	Suryatheja Ananthula/ Jeanne Fourie Zirkelbach	N/A
Division of Medication Error Prevention and Analysis	Tingting Gao	04/22/2022
505(b)(2) Committee	Mary Ann Holovac	N/A

Cross Discipline Team Leader Review

1. Background

This NDA for Pemetrexed Injection (25 mg/mL) 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), approved on February 4, 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 has the same indications as described for ALIMTA, as:

- 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.
- 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.

The proposed drug product also has the same route of administration and contains the same active moiety (pemetrexed) as the approved LD. There is no difference in dosing regimen (500 mg/m^2 as an intravenous infusion over 10 minutes).

The proposed drug product differs from LD product in terms of dosage form (i.e., ready-to-dilute (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 505(b)(2) application by Accord Healthcare Inc. submitted on January 27, 2020, but 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 and infusion rate of the citric acid excipient present in the proposed formulation, consequently, because of the safety concern, the scientific bridge between the proposed product and the relied upon LD product could not be established.

The Applicant resubmitted this NDA on November 17, 2021 and included new nonclinical data to address deficiencies regarding the use of citric acid excipient in the proposed formulation. This Class 2 resubmission also provided for a revision of the finished product

quality control (QC) specifications with respect to the (b) (4) content in the solution drug product during shelf-life.

No clinical pharmacology, safety or efficacy data were submitted in this NDA application.

2. Product Information

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.

To deliver the required pemetrexed dose (calculated based on the patient's body surface area (BSA), 500 mg/m^2), the appropriate volume of the RTD Pemetrexed 25 mg/mL solution is to be withdrawn from the vial(s) and then diluted with 0.9% Sodium Chloride Injection to achieve a total volume of 100 mL for intravenous infusion for over 10 minutes.

The amount of citric acid excipient in the proposed formulation is up to (b) (4) citric acid at the clinical dose of 500 mg/m^2 pemetrexed. Additionally, the Applicant proposed intravenous administration over a 10 minute infusion period, resulting in an infusion rate of approximately (b) (4) mg/kg/minute citric acid, so that potential safety risks at this infusion rate include citric acid intoxication and metabolic alkalosis.

3. Pharmaceutical Quality- ADEQUATE

The OPQ review teams recommended APPROVAL for the current resubmission.

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 t (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 Reviewer recommends for* ***Approval****.*

Process and Facilities: No Action Indicated (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****.*

Quality Microbiology: No Action Indicated (NAI)

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****.*

4. Nonclinical Pharmacology/Toxicology - ADEQUATE

The nonclinical team recommended APPROVAL for the current resubmission.

After FDA issuing the CR letter on November 23, 2020, due to the potential safety risk of the amount of citric acid excipient in the proposed formulation up to (b) (4) the nonclinical team recommended that the Applicant conduct an acute animal toxicity study showing that the amount of citric acid present in the proposed formulation for Pemetrexed Injection is not acutely toxic. The Applicant submitted a proposed protocol for an acute toxicity study in rats to IND 142070 on December 21, 2020; the nonclinical team agreed that the proposed study design appeared sufficient provided that the dose levels for Pemetrexed Injection and the listed drug were at least 75 mg/kg, a dose which is approximately the human equivalent.

The completed acute toxicity study in rats included in the re-submission of NDA 214408 is sufficient to address the safety issue of the amount of citric acid excipient detailed in the complete response letter. The Applicant performed a GLP-compliant study to evaluate acute toxicity of intravenous administration of citric acid in rats. Rats were administered a single 10 minute intravenous infusion of vehicle (saline), 75, 150, or 300 mg/kg citric acid, 75 mg/kg Pemetrexed Injection, or 75 mg/kg reference listed drug (Alimta; Pemetrexed disodium for Injection); a sham (untreated) group was also included. Clinical signs of dullness, tremors, and clonic convulsions occurred in animals administered 300 mg/kg citric acid (1800 mg/m2), but

there were no clinical signs or changes in hematology or clinical chemistry, including calcium levels, in rats administered citric acid doses ≤150 mg/kg (900 mg/m^2) or 75 mg/kg pemetrexed injection or reference product. In male rats administered 300 mg/kg citric acid (approximately 6-times the amount of citric acid at the recommended 500 mg/m^2 pemetrexed dose), serum calcium levels were 5.59% and 5.29% higher than vehicle treated and sham animals, respectively, at 1 hour post-dose on Day 1 but improved by Day 14. Considering that IV administration of citric acid was well tolerated at dose levels approximately three times higher than citric acid levels at the clinical dose based on body surface area, there is sufficient coverage of the citric acid excipient at a relevant infusion rate at the proposed clinical dose.

There are no additional nonclinical recommendations for this NDA. The nonclinical recommendation to the Applicant's proposed labeling is primarily based on the listed drug, were discussed internally, and will be communicated to the Applicant.

5. Clinical Pharmacology

No new clinical pharmacology information was included in the resubmission. Dosing Regimens: Same as per ALIMTA, the reference LD (500 mg/m^2 as an intravenous infusion over 10 minutes).

6. Clinical

No clinical studies have been conducted under the submitted original NDA and the current resubmission and no clinical issues need to be addressed related to this NDA. The clinical team recommended approval in original submission upon satisfactory review from other FDA disciplines.

7. Pediatric Research Equity Act Waiver – NAI

8. Advisory Committee Meeting – NAI

9. Other Relevant Regulatory Issues

NDA-214408-ORIG-1-RESUB-210 will receive a **TENTATIVE APPROVAL** action because of the unexpired patent on the relied upon listed drug.

Per email by Mary Ann Holovac dated April 6, 2022, the following statement will be presented to 505(b)(2) committee, as:

Data/information submitted to support the scientific bridge between the proposed product and listed drug (LD), Alimta (NDA 021462), include: composition comparison, physical characterization of innovator product, chemical evaluation of innovator product and its comparison with Accord's proposed product, and comparison of physico-chemical properties between proposed and LD products after dilution prior to administration.

To demonstrate that differences in proposed product from LD will not impact distribution and elimination [PK/disposition (i.e., renal elimination)], a protein binding study was performed between the proposed product and the LD product. A study was performed to compare the total pemetrexed and

free pemetrexed concentrations in human plasma between the proposed product and the LD. From the performed study, the amounts of total pemetrexed and free pemetrexed are comparable between the proposed product proposed product (Batch#PX05234) and the LD product (ALIMTA, Batch#C994605A) over the drug concentration range tested. Hence it is concluded that there was no significant difference between both products with respect to protein binding/drug distribution.

The concentration of drug substance for proposed drug product after dilution to the final solution is the same as the LD, Alimta. The route of administration and dosing regimens for the proposed drug product are also the same as the LD. Furthermore, the comparative in vitro protein binding study, the comparative physico-chemical characterization study, the comparative acute animal toxicity study as well as the results of the stability studies on the proposed solution drug product demonstrated that no significant differences in bioavailability and safety between the two products are anticipated. Therefore, a scientific bridge has been established between the proposed product and the relied-upon listed drug, Alimta, pursuant to 21 CFR 320.24(b)(6).

10. Labeling

Labeling is aligned with the listed drug Alimta. Accord submitted a Class 2 Resubmission on November 17, 2021, and resubmitted the prescribing information (PI), container labels, and carton labeling on March 24, 2022. DMEPA evaluated proposed PI, container labels, and carton labeling and determined that they can be improved to ensure safe product use. If DO2 plans to revise the statement "(b) (4) to "hazardous drug" in Section 2.7 Preparation and Administration and 16 How Supplied/Storage and Handling, DMEPA recommends updating the container labels and carton labeling with the statement "hazardous drug" to ensure consistency with the PI.

11. Risk Benefit Assessment

Please refer to NDA 021462 (Alimta)

12. Recommendations

The cross disciplinary team lead recommendation for NDA-214408-ORIG-1-RESUB-10 is **TENTATIVE APPROVAL**.

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/

MEI OU
05/11/2022 01:35:18 PM

ERIN A LARKINS
05/11/2022 01:52:15 PM

Cross-Discipline Team Leader Review

Date	April 26, 2022
From	Mei Ou, Ph.D. OPQ/ONDP/Division of Biopharmaceutics
Subject	Cross-Discipline Team Leader Review
NDA	NDA 214408-ORIG-1-RESUB-10
Type of Submission	505(b)(2)
Applicant	Accord Healthcare Inc.
Date of Submission	November 17, 2021
PDUFA Goal Date	May 17, 2022
Established or Proper names	Pemetrexed Injection Solution
Dosage forms / Strength	Solution for Intravenous Injection 25 mg/mL (100 mg/4 mL, 500 mg/20 mL, 850 mg/34 mL and 1000 mg/40 mL)
Proposed Indications	The same as Alimta®: • In combination with pembrolizumab and platinum chemotherapy, in 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. Limitations of Use: Pemetrexed injection is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer. • 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.
Recommendation:	**TENTATIVE APPROVAL**

This CDTL review is based on the primary reviews/memos of:

DICIPLINE	PRIMARY REVIEWER/TL	FINAL REVIEW DATE
Quality IQA	Mei Ou (Application Technical Lead)	04/26/2022
Drug Substance	Paresma Patel	02/17/2022
Drug Product	Tefsit Bekele/Xing Wang	03/09/2022
Process/Facility	Jin Lee/James Norman	02/17/2022
Quality Microbiology	Jason God/Julie Nemecek	02/17/2022
Biopharmaceutics	Gerlie Gieser	03/10/2022
Clinical	Satinder (Mona) Choudhary	N/A
Non-Clinical (Pharmacology/Toxicology)	Melissa Pegues/Claudia Miller	03/10/2022
Clinical Pharmacology	Suryatheja Ananthula/ Jeanne Fourie Zirkelbach	N/A
Division of Medication Error Prevention and Analysis	Tingting Gao	04/22/2022
505(b)(2) Committee	Mary Ann Holovac	N/A

Cross Discipline Team Leader Review

1. Background

This NDA for Pemetrexed Injection (25 mg/mL) 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), approved on February 4, 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 has the same indications as described for ALIMTA, as:

- 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.
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- 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.

The proposed drug product also has the same route of administration and contains the same active moiety (pemetrexed) as the approved LD. There is no difference in dosing regimen (500 mg/m^2 as an intravenous infusion over 10 minutes).

The proposed drug product differs from LD product in terms of dosage form (i.e., ready-to-dilute (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 505(b)(2) application by Accord Healthcare Inc. submitted on January 27, 2020, but 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 and infusion rate of the citric acid excipient present in the proposed formulation, consequently, because of the safety concern, the scientific bridge between the proposed product and the relied upon LD product could not be established.

The Applicant resubmitted this NDA on November 17, 2021 and included new nonclinical data to address deficiencies regarding the use of citric acid excipient in the proposed formulation. This Class 2 resubmission also provided for a revision of the finished product

quality control (QC) specifications with respect to the (b) (4) content in the solution drug product during shelf-life.

No clinical pharmacology, safety or efficacy data were submitted in this NDA application.

2. Product Information

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.

To deliver the required pemetrexed dose (calculated based on the patient's body surface area (BSA), 500 mg/m^2), the appropriate volume of the RTD Pemetrexed 25 mg/mL solution is to be withdrawn from the vial(s) and then diluted with 0.9% Sodium Chloride Injection to achieve a total volume of 100 mL for intravenous infusion for over 10 minutes.

The amount of citric acid excipient in the proposed formulation is up to (b) (4) citric acid at the clinical dose of 500 mg/m^2 pemetrexed. Additionally, the Applicant proposed intravenous administration over a 10 minute infusion period, resulting in an infusion rate of approximately (b) (4) mg/kg/minute citric acid, so that potential safety risks at this infusion rate include citric acid intoxication and metabolic alkalosis.

3. Pharmaceutical Quality- ADEQUATE

The OPQ review teams recommended APPROVAL for the current resubmission.

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) 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 Reviewer recommends for **Approval**.*

Process and Facilities: No Action Indicated (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**.*

Quality Microbiology: No Action Indicated (NAI)

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**.*

4. Nonclinical Pharmacology/Toxicology - ADEQUATE

The nonclinical team recommended APPROVAL for the current resubmission.

After FDA issuing the CR letter on November 23, 2020, due to the potential safety risk of the amount of citric acid excipient in the proposed formulation up to (b) (4) the nonclinical team recommended that the Applicant conduct an acute animal toxicity study showing that the amount of citric acid present in the proposed formulation for Pemetrexed Injection is not acutely toxic. The Applicant submitted a proposed protocol for an acute toxicity study in rats to IND 142070 on December 21, 2020; the nonclinical team agreed that the proposed study design appeared sufficient provided that the dose levels for Pemetrexed Injection and the listed drug were at least 75 mg/kg, a dose which is approximately the human equivalent.

The completed acute toxicity study in rats included in the re-submission of NDA 214408 is sufficient to address the safety issue of the amount of citric acid excipient detailed in the complete response letter. The Applicant performed a GLP-compliant study to evaluate acute toxicity of intravenous administration of citric acid in rats. Rats were administered a single 10 minute intravenous infusion of vehicle (saline), 75, 150, or 300 mg/kg citric acid, 75 mg/kg Pemetrexed Injection, or 75 mg/kg reference listed drug (Alimta; Pemetrexed disodium for Injection); a sham (untreated) group was also included. Clinical signs of dullness, tremors, and clonic convulsions occurred in animals administered 300 mg/kg citric acid (1800 mg/m2), but

there were no clinical signs or changes in hematology or clinical chemistry, including calcium levels, in rats administered citric acid doses ≤150 mg/kg (900 mg/m^2) or 75 mg/kg pemetrexed injection or reference product. In male rats administered 300 mg/kg citric acid (approximately 6-times the amount of citric acid at the recommended 500 mg/m^2 pemetrexed dose), serum calcium levels were 5.59% and 5.29% higher than vehicle treated and sham animals, respectively, at 1 hour post-dose on Day 1 but improved by Day 14. Considering that IV administration of citric acid was well tolerated at dose levels approximately three times higher than citric acid levels at the clinical dose based on body surface area, there is sufficient coverage of the citric acid excipient at a relevant infusion rate at the proposed clinical dose.

There are no additional nonclinical recommendations for this NDA. The nonclinical recommendation to the Applicant's proposed labeling is primarily based on the listed drug, were discussed internally, and will be communicated to the Applicant.

5. Clinical Pharmacology

No new clinical pharmacology information was included in the resubmission. Dosing Regimens: Same as per ALIMTA, the reference LD (500 mg/m^2 as an intravenous infusion over 10 minutes).

6. Clinical

No clinical studies have been conducted under the submitted original NDA and the current resubmission and no clinical issues need to be addressed related to this NDA. The clinical team recommended approval in original submission upon satisfactory review from other FDA disciplines.

7. Pediatric Research Equity Act Waiver – NAI

8. Advisory Committee Meeting – NAI

9. Other Relevant Regulatory Issues

NDA-214408-ORIG-1-RESUB-210 will receive a **TENTATIVE APPROVAL** action because of the unexpired patent on the relied upon listed drug.

Per email by Mary Ann Holovac dated April 6, 2022, the following statement will be presented to 505(b)(2) committee, as:

Data/information submitted to support the scientific bridge between the proposed product and listed drug (LD), Alimta (NDA 021462), include: composition comparison, physical characterization of innovator product, chemical evaluation of innovator product and its comparison with Accord's proposed product, and comparison of physico-chemical properties between proposed and LD products after dilution prior to administration.

To demonstrate that differences in proposed product from LD will not impact distribution and elimination [PK/disposition (i.e., renal elimination)], a protein binding study was performed between the proposed product and the LD product. A study was performed to compare the total pemetrexed and

free pemetrexed concentrations in human plasma between the proposed product and the LD. From the performed study, the amounts of total pemetrexed and free pemetrexed are comparable between the proposed product proposed product (Batch#PX05234) and the LD product (ALIMTA, Batch#C994605A) over the drug concentration range tested. Hence it is concluded that there was no significant difference between both products with respect to protein binding/drug distribution.

The concentration of drug substance for proposed drug product after dilution to the final solution is the same as the LD, Alimta. The route of administration and dosing regimens for the proposed drug product are also the same as the LD. Furthermore, the comparative in vitro protein binding study, the comparative physico-chemical characterization study, the comparative acute animal toxicity study as well as the results of the stability studies on the proposed solution drug product demonstrated that no significant differences in bioavailability and safety between the two products are anticipated. Therefore, a scientific bridge has been established between the proposed product and the relied-upon listed drug, Alimta, pursuant to 21 CFR 320.24(b)(6).

10. Labeling

Labeling is aligned with the listed drug Alimta. Accord submitted a Class 2 Resubmission on November 17, 2021, and resubmitted the prescribing information (PI), container labels, and carton labeling on March 24, 2022. DMEPA evaluated proposed PI, container labels, and carton labeling and determined that they can be improved to ensure safe product use. If DO2 plans to revise the statement "(b) (4) to "hazardous drug" in Section 2.7 Preparation and Administration and 16 How Supplied/Storage and Handling, DMEPA recommends updating the container labels and carton labeling with the statement "hazardous drug" to ensure consistency with the PI.

11. Risk Benefit Assessment

Please refer to NDA 021462 (Alimta)

12. Recommendations

The cross disciplinary team lead recommendation for NDA-214408-ORIG-1-RESUB-10 is **TENTATIVE APPROVAL**.

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/s/

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Cross-Discipline Team Leader Review

Date	November 18, 2020
From	Banu Zolnik, Ph.D. Biopharmaceutics Team Leader, ONDP/Division of Biopharmaceutics
Subject	Cross-Discipline Team Leader Review
NDA	NDA 214408
Type of Submission	505(b)(2)
Applicant	Accord Healthcare Inc.
Date of Submission	January 27, 2020
PDUFA Goal Date	November 27, 2020
Proprietary Name / Established (USAN) names	Pemetrexed Injection
Dosage forms / Strength	Injection, Solution/ 25 mg/mL (100 mg/4 mL, 500 mg/20 mL, 850 mg/34 mL and 1000 mg/40 mL)
Proposed Indications	• 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)
Recommendation:	**COMPLETE RESPONSE**

This CDTL review is based, on the primary reviews/memos of:

DICIPLINE	PRIMARY REVIEWER/TL	FINAL REVIEW DATE
Quality IQA	Banu Zolnik (Application Technical Lead)	11/13/2020
Drug Substance	Katherine Windsor/ Ali Al Hakim	09/25/2020
Drug Product	Tefsit Bekele/ Anamitro Banerjee	10/07/2020
OPMA/Facility	David Anderson/Ying Zhang	05/11/2020
Quality Microbiology	Jason God/Denise Miller	04/28/2020
Biopharmaceutics	Gerlie Gieser/Banu Zolnik	11/12/2020
Clinical	Janice Kim/Nicole Drezner	11/17/2020
Non-Clinical (Pharmacology/Toxicology)	Whitney Helms	11/09/2020
Clinical Pharmacology	Safaa Burns/ Jeanne Fourie-Zirkelbach	06/15/2020
Medication Error Prevention and Analysis	Janine Stewart/Ashleigh Lowery	06/19/2020

Cross Discipline Team Leader Review

1. Introduction

Accord Health Care submitted NDA 214408 on 1/27/2020. The listed drug for this 505(b)(2) Application is NDA 21462 Alimta (Pemetrexed disodium), approved in 2004.

The Applicant is relying on FDA findings of safety and efficacy for Alimta (Pemetrexed for Injection, 100 and 500 mg per vial), NDA 021462.

2. Background

The proposed drug product, Pemetrexed Injection is a sterile, clear, colorless to pale yellow, ready-to-dilute (RTD) solution supplied as 100 mg/4 mL, 500 mg/20 mL, 850 mg/34 mL. 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.

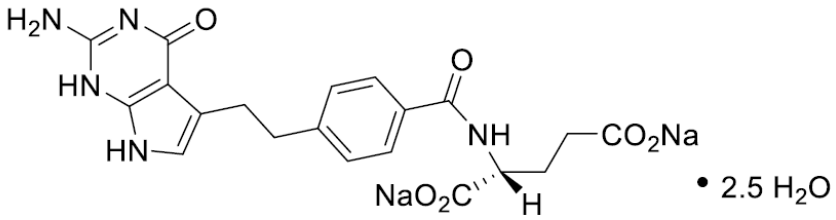
Proposed Indication(s) including Intended Patient Population	• in combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations. (1.1) • in combination with cisplatin for the initial treatment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

3. Pharmaceutical Quality

Drug Substance:.
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 drug substance in the listed drug is a heptahydrate (7 H_2O) form where as in the proposed pemetrexed injection it is a hemipentahydrate (2.5 H_2O) form. The difference in the hydrate form should not impact the drug product as the (b) (4) (b) (4)



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)

Drug Product:
Pemetrexed Injection is a sterile, clear, colorless to pale yellow solution supplied in single-dose vials. Four presentations are available (at 25 mg/mL concentration): 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 listed drug, ALIMTA® (NDA 021-462) marketed by Lilly USA was approved on February 04, 2004. Two presentations of ALIMTA® are available (100 mg and 500 mg) as lyophilized powder in single-dose vials. The lyophilized product requires reconstitution with 0.9% NaCl solution at 25 mg/mL concentration prior to dilution.

The excipients used in the proposed formulation are different from those that are in the listed drug, ALIMTA®. The listed drug consists of pemetrexed disodium drug substance, mannitol, hydrochloric acid, and sodium hydroxide. In the proposed formulation, mannitol is replaced with citric acid, L-methionine, and monothioglycerol (b) (4) Like in ALIMTA®, sodium

hydroxide and hydrochloric acid are used for pH adjustment. Table 1 below summarizes the differences and similarities between Listed Drug and the proposed drug product.

Table 1: Comparison between the Applicant's formulation and LD (Alimta®)

Ingredients	RLD [ALIMTA of Eli Lilly]				Applicant's Pemetrexed Inj.	
	RLD lyophilized formulation		RLD after re-constitution & before dilution (25 mg/mL)	RLD After dilution (b) (4)	Before dilution (25 mg/mL) [proposed formulation]	After dilution (b) (4)
	100 mg	500 mg				
Pemetrexed	100	500	25 mg/mL		25 mg/mL	
Mannitol	106	500	25 mg/mL (approx.)		--	
Anhydrous Citric Acid	--	--	--	--	15 mg/mL	
L-Methionine	--	--	--	--	0.5 mg/mL	
Monothioglycerol	--	--	--	--	4.4 mg/mL	
Sodium hydroxide and /or Hydrochloric acid (for pH adjustment)	q.s. for pH adjustment	q.s. for pH adjustment	q.s. for pH adjustment	q.s. for pH adjustment	q.s. for pH adjustment	q.s. for pH adjustment
						(b) (4)

**concentration (b) (4) mg/mL is with respect to the administration of recommended/maximum daily dose of drug substance (i.e. (b) (4) mg).

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) 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 is granted. This determination is based on ICH Q1A (R2) and ICH Q1E. The applicant provided satisfactory drug product information including stability of the product.

Process and Facilities:

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) (b) (4)

All facilities used to support commercial manufacturing facilities appear to have a favorable cGMP status.

Quality Microbiology:
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.

Biopharmaceutics:
The objective of Biopharmaceutics review is to evaluate bridging of the proposed and the LD products can be established per 21 CFR 320.24.

The noted similarities and differences between the proposed drug product and the relied upon Listed Drug are summarized in Table 2.

	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	For BSA = 1.8 m^2: 9 mg/mL upon dilution with NSS to 100 mL	(25 mg/mL upon reconstitution) For BSA = 1.8 m^2: 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	
pH	Before dilution: 7.7; *After dilution (9 mg/mL): 7.46, 7.37*	Reconstituted/Before dilution: 7.07; *After dilution (9 mg/mL): 6.83*

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

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.

Below are the data/information supporting briding:

1) Difference in crystalline hydrates of the API salt (hemipentahydrate vs heptahydrate)

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. 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 demonstrating visually complete solubility.

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 similar (and the percentage of protein binding were comparable) between the test/proposed product and reference product 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, it is the reviewer's assessment that the removal of mannitol and the addition of the (b) (4) in the proposed drug product would not be anticipated to result in a difference in pemetrexed PK (disposition), 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 (b) (4) (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 ((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. 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. ***However, the Pharmacology/Toxicology Review has potential safety concerns regarding the proposed rate of citric acid infusion. For additional details regarding the citric acid issue, refer to the Pharmacology/Toxicology section of this review.***

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 by (1) reformulating, or (2) submitting additional preclinical data in order to demonstrate the safety of the proposed drug product/formulation in order to establish bridging between the proposed drug product and the listed drug.

Based on the Biopharmaceutics Reviewer's assessment, **overall, the submitted data/information were not determined to be sufficient to establish the scientific bridge between the proposed drug product and the relied upon Listed Drug product due to safety concerns related to citric acid rate of infusion.**

4. Nonclinical Pharmacology/Toxicology

No new nonclinical information was included in the current submission. The CMC team consulted with the pharmacology/toxicology team regarding the proposed a specification for

the [redacted] impurity (NMT [redacted]%) and the justification for two leachables: [redacted] ppm and [redacted] at up to [redacted] ppm. Based on the pharmacology/toxicology review, [redacted] is also a metabolite detectable in multiple species following pemetrexed administration at levels higher than the proposed specification and does not represent a significant safety risk from a toxicological perspective. In addition there is sufficient data to support the safety of [redacted] at this level in the current product. For [redacted] the nonclinical team conveyed concerns regarding the AET proposed by the Applicant based on literature suggesting that [redacted] may have some carcinogenic risk to the CMC team in case these concerns impacted the Applicant's plan for testing. Despite these concerns, given that the actual detected levels of [redacted] the exposure would be ≤ [redacted] µg once every 3 weeks, that pemetrexed itself is genotoxic, and that the indications for pemetrexed are in patients with advanced cancer, the pharmacology/toxicology team concluded that the current levels were acceptable from a safety perspective.

The final issue discussed with pharmacology/toxicology team was the proposed level of the citric acid excipient. While there is a long history of use of citric acid in humans, including as an excipient and as an anticoagulant in infused blood products and the literature includes a known risk of citric acid intoxication and metabolic alkalosis and the amount of citric acid in the proposed formulation is high: up to [redacted] at the 500 mg/m^2 pemetrexed dose. While the Applicant included a justification for this amount of citric acid based on its presence in another drug in the inactive ingredient database, the other product is infused over an hour vs a 10-minute infusion for pemetrexed. The pharmacology/toxicology questioned the safety of this amount of citric acid, not as a total dose, but given as a rapid infusion as acute toxicity data in the literature identified LD50s for citric acid given as an intravenous injection of as low as 42 mg/kg (126 mg/m^2) in mice though lethal doses were higher in larger species given slower infusions. Given the long history of human use of citric acid, the justification for this level of citric acid was discussed with the clinical team, but there was no clear clinical justification for the proposed citric acid infusion rate either. FDA sent an information request to the Applicant requesting additional justification for the infusion rate of justification; however, the response did not fully address the concern that at the typical rate of pemetrexed infusion, this amount of citric acid would not result in citric acid induced alkalosis/calcium fluctuations which could be acutely toxic in patients and in the absence of additional data, the team concluded that infusion rate of citric acid in Pemetrexed Injection is not supported from a safety perspective. To address this data gap, the Applicant plans to conduct an acute animal toxicity study to be submitted in the future NDA resubmission and will submit a protocol in the IND for FDA comment prior to initiating a study. In the absence of the proposed animal study or other additional data to support the infusion rate of citric acid, **the pharmacology/toxicology team does not recommend approval at this time**.

5. Clinical Pharmacology

There is **no** new clinical pharmacology information submitted in this NDA amendment. Minor changes were made in Section 12.3 (Clinical Pharmacology) of the proposed [redacted] labeling. All other prescribing information were acceptable from the clinical pharmacology perspective

6. Clinical

There are no clinical studies conducted to support this NDA. However, the clinical team recommends a Complete Response based on the large dose of citric acid included as an excipient in the pemetrexed infusion, which could lead to symptoms of hypocalcemia. The Applicant did not adequately address these concerns. Please refer to clinical review memo.

7. Advisory Committee Meeting

Current submission did not go to an Advisory Committee Meeting.

8. Other Relevant Regulatory Issues

There are no other additional relevant regulatory issues with this application.

9. Labeling

DMEPA evaluated the Product Information/Prescribing Information, and Proposed Labels and Labeling. The review concludes that the submitted labels and labeling for Pemetrexed Injection may be improved and recommends several revisions. For full details refer to the DMEPA review by Janine Stewart and Ashleigh Lowery dated 6/19/2020.

Labeling Revisions: Several revisions were recommended for the proposed labeling by CMC, Clinical Pharmacology, and DMEPA. For the specific recommendations refer to the individual reviews from these disciplines. Labeling will be finalized when NDA is resubmitted.

10. Recommendations/Risk Benefit Assessment

- ***Recommended Regulatory Action:*** **COMPLETE RESPONSE**

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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