CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208746Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION: APPROVAL

NDA *208746*
Assessment# 3

Drug Product Name	Pemetrexed
Dosage Form	Powders for Injection
Strength	100 mg/vial, 500 mg/vial and 1 gram/vial
Route of Administration	Intravenous Infusion
Rx/OTC Dispensed	Rx
Applicant	HOSPIRA INC
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
Resubmission	12/22/2021	CMC

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Rajan Pragani	Haripada Sarker
Drug Product	Xiao Hong Chen	Xing Wang
Manufacturing	Zhaoyang Meng	Bogdan Kurtyka
Microbiology	Dionne Coker-Robinson	Denise A. Miller
Biopharmaceutics	Om Anand	-
Regulatory Business Process Manager	Rabiya Haider	
Application Technical Lead	Yang Nan	

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

OPQ recommends **APPROVAL** of NDA 208746, Pemetrexed for Injection, 100 mg/vial, 500 mg/vial and 1 gram/vial. OPQ grants thirty-six months expiration period for all three presentations when stored at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Pemetrexed for Injection is a sterile white-to-light yellow or green-yellow lyophilized powder in single-dose vials to be reconstituted for intravenous infusion. Each 100-mg vial of Pemetrexed for Injection contains 100 mg pemetrexed (equivalent to 157 mg pemetrexed ditromethamine) and 106 mg mannitol. Each 500-mg vial of Pemetrexed for Injection contains 500 mg pemetrexed (equivalent to 783 mg pemetrexed ditromethamine) and 500 mg mannitol. Each 1-gram vial of Pemetrexed for Injection contains 1 gram pemetrexed (equivalent to 1.57 gram pemetrexed ditromethamine) and 1 gram mannitol.

Pemetrexed for Injection is recommended to be reconstituted with 0.9% Sodium Chloride Injection, USP (preservative-free) and further diluted with 0.9% Sodium Chloride Injection, USP (preservative-free) prior to intravenous administration.

Proposed Indication(s) including Intended Patient Population	1. Non-Squamous Non-Small Cell Lung Cancer (NSCLC) Pemetrexed for Injection is indicated: • 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 for Injection is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer. 2. Mesothelioma Pemetrexed for Injection is indicated, 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	Refer to the labeling for details.
Maximum Daily Dose	500 mg/m^2
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: *Adequate*

The Applicant cross-references DMF # (b) (4) for the quality of the drug substance pemetrexed ditromethamine dihydrate. In this amendment, the Applicant indicated that the DMF holder, (b) (4) made minor changes in DMF. The DMF (b) (4) has been reviewed recently and is found adequate.

Drug substance assessors recommend the application for Approval.

Drug Product: *Adequate*

In this amendment, the Applicant provided the following updates in the drug product:

- *Addition of an alternative supplier of* (b) (4)
- *Addition of an alternative supplier of seal and change in color of flip-off top*
- *Inclusion of a risk assessments of nitrosamines in the drug product*

Drug product quality reviewers assessed these changes acceptable and recommend the application for Approval.

Labeling: *Adequate*

No major change in labeling from CMC perspective in this resubmission. Inclusion of the "Manufactured by" statement identical to the carton and

container labels were added to the Package Insert by the Applicant, which is acceptable.

Special Product Quality Labeling Recommendation

No labeling issue was found.

Manufacturing: *Adequate*

In this amendment, the Applicant made the following manufacturing changes:

- (b) (4)

OPMA review team considers these changes acceptable and recommends the application for Approval.

Biopharmaceutics: *Adequate*

Refer to previous reviews.

Microbiology: *Adequate*

In this amendment, the Applicant proposed the following major changes related to sterility assurance:

- Addition of an alternate manufacturer for the seal used in the container closure system
- Modifications of the (b) (4) manufacturing area
- (b) (4)
- .

Microbiology team considers these changes acceptable and recommends the application for Approval.

Application Technical Lead Name and Date:

Yang Nan, Ph.D. 05/09/2022

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CHAPTER VII: MICROBIOLOGY

IQA ANDA Assessment Guide Reference

Product Information	Sterile lyophilized powder indicated for use in locally advanced or metastic nonsquamous non-small cell lung cancer. Filled as a 100mg, 500mg, or 1g fill in a 10mL, 50mL, or 100mL vial, respectively; single-dose.
NDA Number	208746 (S/N 0021)
Assessment Cycle Number	2
Drug Product Name / Strength	Pemetrexed (as ditromethamine) for Injection, 100 mg/vial, 500 mg/vial, 1 g/vial
Route of Administration	Intravenous Injection
Applicant Name	Hospira Inc, a Pfizer company
Manufacturing Site	Zydus Hospira Oncology Pvt. Ltd. (ZHOPL), Plot No.3, Pharmez, Special Economic Zone, Sarkhej Bavla Highway, N.H, No. 8A, Matoda,Taluka Sanand District Ahmedabad – 382213 Gujarat, India
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Theme:

☒ N/A	☐ Depyrogenation Validation Data
☐ Product Sterility Assurance	☐ Product Release and/or Stability Specifications
☐ (b) (4) Data	☐ Validation for Product Release and/or Stability Test Method
☐ Validation of Product Test	☐ Other (Requires Division Director Approval)
☐ Due to Consult	

Justification: *view justification statements found at:* **Justification Statements**

N/A
Other (Requires Division Director Approval) – *Assessor writes-in justification here if "other" selected as theme.*

Assessment Summary: The submission is in response to a Tentative Approval Letter, dated 01/08/2021. In the previous review cycle, the application was recommended by the Division of Microbiology Assessment (DMA) (refer to N208746MR01.docx, dated 05/01/2017, by Y. Chabrier-Rosello). Changes related to sterility assurance include an addition of an alternate seal manufacturer, (b) (4) , a change in the commercial batch size from (b) (4) L to (b) (4) L for the 100mg/vial presentation and (b) (4) L to (b) (4) L for the 500mg/vial presentation, and modifications of the (b) (4) manufacturing area. Adequate data from (b) (4) validation studies are provided to support the changes that are most likely to impact sterility assurance of the drug product. Therefore, the submission **is recommended** for approval on the basis of sterility assurance.

List Submissions Being Assessed (table):

Date Submitted to FDA	Date Received by FDA	Date Assigned to Reviewer
12/22/2021	12/22/2021	01/14/2022

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

Remarks: The submission is in e-CTD format. The original microbiology review was completed and determined to be adequate in N208746MR01.docx, dated 05/01/2017, by Y. Chabrier-Rosello.

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): N/A

Supporting Documents:

- The DMA review, N208746MR01.docx, dated 05/01/2017, by Y. Chabrier-Rosello (Adequate) is referenced for the following information:
  - Drug product composition and container closure system information
  - (b) (4)
  - (b) (4)
- (b) (4) studies following facility changes to manufacturing (b) (4) in N(b) (4)MR01.docx, dated 07/28/2021, by K. Paul

Select Number of Approved Comparability Protocols: 0

The submission is in response to a Tentative Approval Letter, dated 01/08/2021. In the previous review cycle, the application was recommended by DMA (refer to N208746MR01.docx, dated 05/01/2017, by Y. Chabrier-Rosello); however, the sponsor has provided updated information in the response to the Tentative Approval Letter. There are numerous CMC changes included in the submission; however, those closely related to sterility assurance are described and assessed. The changes since the previous DMA review that are related to sterility assurance include the following:

1) An alternate manufacturer for the seal used in the container closure system (CCS).
2) (b) (4)
3) A change in the commercial batch size from (b) (4) L to (b) (4) L for the 100mg/vial presentation and (b) (4) L to (b) (4) L for the 500mg/vial presentation.
4) Modifications of the (b) (4) manufacturing area. The manufacturing area modifications include (b) (4)
5) (b) (4)
6) (b) (4)

The following information is provided in the submission supporting the proposed changes: validation information for the (b) (4) , and (b) (4) results to demonstrate that the recent facility improvements pose minimal risk to sterility assurance. There are no proposed changes to the drug product composition, manufacturing process, hold times, or specifications for release and stability.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –**
  There are no changes proposed to the drug product composition. The change to the batch size is a reduction in the commercial batch size from (b)(4) L to (b)(4) L for the 100mg/vial presentation and (b)(4) L to (b)(4) L for the 500mg/vial presentation.

- **Description of container closure system –**
  There is a minor change in the manufacturer of the seals, but no other changes to the CCS are proposed. For ease of reference, CCS information is summarized in the table below.

Component	Drug Product	Vial Size	Description	Item No.	Manufacturer
Vial	100mg	10mL	Type (b)(4) clear glass,	(b)(4)	
	500mg	50mL			
	1g	100mL			
Stopper	All Presentations	-	20mm (b)(4) , grey,		
Seal	All Presentations	-	20mm aluminum flip-off seal		
			20mm aluminum flip-off seal		

Assessment: The provided drug product composition and CCS information was previously reviewed and determined to be adequate in N208746MR01.docx, dated 05/01/2017, by Y. Chabrier-Rosello (Adequate). The change in aluminum flip-off seals used in the CCS has no impact on the sterility assurance of the drug product. The decrease in the commercial batch size poses minimal risk to sterility assurance.

Adequate

(b)(4)

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Denise Miller

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FDA U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 208746
Assessment #2

Drug Product Name	Pemetrexed
Dosage Form	For Injection
Strength	100 mg/vial, 500 mg/vial and 1 gram/vial
Route of Administration	Intravenous Infusion
Rx/OTC Dispensed	Rx
Applicant	HOSPIRA INC
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Resubmission	07/10/2020	CMC

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Karina Zuck	Ali H Al Hakim
Drug Product	Xing Wang	Anamitro Banerjee
Manufacturing	Zhaoyang Meng	Bogdan Kurtyka
Microbiology	Denise Miller	Bryan S Riley
Regulatory Business Process Manager	Kristine Leahy	
Application Technical Lead	Xing Wang	

U.S. FOOD & DRUG ADMINISTRATION

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Facility deficiency listed in the Complete Response Letter issued on July 10, 2017 have been adequately addressed.

OPQ recommends **APPROVAL** of NDA 208746, Pemetrexed for Injection, 100 mg/vial, 500 mg/vial or 1 gram/vial. OPQ grants thirty-six months expiration period for all three presentations when store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Pemetrexed for Injection is a sterile white-to-light yellow or green-yellow lyophilized powder in single-dose vials to be reconstituted for intravenous infusion. Each 100-mg vial of Pemetrexed for Injection contains 100 mg pemetrexed (equivalent to 157 mg pemetrexed ditromethamine) and 106 mg mannitol. Each 500-mg vial of Pemetrexed for Injection contains 500 mg pemetrexed (equivalent to 783 mg pemetrexed ditromethamine) and 500 mg mannitol. Each 1-gram vial of Pemetrexed for Injection contains 1 gram pemetrexed (equivalent to 1.57 gram pemetrexed ditromethamine) and 1 gram mannitol.

Reconstitution and dilution of Pemetrexed for Injection is recommended with (b) (4) 0.9% Sodium Chloride Injection, USP (preservative-free) with further dilution required prior to intravenous administration with 0.9% Sodium Chloride Injection, USP (preservative-free) (b) (4)

Proposed Indication(s) including Intended Patient Population	Pemetrexed for Injection is a folate analog metabolic inhibitor indicated: • 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 for 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.
Maximum Daily Dose	500 mg/m^2 administered as an intravenous infusion over 10 minutes on Day 1 of each 21-day cycle.
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

The sponsor submitted an amendment on July 10, 2020 in response to a CR Letter dated July 10, 2017. The CR letter did not include drug substance related deficiencies or requests. In addition to respond to the CR letter, the sponsor notifies of multiple drug substance changes made by the referenced DMF (b) (4) for Pemetrexed ditromethamine dihydrate and proposes (b) (4) from the drug substance specification. DMF (b) (4) was found adequate in support of NDA 208746 by K. Zuck on August 17, 2020. The previous drug substance quality review, performed on June 1, 2017 by Dr. Sharon Kelly, recommended approval of the drug substance pending satisfactory facility inspections. Currently, the DMF manufacturing facility ((b) (4)), is classified as "voluntary action indicated" (VAI) after the (b) (4) inspection. The drug substance information provided is adequate to support approval of NDA 208746.

Drug Product: Adequate

The drug product sections of the application were found adequate in last review cycle. However, the application received Complete Response due to facility deficiency (b) (4). In this submission, the applicant submitted (1) an amendment to previously submitted elemental impurity risk assessment report ((b) (4) testing result), and accordingly updated drug product specifications; (2) updated stability data to extend the proposed shelf-life of the drug product to 36 months when stored at controlled room temperature (20 – 25°C; 68 – 77°F). The application remains adequate from a drug product perspective.

Labeling: Adequate

Minor edit on storage temperature will be conveyed to OND and the applicant during labeling review.

Manufacturing: Adequate

In the last round review (b) (4), drug substance facility was found inadequate-major. Process was found to be adequate. Facility is found adequate in current review, and there is no change to the adequate assessment of Process.

Biopharmaceutics: Adequate

Refer to previous reviews. No updates in this resubmission.

Microbiology: Adequate

Refer to previous reviews. No updates in this resubmission.

Application Technical Lead Name and Date:

Xing Wang

Xing Wang

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U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

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

Document	Application Number	Description
NDA	21462	LD, Alimta, Pemetrexed for injection, 100 or 500 mg pemetrexed for injection per vial

2. CONSULTS

None

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LABELING

IQA Review Guide Reference

{For NDA Only}

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	PEMETREXED FOR INJECTION
Dosage form, route of administration	Lyophilized powder, for intravenous use
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	100 mg, 500 mg or 1 gram lyophilized powder in a single dose vial

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	(b) (4)

3. *Section 3 Dosage Forms and Strengths*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	For injection
Strengths: in metric system	100 mg, 500 mg or 1 gram
Active moiety expression of strength with equivalence statement (if applicable)	Pemetrexed
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	white to light-yellow or green-yellow lyophilized powder in single-dose vials

4. *Section 11 Description*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Pemetrexed for Injection
Dosage form and route of administration	Pemetrexed for Injection is a sterile white-to-light yellow or green-yellow lyophilized powder in single-dose vials to be reconstituted for intravenous infusion.
Active moiety expression of strength with equivalence statement (if applicable)	Each 100-mg vial of Pemetrexed for Injection contains 100 mg pemetrexed (equivalent to 157 mg pemetrexed ditromethamine) and 106 mg mannitol. Each 500-mg vial of Pemetrexed for Injection contains 500 mg pemetrexed (equivalent to 783 mg pemetrexed ditromethamine) and 500 mg mannitol. Each 1-gram vial of Pemetrexed for Injection contains 1 gram pemetrexed (equivalent to 1.57 gram pemetrexed ditromethamine) and 1 gram mannitol.
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Adequate
Statement of being sterile (if applicable)	Yes
Pharmacological/ therapeutic class	folate analog metabolic inhibitor
Chemical name, structural formula, molecular weight	Provided
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	Not provided. (b) (4).

5. ***Section 16 How Supplied/Storage and Handling***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Adequate
Available units (e.g., bottles of 100 tablets)	Carton containing one (1) single-dose vial
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Adequate
Special handling (e.g., protect from light)	Provided
Storage conditions	Store (b) (4) at 20-25°C (68-77°F) [see USP Controlled Room Temperature]. Change to: Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Distributed by: Hospira, Inc., Lake Forest, IL 60045 USA

Reviewer's Assessment of Package Insert: ***Adequate***
Prescribing Information complies with all regulatory requirements from a CMC perspective. Minor edit on storage temperature has been conveyed to OND and the applicant through labeling review meeting.

II. Labels:

1. ***Container and Carton Labels***

(b) (4)

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Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Adequate	Adequate
Dosage strength	Adequate	Adequate
Net contents	Adequate	Adequate
"Rx only" displayed prominently on the main panel	Yes	Yes
NDC number (21 CFR 207.35(b)(3)(i))	Yes	Yes
Lot number and expiration date (21 CFR 201.17)	Yes	Yes
Storage conditions	Yes (to be revised)	Yes (to be revised)
Bar code (21CFR 201.25)	Yes	Yes
Name of manufacturer/distributor	Yes	Yes
And others, if space is available	Caution: Cytotoxic agent	Caution: Cytotoxic agent

Reviewer's Assessment of Labels: ***Adequate***
Minor edit to be conveyed to OND and the applicant: change from
Store (b) (4) ***at 20-25°C (68-77°F) [see USP Controlled Room Temperature].***
to
Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

List of Deficiencies: None

Overall Assessment and Recommendation: Adequate

Primary Labeling Reviewer Name and Date:

Xing Wang

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

Anamitro Banerjee

Xing Wang

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Recommendation:
NDA: COMPLETE RESPONSE

NDA 208746
Review # 1

Drug Name/Dosage Form	Pemetrexed (as ditromethamine) for Injection
Strength	25 mg/mL in 100 mg/vial, 500 mg/vial, 1 g/vial
Route of Administration	Intravenous Injection
Rx/OTC Dispensed	Rx
Applicant	Hospira, Inc., a Pfizer company
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0003 (4) Original NDA	*September 15, 2016*	*CMC*
0004 (5) Quality Amendment	*February 07, 2017*	*Drug Product*
0006 (7) Quality Amendment	*March 08, 2017*	*CMC*
0007 (8) Quality Amendment	*April 24, 2017*	*Microbiology*
0008 (9) Quality Amendment	*May 22, 2017*	*Drug Substance*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Sharon Kelly	Ben Stevens
Drug Product	Xing Wang	Anamitro Banerjee
Process	Zhaoyang Meng	Bogdan Kurtyka
Microbiology	Yeissa Chabrier-Rosello	Marla Stevens Riley
Facility	Wendy Zhang	
Biopharmaceutics	Om Anand	Okpo Eradiri
Regulatory Business Process Manager	Steve Kinsley	NA
Application Technical Lead	Anamitro Banerjee	NA
Laboratory (OTR)	NA	
ORA Lead	Paul Perdue	
Environmental	Xing Wang	Anamitro Banerjee

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, see comments	6/24/2016	Adequate pending a satisfactory facility inspection
	Type III					Sufficient information provided
	Type III					Sufficient information provided
	Type III					Sufficient information provided

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21462	Listed drug (ALIMTA)

2. CONSULTS

None

Executive Summary

I. Recommendations and Conclusion on Approvability

***COMPLETE RESPONSE** is recommended for this NDA from the CMC perspective.*

The NDA may not be approved until the inspectional findings at the (b) (4) drug substance manufacturing facility are satisfactorily resolved.

Action letter language (to be communicated to the applicant):

During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

II. Summary of Quality Assessments

A. Product Overview

This submission is a 505(b)(2) application, referencing the lyophilized cake formulation, Alimta (NDA 21462). The listed drug (LD) Alimta is available in 100 mg and 500 mg single dose vials.

The proposed Pemetrexed (as ditromethamine) for Injection is a sterile lyophilized powder (100 mg/vial, 500 mg/vial, and 1 g/vial presentations), intended to be reconstituted and then diluted with a suitable intravenous solution prior to administration. The drug product is a white to either light yellow or green-yellow powder in the form of a lyophilized powder. The reconstituted solution (25 mg/mL concentration) is clear, colorless to pale yellow or a green yellow solution, free from visible particulate matter; presented in clear Type (b) (4) glass vials. The vials are closed with (b) (4) closures and aluminum seals with plastic flip-off tops. This product is an (b) (4) product containing no antimicrobial preservatives.

The applicant is relying on FDA's finding on safety and efficacy for the listed drug Alimta.

Proposed Indication(s) including Intended Patient Population	Pemetrexed for injection is a folate analog metabolic inhibitor indicated for: • Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer: • Initial treatment in combination with

	cisplatin. ○ Maintenance treatment of patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. ○ After prior chemotherapy as a single-agent. • Mesothelioma: in combination with cisplatin Not indicated for treatment of patients with squamous cell non-small cell lung cancer
Duration of Treatment	NA
Maximum Daily Dose	500 mg/m^2 on day 1 of 21 day cycle
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug substance:

Pemetrexed ditromethamine drug substance is a non-hygroscopic, white to cream colored crystalline powder, soluble in water and slightly or sparingly soluble in organic solvents. The applicant states that the manufacturing process produces only one polymorphic form (based on three batches) with a melting point of approximately 180°C. The drug substance is chiral containing one stereogenic center. The applicant claims that the drug substance has a pKa of 4.78 (this value should be for the free acid form as the salt does not contain acidic proton that could have a pKa of 4.78). Applicant refers to (b) (4) (LOA provided). The DMF was last reviewed by Dr. Sharon Kelly June 24, 2016 and found to be adequate pending a satisfactory facility inspection. The applicant provided specifications and batch data, however referred to the DMF for most of the information.

(b) (4)

The long term storage condition is (b) (4) with a retest period of (b) (4) months. The applicant refers to the DMF for stability data.

The drug substance reviewer recommended approval for this NDA pending satisfactory facility inspection.

Drug Product:

(b) (4)

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(b) (4)

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Prior to intravenous infusion, the drug product is reconstituted and further diluted with 0.9% sodium chloride injection, USP. (b) (4) . The reconstituted solution is clear, colorless to pale yellow, to green yellow solution (b) (4) . The strength of the reconstituted solution is 25 mg/mL with a pH between (b) (4). The reconstituted solution must be further diluted prior to infusion.

The drug product specifications include testing for description of the powder as well as the reconstituted solution, identification, pH, color and clarity of solution, assay, related substances, water content, reconstitution time, uniformity of dosage units, particulate matter, bacterial endotoxin, sterility, extractable volume, and (b) (4) .

The applicant provided 12 months stability data under long term and intermediate storage conditions, and 6 months stability data under accelerated storage conditions for three representative batches for each presentation. Based on the data presented, (b) (4) months of expiration dating period may be granted for the drug product when stored at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (59°F and 86°F). Based on in-use stability data provided in the application, the reconstituted and further diluted solution may stored under refrigerated conditions (2°C to 8°C) for 24 hours (b) (4).

The applicant is requesting categorical exclusion for EA as per 21 CFR 25.15(d)

Facilities:

The drug substance manufacturer ((b) (4)) has an unresolved facility risk (OAI and Warning Letter) that prevents approval of this application.

All the other facilities are currently acceptable.

Biopharmaceutics:

The biopharmaceutics review assessed the adequacy of the Applicant's biowaiver request for the proposed drug product, pemetrexed ditromethamine. Per 21 CFR 320.24(b)(6), the supporting data and information for the biowaiver request were evaluated to determine if the proposed drug product was adequately bridged to the LD

(pemetrexed disodium). The proposed and LD products contain different salts, which are predominantly dissociated in solution prior to infusion. The use of the ditromethamoine salt (by the Applicant) as a pharmaceutical alternative to the disodium salt would not therefore be expected to impact the disposition kinetics of pemetrexed. In addition to the different salt forms, the proposed drug product (b) (4) .

The Applicant submitted data and information to demonstrate that diluted solutions of the proposed and LD products were similar in their physicochemical properties (osmolality, pH) and protein binding. The intracellular akalinizing effect of tromethamine in the proposed drug product was also assessed in interdisciplinary discussions and found to be inconsequential in the disposition kinetics of pemetrexed.

The totality of the data submitted in the Application demonstrate that the proposed drug product has been adequately bridged to the listed drug; therefore an in vivo pharmacokinetic study is not needed. The Biopharmaceutics Reviewer recommends approval of this NDA.

C. Special Product Quality Labeling Recommendation

No labeling recommendations were made during this review cycle.
The listed drug NDA holder is currently updating the PI. Hence, the labeling submitted in this application, which is consistent with the current label of the listed drug, was not reviewed.

D. Final Risk Assessment (see Attachment)

See attached.

Anamitro Banerjee

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E. List of Deficiencies for Complete Response

I. Drug Substance Deficiencies
NA

II. Drug Product Deficiencies
NA

III. Environmental Deficiencies
NA

IV. Labeling Deficiencies
NA

V. Process Deficiencies
NA

VI. Facilities Deficiencies
1) During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

VII. Biopharmaceutics Deficiencies
NA

VIII. Microbiology Deficiencies
NA

IX. Other Deficiencies (specify discipline)
NA

Application Technical Lead Name and Date: Anamitro Banerjee, PhD, June 09, 2017

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ENVIRONMENTAL ANALYSIS

Since Pemetrexed (as ditromethamine) for Injection is being submitted as an NDA, the categorical exclusions of 21 CFR 25.31 apply and are outlined below as per21 CFR 25.15(d).

Pemetrexed (as ditromethamine) for Injection will not be indicated for administration at a higher dose level, nor for a longer duration, or for different indications than those that are in effect. Therefore, it is excluded from the requirements of 21 CFR 25, since the action requested is both included within an excluded category and meets all of the criteria for this exclusion. To the applicant's knowledge, no extraordinary circumstances exist.

Reviewer's Assessment:
The EA statement is adequate --- confirmed with Dr. Raanan Bloom.

Primary EA Reviewer Name and Date:

Xing Wang, Ph.D., ONDP/DNDPI/NDPBII

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

Anamitro Banerjee, Ph.D., Acting Branch Chief, ONDP/DNDPI/NDPBII

Xing Wang

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Anamitro Banerjee

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CHAPTER VII: Biopharmaceutics

NDA: 208746-ORIG-RESUB-4

Drug Product Name: Pemetrexed[1] for Injection

Strength(s): 25 mg/mL [100 mg/vial, 500 mg/vial, 1 g/vial]

Route of Administration: Intravenous (IV) infusion

Indication: Lung Cancer

Applicant Name: Hospira

EXECUTIVE SUMMARY:

The proposed drug product, Pemetrexed for Injection 25 mg/mL [100 mg/vial, 500 mg/vial, 1 g/vial)], is a lyophilized powder for solution, for intravenous (IV) administration after reconstitution and dilution. The proposed drug product has the same active moiety (pemetrexed), and is the same dosage form, route of administration [IV use] and indication [locally advanced or metastatic nonsquamous non-small cell lung cancer and malignant pleural mesothelioma] as the Listed Drug (LD), Alimta® (pemetrexed) 25 mg/mL [100 mg/vial, 500 mg/vial].

The proposed product and the reference product are different with regard to the salt of the active ingredient [pemetrexed ditromethamine (proposed), vs. pemetrexed disodium (LD)], differences in pH adjusting excipients NaOH and HCl (b) (4)

In addition to the 100 mg/vial and 500 mg/vial Alimta® presentations, the Applicant also proposed an additional presentation of 1 g/vial.

The additional information, pH and osmolality of the proposed drug product and the LD, after reconstitution and dilution, literature information on tromethamine (b) (4), and in vitro solubility studies, indicates that the differences in the salt form (b) (4) are not expected to affect the disposition kinetics of pemetrexed in the proposed drug product when administered via the IV route. The disposition kinetics of pemetrexed should be similar from these two products (b) (4) (b) (4).

The Applicant's request for a waiver of the in vivo study for the proposed drug product, Pemetrexed Injection, 25 mg/mL [100 mg/vial, 500 mg/vial, 1 g/vial)], is granted. The data submitted in the Application demonstrate that the proposed drug product has been

[1] as ditromethamine

adequately bridged to the listed drug; therefore an in vivo pharmacokinetic study is not needed.

From the Biopharmaceutics perspective, NDA 208746 for Pemetrexed for Injection 25 mg/mL [100 mg/vial, 500 mg/vial, 1 g/vial)], is recommended for **APPROVAL**.

SUBMISSION:

Hospira submitted the current NDA for Pemetrexed for Injection, 25 mg/mL [100 mg/vial, 500 mg/vial, 1 g/vial)], lyophilized powder for intravenous (IV) infusion under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. This 505 (b)(2) Application relies for approval, on FDA's findings of safety and effectiveness for the listed drug (LD), Alimta® (pemetrexed) for Injection lyophilized powder for intravenous use 25 mg/mL [Eq 500 mg base/vial and Eq 100 mg base/vial] marketed by Eli Lilly and Company under the approved NDA, 021462.
Pemetrexed (as ditromethamine) for Injection is indicated for the treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer and malignant pleural mesothelioma in combination with cisplatin.

BIOPHARMACEUTICS REVIEW:

The LD, Alimta® (pemetrexed) for Injection, 25 mg/mL, is a white to either light-yellow or green-yellow lyophilized powder available in sterile single-use vials containing 100 mg or 500 mg pemetrexed. Each 100-mg or 500-mg vial of Alimta® contains pemetrexed disodium equivalent to 100 mg pemetrexed and 106 mg mannitol or 500 mg pemetrexed and 500 mg mannitol, respectively. Per the labeling, hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

The LD, as specified in the Alimta® product label, must be reconstituted with 4.2 ml (for the 100-mg vial) or 20 mL (for 500-mg vial) of 0.9% Sodium Chloride Injection (preservative free) which gives a solution containing 25 mg/mL pemetrexed.
An appropriate quantity of the reconstituted pemetrexed solution must be further diluted into a solution of 0.9% Sodium Chloride Injection (preservative free), so that the total volume of solution is 100 ml. Pemetrexed is administered as an intravenous infusion over 10 minutes.

Hospira developed Pemetrexed for Injection using a different salt of the active ingredient, pemetrexed ditromethamine, compared to the LD which contains pemetrexed disodium.
Each vial of the proposed product contain pemetrexed ditromethamine equivalent to either 100 mg or 500 mg of the active moiety (pemetrexed) in accordance with the LD label claim.

In addition to the 100 mg/vial and 500 mg/vial Alimta® presentations, Hospira also proposes a 1 g/vial presentation to facilitate administration of pemetrexed in patients exceeding a body surface area (BSA) of 1 m^2 (e.g. based on the recommended dose of

500 mg/m2 BSA, an average adult patient (1.8 m^2 BSA) would require 900 mg pemetrexed).

Alimta® should be reconstituted with 0.9% Sodium Chloride Injection (b) (4) Hospira's Pemetrexed (as ditromethamine) for Injection product is intended for reconstitution with (b) (4) 0.9% Sodium Chloride Injection (b) (4). In addition, the reconstituted Alimta® should be further diluted with 0.9% Sodium Chloride Injection (b) (4), Hospira's Pemetrexed (as ditromethamine) for Injection reconstituted solution must be further diluted to 100 mL with (b) (4) 0.9% Sodium Chloride Injection (b) (4) prior to intravenous infusion.

In Table 1 below, a side-by-side comparison is provided to demonstrate that the conditions of use, active ingredient, route of administration, dosage form, strengths of the proposed drug product are similar to the LD.

Table 1. Comparison of the proposed product, Pemetrexed Injection, 25 mg/mL, and the LD product, Alimta® (pemetrexed) 25 mg/mL

	Listed Drug	**Proposed Product**
	Eli Lilly and Company. Alimta®	Hospira, Inc. Pemetrexed for Injection
Conditions of Use	Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer: - Initial treatment in combination with cisplatin - Maintenance treatment of patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. - After prior chemotherapy as a single agent. Mesothlioma: in combination with cisplatin.	Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer: - Initial treatment in combination with cisplatin - Maintenance treatment of patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. - After prior chemotherapy as a single agent. Mesothlioma: in combination with cisplatin.
Active Ingredient(s)	Pemetrexed (as Pemetrexed disodium)	Pemetrexed (as Pemetrexed ditromethamine)
Inactive Ingredient(s)	Mannitol Hydrochloric acid Sodium hydroxide	Mannitol
Route of Administration	Injection (Intravenous)	Injection (Intravenous)
Dosage Form	Injection, Powder, For Solution	Injection, Powder, For Solution
Strength	25 mg/mL	25 mg/mL

Presentations	100 mg/vial 500 mg/vial	100 mg/vial 500 mg/vial 1 g/vial
Recommended diluent(s) for reconstitution	0.9% Sodium Chloride for Injection	0.9% Sodium Chloride for Injection (b) (4)
Recommended diluent(s) for further dilution for intravenous infusion	0.9% Sodium Chloride for Injection	0.9% Sodium Chloride for Injection (b) (4)

Table 2 below provides the proposed product formulation prior to lyophilization.

Table 2. Comparison of the proposed product formulation, prior to lyophilization

Component	100 mg/vial[2]	500 mg/vial[2]	1 g/vial[2]	Function
Pemetrexed Ditromethamine [as Pemetrexed base]	156.68 mg (100 mg)[3]	783.4 mg (500 mg)	1566.8 mg (1000 mg)	Active ingredient
Mannitol	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Water for Injection[4]			(b) (4)	
			(b) (4)	

Table 3 below provides a summary of composition for Hospira's Pemetrexed for Injection 25 mg/mL compared to the LD.

Table 3: Comparison of the proposed Pemetrexed Injection and the LD, after reconstitution

				LD	
Component	**100 mg/vial[6]**	**500 mg/vial[2]**	**1 g/vial[2]**	**100 mg/vial**	**500 mg/vial**
Pemetrexed Ditromethamine [as Pemetrexed base]	25 mg/mL[7]	25 mg/mL	25 mg/mL	--	--
Pemetrexed Disodium [as Pemetrexed base]	--	--	--	25 mg/mL	25 mg/mL

[2] Nominal quantity per unit

[3] These amounts refer to the label claim. 100 mg/vial contains (b) (4)% overfill, 500 mg/vial and 1 g/vial contains (b) (4)% overfill each.

[4] Removed during lyophilization.

[5] (b) (4)

[6] Nominal quantity per unit

[7] Pemetrexed content in reconstituted solution

Mannitol	(b) (4)				
HCl	--	--	--	q.s.	q.s.
NaOH	--	--	--	q.s.	q.s.
Reconstitution volume (0.9% NaCl)	4.2 mL	20 mL	40 mL	4.2 mL	20 mL
Total Volume after Reconstitution	(b) (4)				

As per label information[9] of Alimta®, hydrochloric acid and/or sodium hydroxide may have been added to adjust pH. Pemetrexed (as ditromethamine) for Injection is not pH adjusted with either sodium hydroxide or hydrochloric acid (b) (4).
Table 4 below provides comparison of the physicochemical properties of the proposed Pemetrexed (as ditromethamine) for Injection and the LD, after reconstitution (25 mg/mL). The data in table 4 demonstrate that the pH of the proposed product and the LD, after reconstitution is similar. The data in table 4 also demonstrate that the osmolarity (mOsml/L) of the proposed product, and the LD, after reconstitution with 0.9% NaCl are similar. (b) (4)
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The infusion solutions (9 mg/mL)) of Pemetrexed (as ditromethamine) for Injection were prepared using 0.9% Sodium Chloride Injection (b) (4) the Alimta® infusion solution was prepared using 0.9% Sodium Chloride Injection in accordance with the respective prescribing information. A comparison of the results is presented in Table 5 below. The pH of the infusion solutions (9 mg/mL) were comparable to the results observed for the reconstituted solution. Osmolarity of the Pemetrexed (as ditromethamine) for Injection infusion solution in 0.9% Sodium Chloride Injection was found to be similar (e.g. within ±10 %) as the LD, Alimta®. (b) (4)
(b) (4)

[8] As reported by the Applicant
[9] https://www.accessdata fda.gov/drugsatfda_docs/label/2008/021462s015lbl.pdf
[10] USP <785> Osmolality and Osmolarity

Table 4: Comparative physicochemical data of Pemetrexed for Injection and the Listed Drug, Alimta, after reconstitution, (25 mg/mL)

Parameter	Pemetrexed (as ditromethamine) for Injection – Hospira						ALIMTA® - Eli Lilly (US)	ALIMTA® - Eli Lilly (US)
	100 mg/vial		500 mg/vial		1 g/vial		500 mg/vial	100 mg/vial
	Batch No.: PD11502		Batch No.: PD21502		Batch No.: PD31503		Batch No.: C523098A	Batch No.: C366965A
	Diluent: 0.9% NaCl	(b) (4)	Diluent: 0.9% NaCl	(b) (4)	Diluent: 0.9% NaCl	(b) (4)	Diluent: 0.9% NaCl	
pH	6.4		6.4		6.4		--	7.1
Reconstitution time (seconds)	11		28		79		--	22
Osmolarity (mOsml/L)	518		507		520		533	536
Specific Gravity	1.0266		1.0267		1.0272		1.0263	1.0319
Surface Tension @25°C (dynes)	53.7		60.2		59.4		64.7	56.4
Viscosity (cS)	1		1		1		1	1.2
Buffering Capacity ((Eq/L)/pH)	0.0111		0.00114		0.0115		0.0009	0.00150

Table 5: Comparative physicochemical data of Pemetrexed for Injection and the Listed Drug, Alimta, after reconstitution and dilution, (9 mg/mL)

Parameter	Acceptance Criteria	Pemetrexed (as ditromethamine) for Injection – Hospira						ALIMTA® - Eli Lilly (US)
		100 mg/vial		500 mg/vial		1 g/vial		500 mg/vial
		Batch No.: PD11502 (tested 13 months after manufacture)		Batch No.: PD21502 (tested 13 months after manufacture)		Batch No.: PD31503 (tested 13 months after manufacture)		Batch No.: C523098A (28 months from expiry)
		Diluent: 0.9% NaCl	(b) (4)	Diluent: 0.9% NaCl	(b) (4)	Diluent: 0.9% NaCl	(b) (4)	Diluent: 0.9% NaCl
pH	(b) (4)	6.3		6.3		6.3		Not tested[1]
Osmolarity (mOsmol/L)		378		373		378		370

[1] RLD pH at 9 mg/mL infusion concentration was not tested. The pH range of RLD infusion solutions (Batch No. C366965A) at 5 mg/mL and 14 mg/mL during compatibility studies was pH 6.7 to 7.0. Refer to *Section 3.2.P.2.6* for further details.

BIOWAIVER REQUEST

In this NDA submission, the Applicant is requesting that the Agency waive the CFR's requirement to provide in vivo bioavailability/bioequivalence (BA/BE) data for their product. The Applicant stated that the proposed drug product contains the same active moiety as the LD Alimta®, conjugated to a different salt (ditromethamine salt instead of disodium salt). Each vial contains pemetrexed ditromethamine equivalent to either 100 mg or 500 mg of the active moiety (pemetrexed) in accordance with the LD label claim. In addition, the Applicant proposes 1 g/vial presentation containing pemetrexed ditromethamine equivalent to 1000 mg pemetrexed. Following reconstitution, all products contain the same amount of pemetrexed (25 mg/mL).

The Applicant asserts that in an aqueous environment, both Pemetrexed (as ditromethamine) and Alimta®, Pemetrexed (as disodium) release the free pemetrexed ions from the ditromethamine and sodium salts respectively. The two preparations will provide identical amounts of pemetrexed to the systemic circulation following reconstitution and further dilution for intravenous administration. The pharmacokinetics of pemetrexed are considered independent of salt form given that pemetrexed will be predominantly dissociated in solution at the point of administration.

Therefore, the use of pemetrexed ditromethamine as a pharmaceutical alternative to pemetrexed disodium would not be expected to impact the rate and extent to which the active moiety becomes available at the site of drug action.

The Applicant cited 21 CFR (b) (4) in support of the biowaiver request.

Reviewer's Initial Assessment of the Biowaiver Request: Deficient

The proposed lyophilized powder formulation is similar to the LD formulation except with regard to the salt form of pemetrexed and differences in pH adjusting excipients NaOH and HCl. On reconstitution, the amounts of mannitol in the two formulations are similar. A different salt of the active ingredient (pemetrexed ditromethamine) is used in Hospira's formulation compared to the LD formulation, which contains pemetrexed disodium.

In addition to the 100 mg/vial and 500 mg/vial Alimta® presentations, Hospira also proposes a 1 g/vial presentation.

For initial reconstitution (25 mg/mL pemetrexed), Alimta® is reconstituted with 0.9% NaCl Injection (b) (4) Hospira's Pemetrexed (as ditromethamine) for Injection product (b) (4) reconstituted with (b) (4) 0.9% NaCl Injection (b) (4) .

The similarity in physicochemical properties (pH and osmolarity) of the proposed Pemetrexed (as ditromethamine) for Injection and the LD, after reconstitution (25 mg/mL), is demonstrated in Table 4. In addition, the similarity in physicochemical properties of the proposed Pemetrexed (as ditromethamine) for Injection and the LD,

after reconstitution and dilution, (9 mg/mL), is demonstrated in Table 5.

In an information request[11] (dated 02/15/2017), the Applicant was informed that their biowaiver request can considered under 21 CFR 320.24(b)(6). In support of this consideration, the Applicant was asked to provide additional information on comparative in-vitro protein binding data and dissociation of the proposed drug product vs. Alimta. In addition, the Applicant was asked to provide available information indicating lack of potential effects of the differences in the salt form (b) (4) , on the disposition kinetics of Pemetrexed in human subjects.

The Applicant responded[12] [dated: 03/08/2017] to the information request:

Briefly, the Applicant stated that the pK_a value for pemetrexed ditromethamine (4.78) is comparable to the pK_a value of pemetrexed disodium (4.85). The comparative solubility of Pemetrexed disodium and Pemetrexed ditromethamine in aqueous solution provided in in Table 6 below:

Table 6. Solubility of pemetrexed ditromethamine and pemetrexed disodium drug substance (b) (4)

Aqueous Solution	Pemetrexed disodium	Pemetrexed ditromethamine
(b) (4)		
0.9% Sodium Chloride	98.5 mg/mL	186.5 mg/mL
(b) (4)		

The Applicant reported that upon reconstitution of Pemetrexed (as ditromethamine) for Injection, the concentration of pemetrexed ditromethamine is 39.17 mg/mL which is equivalent to 25 mg/mL pemetrexed. This is significantly lower than the determined solubility in the proposed diluent (b) (4) 0.9% sodium chloride (186.5 mg/mL) (b) (4) . Therefore upon reconstitution, pemetrexed ditromethamine is expected to undergo complete dissolution. The Applicant further reported that the pH of the diluted infusion solutions at 5 mg/mL and 14 mg/mL during in-use stability studies is between 6.3 and 7.0. Following dissolution, the degree to which pemetrexed, a weak acid, is ionized is highly dependent on the pH of the solution. Given the comparable dissociation constant (pK_a) for pemetrexed disodium (4.85) and pemetrexed ditromethamine (4.78), the extent of ionization of both salts upon reconstitution and dilution can be considered equivalent.

The Applicant also stated that based on the comparative physiochemical data, a plasma protein binding study is deemed not necessary. Specifically, as explained above, pemetrexed is expected to be present in the ionized form in the diluted infusion solution

[11] \\cdsesub1\evsprod\nda208746\0006\m1\us\fda-info-request.pdf
[12] \\cdsesub1\evsprod\nda208746\0006\m1\us\response.pdf

and at physiological pH of 7.4 (in blood stream). The rate and extent to which the active moiety (free pemetrexed) becomes available when diluted is therefore expected to be the same irrespective of the salt form of pemetrexed.

The Applicant also reported that the percent protein binding of pemetrexed (as disodium) is well characterized and established through nonclinical and clinical studies undertaken by the innovator. Briefly, the percentage protein binding is approximately 46%, 54% to 58%, and 81% in dog, mouse, and human plasma, respectively. There is no dependence on concentration which is consistent with the magnitude of protein binding.

In another study, the protein binding of [^{14}C]-pemetrexed in human plasma was reported to be approximately 80.3% to 83.9% in the concentration range of 0.5 to 200 µg/mL and there were no difference observed as a function or renal impairment.

Pemetrexed is primarily eliminated, unchanged, in the urine and metabolism plays a minor role in the clearance of pemetrexed. Up to 70% to 90% of pemetrexed administered is recovered unchanged in the urine within the first 24 hours of dosing with a total systemic clearance of 91.8 mL/min and a $t_{1/2}$ of 3.5 hours. Between patient variability in clearance is moderate at 13.5%. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration increase proportionally with dose. The pharmacokinetics of pemetrexed is reported to be consistent over multiple treatment cycles.

Reviewer's Assessment of the response: Adequate

The Applicant's reasoning that, based on the solubility data and physicochemical properties of pemetrexed ditromethamine and pemetrexed sodium, both salts are expected to be dissociated to similar extent is acceptable. Therefore, the rate and extent to which the active moiety (free pemetrexed) becomes available when diluted is expected to be the same irrespective of the salt form of pemetrexed is acceptable and adequate.

In response to the information request regarding the lack of potential effects of the differences in the salt form (b) (4) , on the disposition kinetics of Pemetrexed in human subjects, the Applicant provided information reported in the literature. The Applicant's response and this Reviewer's assessments are provided below.

Impact of tromethamine salt on the disposition of pemetrexed:

The Applicant provided literature [Brasch eta al] information demonstrating that tromethamine (THAM) is rapidly removed from systemic circulation; in patients with adequate renal function the elimination of THAM resembles that in healthy subjects where a rapid renal elimination terminal (α) phase is followed by a second (β) phase representing movement of THAM into peripheral tissue compartments. In this study[13] THAM was excreted by the kidneys in its protonated form at a rate calculated to be slightly greater than creatinine clearance.

In a study reported in literature[13], in healthy volunteers, at the end of the 30-min infusion a dose of 121 mg/kg (approximately 8.4 g based on a 70 kg adult) the Cmax was 565 µg/mL. For the first 30 minutes, 25% of the administered dose is eliminated into the urine and represents approximately 2100 mg of THAM excreted from the body at an estimated rate of 70 mg THAM/minute.

The Applicant further stated that for a 1.8 m^2 patient receiving 500 mg/m^2 Pemetrexed (as ditromethamine) for Injection, a total loading of 512 mg tromethamine is predicted that would be administered on Day 1 of a 21-day cycle of a pemetrexed treatment regimen. As pemetrexed is administered in a total volume of 100 mL this equates to a tromethamine infusion rate of approximately 51 mg/min compared with a predicted THAM renal excretion rate of 70 mg/min.

The Applicant reported that in the clinical setting, pemetrexed is primarily eliminated, unchanged, in the urine and metabolism plays a minor role in the clearance of pemetrexed. Pemetrexed undergoes limited hepatic metabolism. In patients with normal renal function (creatinine clearance of 90 mL/min) up to 70% to 90% of the pemetrexed dose is recovered unchanged within the first 24 hours following administration, with a total systemic clearance of 91.8 ml/min and a $t_{1/2}$ of 3.5 hours. Pemetrexed clearance decreases, and exposure (AUC) increases, as renal function decreases; Almita treatment should not be administered to patients whose creatinine clearance is <45 mL/min[14].

(b) (4)

[redacted]

[13] Brasch eta al; Pharmacokinetics of TRIS (hydroxymethyl-) aminomethane in Healthy Subjects and in Patients with Metabolic Acidosis: Eur J Clin Pharmacol (1982) 22:257-26.

[14] Almita Label

(b) (4)

[redacted]

(b) (4)

[redacted]

Reviewer's Assessment of the response: Adequate

It is noted that Tromethamine is included in the formulation as a salt form of pemetrexed while the reference drug does not have it in the formulation. Tromethamine act as a proton acceptor and actively binds to hydrogen ions. Tromethamine is eliminated mainly via the renal route. Tromethamine produces an intracellular alkalinizing effect. The primary mechanism by which Tromethamine produces an immediate intracellular alkalinizing effect is the reduction of capillary and interstitial pCO2, which causes the rapid diffusion of carbon dioxide out of the cell. This is probably the only significant mechanism by which Tromethamine increases intracellular pH in organs such as the brain, and skeletal or cardiac muscle, into which tissue uptake of Tromethamine is very slow. The effect of Tromethamine on renal clearance initially raised the question as to whether Tromethamine will cause a PK interaction with pemetrexed changing its in vivo disposition. Based on several internal discussions with the review team in OCP, it was

(b) (4)

[redacted]

concluded that the effect of Tromethamine on the disposition of pemetrexed should be low (if at all) and will be dependent on the concentration of Tromethamine in the formulation.

(b) (4)

This Reviewer notes that for the drug product proposed in the current NDA, Pemetrexed ditromethamine for Injection includes approximately 57 mg of tromethamine in 100 mg/vial. Therefore, a maximum pemetrexed dose (900 mg) of pemetrexed ditromethamine containing 0.513 g of tromethamine is likely to have negligible effect on physiological pH, and is not likely to affect the in vivo disposition of pemetrexed.

This Reviewer agrees that the tromethamine levels present in Pemetrexed (as ditromethamine) for Injection are not expected to affect the disposition of pemetrexed from systemic circulation.

(b) (4)

The Applicant's response to the information response is adequate and acceptable.

Reviewer's Final Assessment: Adequate

This 505 (b)(2) Application relies, for its approval, on FDA's findings of safety and effectiveness for the listed drug. In addition, the NDA includes a biowaiver request for the conduct of bioavailability/bioequivalence study(ies).

(b) (4)

-

[18] (b) (4)

- (b) (4)

The proposed drug product, Pemetrexed for Injection 25 mg/mL [100 mg/vial, 500 mg/vial, 1 g/vial)], is a lyophilized powder for solution, for intravenous (IV) administration after reconstitution and dilution, and has the same active moiety (pemetrexed), and is the same dosage form, route of administration [IV use] and indication [locally advanced or metastatic nonsquamous non-small cell lung cancer and malignant pleural mesothelioma] as the LD.

However, the proposed product and the reference product are different with regard to the salt of the active ingredient [pemetrexed ditromethamine (proposed), vs. pemetrexed disodium (in LD)], differences in pH adjusting excipients NaOH and HCl (b) (4)

In addition to the 100 mg/vial and 500 mg/vial Alimta® presentations, the Applicant also proposed an additional vail presentation i.e. 1 g/vial.
As supported by the additional information [literature, pH and osmolality and in vitro solubility studies], the differences in the salt form (b) (4) are not expected to affect the bioavailability of pemetrexed in the proposed drug product when administered via IV route.

The criteria for a biowaiver under (b) (4) is not fully met in this NDA. However, per 21 CFR 320.24(b)(6), FDA can rely on any other approach deemed adequate to establish the bridge (bioavailability/bioequivalence) between the listed and proposed drug products.

Specifically for NDA 208746, the difference in the salt form of pemetrexed [pemetrexed ditromethamine vs. pemetrexed disodium)] compared to the LD (b) (4) are not expected to have an impact on the disposition kinetics of pemetrexed from the Applicant's proposed formulation as compared to the reference formulation. Therefore, Based on the totality of the information provided, the Applicant's request for a waiver of the in vivo study for their proposed product, Pemetrexed for Injection 25 mg/mL [100 mg/vial, 500 mg/vial, 1 g/vial)], is granted.

RECOMMENDATION

A waiver of the in vivo bioequivalence study requirement is granted. From the Biopharmaceutics perspective, NDA 208746 for Pemetrexed for Injection 25 mg/mL [100 mg/vial, 500 mg/vial, 1 g/vial)], is recommended for **APPROVAL**.

SIGNATURE BLOCK

Om Anand, Ph.D. [Date: 05/10/2017]

Biopharmaceutics Reviewer
Division of Biopharmaceutics
Office of New Drug Products/OPQ

Okpo Eradiri, Ph.D. [Date: 05/25/2017]

Acting Biopharmaceutics Lead
Division of Biopharmaceutics
Office of New Drug Products/OPQ

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MICROBIOLOGY

Product Background: -

NDA: 208746

Drug Product Name / Strength: Pemetrexed (as ditromethamine) for Injection/ 25 mg/ml

Route of Administration: Intravenous injection

Applicant Name: Hospira Inc., a Pfizer company, 275 N. Field Dr., Bldg. H2-2, Dept. 0392, Lake Forest, IL 60045

Manufacturing Site: Zydus Hospira Oncology Pvt. Ltd. (ZHOPL), Plot No.3, Pharmez, Special Economic Zone Sarkhej Bavla Highway, N.H., No.8A, Matoda, Taluka Sanand, Ahmedabad District, Gujarat, India 382213

Method of Sterilization: (b) (4)

Review Summary: Recommended for Approval

List Submissions being reviewed: 9/15/2016, 3/8/2017 and 4/24/2017

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: No outstanding issues remain.

Supporting/Related Documents: DMF (b) (4) . A LOA is provided. The relevant information was reviewed in D (b) (4) M14R01.doc by D. Schu (dated 4/5/2016). The review was deemed adequate.

Remarks Section: This is an eCTD submission. The review includes the responses to information requests sent on 2/15/2017 and 4/10/2017. The final review document (N208746MR01.doc) will be placed in Panorama. Some of the tables in this review are adapted from the original submission.

S. Drug Substance

The drug substance is not provided as sterile; therefore, a microbiology review of the drug substance is not conducted.

P.1 Description of the Composition of the Drug Product

Drug product is a sterile white to light yellow or green-yellow powder available as a lyophilized plug, intended to be reconstituted and then diluted prior to administration. The reconstituted solution is clear, colorless to pale yellow or a green yellow solution, free from visible particulate matter.

Drug product composition:

Ingredient	Content mg/ml
Pemetrexed ditromethamine	39.17
Mannitol, USP	(b) (4)
WFI, USP	
(b) (4)	

Description of the container closure system:
The drug product is supplied as 25 mg/ml and packaged in three different configurations: 100 mg/vial (10 ml vial/20 mm stopper), 500 mg/vial (50 ml vial/20 mm stopper) and 1 g/vial (100 ml vial/20 mm stopper). The descriptions and supplier information for the container closure systems used for the 3 drug product presentations are provided in the table below.

Primary Packaging Component	Description	Supplier Name and Address
Container	Type (b) (4) Clear Glass Vial 10 mL 50 mL 100 mL	(b) (4)
Closure	20 mm Gray (b) (4) Rubber Closure (b) (4)	
Seal	20 mm, Aluminum Seal, Flip-Off top	

Acceptable

Reviewer's Assessment: Example: The firm provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

(b) (4)

(b) (4)

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

(Package Insert; P.2 Compatibility)

The package insert refers to the subject drug product as single-dose and single-use vial; the container label states single-use vial The recommended storage temperature before use is 20-25ºC (68-77ºF).

The package insert states that the drug product, prior to intravenous administration, is reconstituted with 0.9% Sodium Chloride Injection, USP (preservative free) (b) (4) , followed by further dilution (b) (4) " There is the statement to discard any unused portion. The container label states to "use within 24 hours after reconstitution."

The firm provided adventitious microbial studies to support the storage conditions after reconstitution and further dilution of the drug product with the proposed diluents (0.9% Sodium Chloride Injection, USP (preservative free), (b) (4) . The studies are described below.

Adventitious microbial studies:
The studies were conducted using the 100 mg/vial configuration; all configurations after reconstitution have the same concentration, 25 mg/ml. (b) (4) vials were reconstituted with 4.2 ml of 0.9% Sodium Chloride Injection and further diluted to 100 ml with 0.9% Sodium Chloride Injection to a final concentration of 1 mg/ml. Each vial was inoculated with compendial organisms at a concentration of ≤100 CFU/10 ml. Samples were taken at time points 0, 24 and 48 hours and assessed for microbial growth. An inoculum control was used for each of the compendial organisms (b) (4) and sampled at each time point; a negative control of product only, was used. The table below describes the storage conditions and the time points sampled.

Recommended Storage Condition	Diluent Details		Testing intervals		
	Reconstitution	Further dilution to 100 mL			
[redacted] (b) (4)					
2-8 °C for 48 hrs	0.9% Sodium Chloride Injection	0.9% Sodium Chloride Injection	0 hours	24 hours	48 hours

Acceptance criteria:

[redacted] (b) (4)

Results:

[redacted] (b) (4)

Further dilution in 0.9% Sodium Chloride Injection, stored at 2-8°C:

Name of Microorganisms	Count in cfu/10 mL		
	0 hrs	24 hrs	48 hrs
Escherichia coli ATCC 8739	72	66	61
Inoculum control	75	74	68
Staphylococcus aureus ATCC 6538	25	25	23
Inoculum control	28	27	24
Pseudomonas aeruginosa ATCC 9027	68	58	54
Inoculum control	70	61	57
Candida albicans ATCC 10231	31	29	26
Inoculum control	32	31	28
Aspergillus brasiliensis ATCC16404	21	19	18
Inoculum control	22	20	19
Negative control (SCDA)	No Growth	No Growth	No Growth
Negative control (SDA)	No Growth	No Growth	No Growth

The results in the table above show that the test samples showed no increase in total CFUs through the duration of the assay. The inoculum control for each of the organisms remained viable for the duration of the study, and the negative controls showed no growth. The firm also provided log reduction values for the above results. The log reductions observed for all organisms at 0, 24 and 48 ranged from 0.04-0.11 logs, 0.10-0.12 logs and 0.13-0.15 logs, respectively. No log increases were observed when the stored at 2-8ºC; all the acceptance criteria were met. Therefore, the reconstituted (in 0.9% Sodium Chloride Injection) and further diluted (in 0.9% Sodium Chloride Injection) drug product does not support microbial growth after reconstitution and further dilution.

Acceptable

Reviewer's Assessment: The storage conditions for the reconstituted product of no more than 24 hours at 2-8ºC does not require data supporting these storage conditions; however, since the firm provided the studies and this is an innovator drug, the studies were presented for future reference. The proposed storage conditions for the reconstituted and further diluted drug product were supported by adequate studies and results. Therefore, the recommended storage conditions indicated in the package insert are deemed adequate.

Post-Approval Commitments:

Reviewer's Assessment: Not applicable

Lifecycle Management Considerations

Reviewer's Assessment: Some of the possible manufacturing changes that could affect the microbiological quality of the subject drug product are: (b) (4) .

List of Deficiencies: None

Primary Microbiology Reviewer Name and Date: Yeissa Chabrier-Roselló, Ph.D. (5/1/2017)
Secondary Reviewer Name and Date: Marla Riley-Stevens, Ph.D. **I concur** (5/1/2017)

Marla
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ATTACHMENT I: Final Risk Assessments

A. Final Risk Assessment - NDA

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipments • Site	H	(b) (4)	Acceptable	
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipments • Site	M		Acceptable	
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		Acceptable	
Physical stability (solid state)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		Acceptable	
Uniformity of Dose (Fill volume/deliverable volume)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		Acceptable	
Osmolality	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		Acceptable	
pH	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		Acceptable	

Particulate Matter	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	M	(b) (4)	Acceptable	
Leachables extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		Acceptable	
Re-dispersability/ reconstitution time	• Formulation • Process parameters • Scale/equipment • Site	M		Acceptable	
Moisture content	• Formulation • Container closure • Process parameters • Scale/equipment • Site	L		Acceptable	
Appearance (caking)	• Formulation • Container closure • Process parameters • Scale/equipment • Site	M		Acceptable	
Appearance (color/turbidity)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		Acceptable	
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		Acceptable	

Anamitro Banerjee -S

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