CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215179Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	215179
Applicant Name	Shilpa Medicare LTD
Drug Product Name	Pemetrexed Injection
Dosage Form.	Injection
Proposed Strength(s)	100 mg/10 mL, 500 mg/50 mL, 1,000 mg/100 mL
Route of Administration	Intravenous
Maximum Daily Dose	500 mg/m^2
Rx/OTC Dispensed	Rx
Proposed Indication	• in combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous nonsmall cell lung cancer (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 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)
Drug Product Description	Pemetrexed Injection is a sterile clear, colorless to pale yellow to green-yellow ready-to-use solution in single-

	dose vials. Each milliliter of solution contains 10 mg of pemetrexed (equivalent to 12.1 mg pemetrexed disodium hemipentahydrate), 10 mg of mannitol, 9 mg of sodium chloride, 1 mg of Lcysteine hydrochloride, sodium hydroxide and/or hydrochloric acid to adjust pH and water for injection.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. **An expiration dating period of 18 months may be granted when stored at the proposed storage conditions.**		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Haripada Sarker	Haripada Sarker
	Drug Product/ Labeling	William M Adams	Xing Wang
	Manufacturing	Yan Zheng	David Anderson
	Biopharmaceutics	Gerlie Gieser	Gerlie Gieser
	Microbiology	Janson God	Julie Nemecek
	Other (specify):	N/A	
	RBPM	Janell Artis	
	ATL	Xing Wang	
Consults	None		

2. Final Overall Recommendation - *Approval*

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The NDA is re-submitted in response to FDA's complete response (CR) letter dated April 14, 2022. Drug substance and microbiology were found adequate in the last round of product quality review, and no new related CMC information was submitted. Resolution of key product quality issues was attained by manufacturing new vial product batches at a GMP compliant site; establishing and justifying the shelf-life specification criteria; addressed the manufacturing process issues for the 10 mL vial product and submitting adequate and acceptable long term stability studies on vial product batches that are representative of the proposed commercial drug product. The (b) (4) *and the L-cysteine content of the drug product are monitored at release and during stability. An adequate scientific bridge had been established between the proposed drug product and the LD product, i.e., in accordance with 21 CFR 320.24(b)(6).* (b) (4) *Cadila is the newly proposed manufacturing site, and it is an approved facility. All associated manufacturing, testing, packaging facilities were deemed acceptable. Overall, the applicant provided sufficient information in this resubmission to assure the identity, strength, purity, and quality of the proposed drug product. Based on the OPQ review team's evaluation of the information provided in the submission, OPQ recommends* ***APPROVAL of NDA 215179 PEMETREXED INJECTION, for intravenous use.***

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate

QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: None

Xing Wang

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Approval based USPI in amendment SD-042 dated 04/06/2023

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling	Assessor's Comments
Product Title in Highlights		
Established name(s)[1]	Adequate	Pemetrexed Injection
Route(s) of administration	Adequate	Intravenous infusion over 10 minutes
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	10 mg/mL solution as 0100 mg/010 mL vial 0500 mg/050 mL vial 1000 mg/100 mL vial
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Adequate	Single dose vial
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety.	Adequate	(b) (4) [redacted]

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling	Assessor's Comments
DOSAGE AND ADMINISTRATION section		

[1] Established name = Pemetrexed Injection, for intravenous use

Special instructions for product preparation	N/A	
Important administration instructions	N/A	
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	Adequate	Statement is present in section 2.7 Preparation for Administration
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	Adequate	USP monograph does not include labeling requirements
For radioactive products	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs".	Adequate	Hazard drug statement in sections 2.7 and 16 with OSHA reference provided in section 15.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	(b) (4)
Strength(s) in metric system	Adequate	10 mg/mL solution as 0100 mg/010 mL vial 0500 mg/050 mL vial 1000 mg/100 mL vial
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety	Adequate	(b) (4)
A description of the identifying characteristics of the dosage forms	N/A	sterile clear, colorless to pale yellow to green yellow ready-to-use solution
Assess if the tablet is scored.	N/A	
For injectable drug products for parental administration, use appropriate package type term	Adequate	Single dose vial

Section 11 (DESCRIPTION)

Item	Items in Proposed Labeling	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Adequate	Pemetrexed Injection (proprietary name is not proposed)
Dosage form(s) and route(s) of administration	Adequate	[redacted] (b) (4)
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement	Adequate	10 mg of pemetrexed equivalent to 12.1 mg pemetrexed disodium hemipentahydrate
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	L-cysteine HCl [redacted] (b) (4) USP mannitol USP sodium chloride NF sodium hydroxide NF or hydrochloric acid NF water for injection USP
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients.	Adequate	10 mg of mannitol 9 mg of sodium chloride 1 mg of L-cysteine HCl USP sodium hydroxide NF or hydrochloric acid NF for adjustment to pH [redacted] (b) (4) water for injection USP
If alcohol is present	N/A	
Sterility statement (if applicable)	Adequate	Included in sections 11 and 16
Pharmacological/Therapeutic class	Adequate	Highlights of Prescribing Information, Indications and Usage states "Pemetrexed is a folate analog metabolic inhibitor."
Chemical name, structural formula, molecular weight	Adequate	drug name: Pemetrexed Disodium Hemipentahydrate chemical name: disodium N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl] benzoyl]-L-glutamic acid hemipentahydrate molecular formula: $C_{20}H_{19}N_5Na_2O_6 \cdot 2.5\ H_2O$ molecular weight: 516.41
If radioactive	N/A	
Other important chemical or physical properties	N/A	

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling	Assessor's Comments
For oral prescription drug products	N/A	
Remove statements that may be misleading or promotional	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement	Adequate	USP monograph does not include labeling requirements

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Items in Proposed Labeling	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	(b) (4)
Strength(s) in metric system	Adequate	10 mg/mL
Available units (e.g., bottles of 100 tablets)	Adequate	0100 mg/010 mL vial 0500 mg/050 mL vial 1000 mg/100 mL vial
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	sterile clear, colorless to pale yellow to green yellow ready-to-use solution in a single dose vial NDC 63759-3048-1: Carton containing one single-dose vial, 100 mg/10 mL NDC 63759-3049-1: Carton containing one single-dose vial, 500 mg/50 mL NDC 63759-3050-1: Carton containing one single-dose vial, 1,000 mg/100 mL
Assess if the tablet is scored.	N/A	
For injectable drug products for parental administration, use appropriate package type term	Adequate	Single dose vial
Special handling about the supplied For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	Hazard drug statement in sections 2.7 and 16 with OSHA reference provided in section 15.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling	Assessor's Comments
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
Latex	N/A	
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. Please include your comments about other sections of labeling if they contain product quality information.

None

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	Manufactured by: Zydus Lifesciences Limited, Ahmedabad, India. Manufactured for: Shilpa Medicare Limited, Jadcherla-509301, India.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information): Acceptable based on document submitted in amendment SD-042 dated 04/06/2023.

What are the ingredients in Pemetrexed Injection?
Active ingredient: pemetrexed
Inactive ingredients: mannitol, sodium chloride, L-cysteine hydrochloride, sodium hydroxide, hydrochloric acid, water for injection.

Manufactured by:
Zydus Lifesciences Limited, Ahmedabad, India.

Manufactured for:
Shilpa Medicare Limited, Jadcherla 509301, India

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

Draft vial labels are submitted in amendment SD-033 dated 04/08/2022, and SD-042 dated 04/06/2023.

* Pemetrexed Injection 100 mg/10 mL – green/green
* Pemetrexed Injection 500 mg/50 mL -blue/green
* Pemetrexed Injection 1,000 mg/100 mL – brown/green

Noted that the issue date is vertical on the 10 mL and 50 mL vial labels, while it is horizontal on the 100 mL vial label.

(b) (4)

(b) (4)

[redacted]

3.2 Carton Labeling

Draft carton labels are provided in amendment SD-033 dated 04/08/2022.

* Pemetrexed Injection 100 mg/10 mL – green/green
* Pemetrexed Injection 500 mg/50 mL – blue/green
* Pemetrexed Injection 1,000 mg/100 mL – brown/green

Draft carton labels are submitted in amendment SD-033 dated 04/08/2022, and SD-042 dated 04/06/2023.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Items in Proposed Labeling	Assessor's Comments about Carton Labeling
Established name[2], (font size and prominence)	Adequate	Pemetrexed Injection, acceptable font and prominence
Strength(s) in metric system	Adequate	10 mg/mL
Route(s) of administration	Adequate	For Intravenous infusion only
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	Adequate	Each mL contains 10 mg pemetrexed (equivalent to 12.1 mg pemetrexed disodium hemipentahydrate)
Net contents (e.g., tablet count, volume of liquid)	Adequate	0100 mg/010 mL vial 0500 mg/050 mL vial 1000 mg/100 mL vial
"Rx only" displayed on the principal display	Adequate	Statement is present.
NDC	Adequate	010 mL vial: NDC 63759-3048-1 050 mL vial: NDC 63759-3049-1 100 mL vial: NDC 63759-3050-1
Lot number and expiration date	Adequate	Block is included
Storage conditions.	Adequate	Store at 20°c to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]. BUD is not used.
For injectable drug products for parental administration, use appropriate package type term	Adequate	Single dose vial
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order.	Adequate	Each mL contains: 10 mg pemetrexed (equivalent to 12.1 mg pemetrexed disodium hemipentahydrate) Only the active ingredient is listed.
If alcohol is present	N/A	
Linear Bar code	Adequate	Present on vial and carton labels.

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Items in Proposed Labeling	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor /packer	Adequate	Manufactured by: Zydus Lifesciences Limited, Ahmedabad, India. Manufactured for: Shilpa Medicare Limited, Jadcherla-509301 , India.
If there is a Medication Guide	N/A	Medication Guide is not submitted.
Text on Ferrule and Cap overseal	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement	Adequate	USP monograph has no labeling requirements.
When a drug product differs from the relevant USP standard of strength, quality, or purity.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: ***{Adequate)***

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

None

ITEMS FOR ADDITIONAL ASSESSMENT

There are no inappropriate or inconsistent of product quality information in the labels or labeling. Applicant follows the label and labeling information currently approved in the RLD – Eli Lilly's NDA 21462 for Alimta (Pemetrexed disodium): powder, intravenous use.

Overall Assessment and Recommendation:

Adequate to support NDA approval

Primary Labeling Assessor Name and Date: William Adams, 04/07/2023

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

William Adams

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Xing Wang

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	NDA-215179-ORIG-1-RESUB-34 NDA215179 - (0034)
Assessment Cycle Number	NDA Resubmission after Complete Response #2
Drug Product Name/ Strength	Pemetrexed Injection 10 mg/mL (presented as 100 mg/10 mL, 500 mg/50 mL, 1000 mg/100 mL solution in single-dose vials)
Route of Administration	For Intravenous Infusion
Applicant Name	Shilpa Medicare LLC
Therapeutic Classification/ OND Division	Anticancer: Folate analog metabolic inhibitor Division of Oncology 2
Listed Drug Product Relied Upon	ALIMTA® lyophilized powder for reconstitution and further dilution [NDA 21462]
Proposed Indication	Treatment of non-squamous, non-small cell lung cancer
RECOMMENDATION	**Adequate**

Background:
This 505(b)(2) NDA for Pemetrexed Injection (10 mg/mL) relies for approval, at least in part, on the FDA's efficacy and safety findings for the Listed Drug (LD) product, ALIMTA® (pemetrexed) lyophilized powder for Injection (NDA 021462).The chemical compositions of the proposed pemetrexed 10 mg/mL solution drug product and the relied upon Listed Drug product's final infusion solution (prepared from reconstitution of the lyophilized powder and further dilution) are qualitatively the same, except for the presence of (b) (4) (L-cysteine hydrochloride (b) (4)) in the proposed drug product's formulation (b) (4) To deliver the required pemetrexed dose (calculated based on the patient's body surface area), the appropriate volume (i.e., not necessarily 100 mL) of the proposed 10 mg/mL solution in vial product is transferred into an empty IV bag immediately prior to IV infusion that is then administered to the patient with the aid of an infusion pump.

In the Biopharmaceutics Review of the original NDA, it was concluded that the scientific bridge between the proposed drug product and the relied upon LD product could not be established completely because the Applicant was not able to provide the requested data that would demonstrate that the difference in handling and preparation between the proposed solution injectable drug product and (the final infusion of) the LD product would not result in a significant difference in "delivered dose" of pemetrexed to the patient. In the Biopharmaceutics Review, it was also acknowledged that ***i***) the proposed drug product manufacturer (b) (4) received (b) (4) (b) (4) and ***ii***) the bridging assessment will be revisited should new registration batches of the proposed drug product be manufactured for the

satisfactory resolution of the outstanding manufacturing facility deficiency. Additionally, FDA recommendations related to the 'Dosage and Administration' sections and other parts of the proposed labeling were deferred for a later time.

In the Biopharmaceutics Review of the Class 2 NDA Resubmission dated 10/14/2021, it was acknowledged that based on the results of the repeat comparative *in vitro* physicochemical, *in vitro* protein binding and delivered dose studies,the drug product lots manufactured by the proposed new drug product manufacturing site (Cadila Healthcare Limited/India) exhibited comparable characteristics to the final infusion of ALIMTA. However, due to Drug Product deficiencies related to long-term stability and leachables, adequacy of the scientific bridge could not be concluded. On April 14, 2022, FDA issued a Complete Response (CR) Letter citing deficiencies related to the quality of the primary registration drug product lots manufactured by Cadila/Zydus, and labeling.

In the current Class 2 505(b)(2) NDA Resubmission (RESUB-34), the Applicant successfully addressed the Drug Product deficiencies.

Biopharmaceutics Assessment: *Adequate Scientific Bridge*
In a previous review cycle, this Biopharmaceutics Reviewer determined that adequate evidence of *in vitro* comparability between the final proposed to-be-marketed drug product and the relied upon Listed Drug (LD) product were submitted. Additionally, the Pharmacology/Toxicology Reviewer concluded that the level of L-cysteine (b) (4)) in the proposed drug product is acceptable from a safety/toxicity perspective.

Given that the outstanding CMC/Drug Product and labeling related deficiencies were resolved during the current review cycle, it can now be concluded that an adequate scientific bridge had been established between the proposed drug product and the LD product, i.e., in accordance with 21 CFR 320.24(b)(6).

Recommendation:
From the Biopharmaceutics perspective, NDA 215179 is recommended for APPROVAL.

Biopharmaceutics Assessor's Name and Date: Gerlie Gieser, Ph.D. (4/20/2022)

Gerlie Gieser

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RECOMMENDATION

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

NDA 215179
Review #2

Drug Product Name	Pemetrexed Injection
Dosage Form	Solution for Intravenous Injection
Strength(s)	10 mg/mL (presented as 100 mg/10 mL, 500 mg/50 mL and 1 g/100 mL)
Route of Administration	Intravenous Injection
Rx/OTC Dispensed	Rx
Applicant	Shilpa Medicare LTD

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SN-20 Resubmission NDA Class 2	10/14//2021	ONDP-All
SN-21 Response to Information Request	11/24/2021	Process and Facilities
SN-22 Quality Amendment – updated stability data (3 months)	11/30/2021	Drug Product
SN-23 Response to Information Request	01/06/2022	Process and Drug Product
SN-24 Response to Information Request	01/07/2022	Microbiology
SN-25 Response to Information Request	01/18/2022	Biopharmaceutics
SN-26 Response to Information Request	02/10/2022	Process and Facilities
SN-27 Response to Information Request	02/24/2022	Biopharmaceutics
SN-28 Response to Information Request	03/04/2022	Drug Product
SN-29 Response to Information Request	03/07/2022	Process and Facilities
SN-30 Patent Information Amendment	03/08/2022	505(b)(2) Committee
SN-31 Administrative Correspondence	03/28/2022	All

QUALITY ASSESSMENT TEAM

DISCIPLINE	PRIMARY REVIEWER/ SECONDARY REVIEWER	BRANCH/DIVISION
Drug Substance	Haripada Sarker	OPQ/ONDP/DNDPAPI
Drug Product	Mike (William) Adams/ Xing Wang	OPQ/ONDP/DNDPI
Facility/Process	Yan Zheng/David Anderson	OPQ/OPMA/DMAIV
Microbiology	Jason God/Julie Nemecek	OPQ/OPF/DMA
Biopharmaceutics	Gerlie Gieser	OPQ/ONDP/DB

Regulatory Business Process Manager	Rabiya Haider	OPQ/OPRO/RBPMI
Application Technical Lead	Mei Ou	OPQ/ONDP/DB
Laboratory (OTR)	NA	NA
ORA Lead	NA	NA

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
ALIMTA	NDA 021462	Listed Drug Product

2. CONSULTS

None

Executive Summary

I. Recommendations and Conclusion on Approvability

From a Pharmaceutical Quality perspective, NDA 215179-ORIG-1-RESUB-20 is recommended for COMPLETE RESPONSE.

Summary of Quality Assessments

A. Product Overview

Shilpa Medicare Ltd submitted the original NDA 215179 on August 27, 2020, and the resubmission NDA-215179-ORIG-1-RESUB-20 on October 14, 2021, for Pemetrexed injection (10 mg/mL), a sterile solution.

This 505(b)(2) NDA for Pemetrexed Injection relies for approval, at least in part, on the FDA's efficacy and safety findings for the Listed Drug (LD) product, ALIMTA® (pemetrexed) lyophilized powder for injection (NDA 021462). ALIMTA was approved on February 04, 2004, for the treatment of patients with locally advanced or metastatic non-squamous non-small cell lung cancer as well as mesothelioma and is available as a lyophilized powder (100 mg and 500 mg per vial).

Pemetrexed Injection, 10 mg/mL is a clear, colorless to pale yellow to greenish yellow solution presented in a 10 mL (100 mg), 50 mL (500 mg) and 100 mL (1000 mg) single-dose glass vial. Product strength is based on Pemetrexed as the anhydrous, solvent-free freebase. The proposed product differs from ALIMTA® by the inclusion of L-Cysteine as an (b) (4) and in the presentation of a solution which does not need to be diluted before administration.

The drug product manufacturing and control site at (b) (4) submitted in the original NDA (amendment SN-01) was found to be out of GMP compliance and classified Official Action Indicated (OAI). The original NDA received a Complete Response (CR) Letter on June 24, 2021. The complete response, submitted on October 14, 2021 (amendment SN-20), included the addition of Cadila Healthcare as an alternate drug product manufacturing and control site with a change from (b) (4) (b) (4)

Review cycle #2 addresses the product quality, facilities, and labeling deficiency comments cited by FDA in the CR letter issued on June 24, 2021, and the additional data for supporting the alternate manufacturing site, Cadila Healthcare.

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

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

B. Quality Assessment Overview

DRUG SUBSTANCE: ADEQUATE
The NDA is re-submitted in response to FDA's complete response (CR) letter dated June 24, 2021, for non-API issues. API information are cross-referenced to DMF (b) (4) which is reviewed by Katherine Windsor dated 3/11/2021 to support the NDA 215179. In addition to the response to CR letter, the applicant also proposes inclusion of alternate Finished Dosage Form Manufacturing Facility for manufacturing & testing of Pemetrexed Injection, 100 mg/10 mL, 500 mg/50 mL, and 1000 mg/100 mL (10 mg/mL). This NDA was recommended for approval from the CMC perspective during the last review cycle (Review-1) by Katherine Windsor dated 3/11/2021. The NDA remains approvable. *The Drug Substance Reviewer recommended for **Approval**.*

DRUG PRODUCT: INADEQUATE

The drug product manufacturing and control site at [redacted] submitted in amendment SN-01 was found to be out of GMP compliance and classified OAI. The NDA received a CR letter 24 Jun 2021. The complete response, submitted 14 Oct 2021, included the addition of Cadila Healthcare as an alternate drug product manufacturing and control site with a change from [redacted]

This review cycle addresses the CMC for the alternate manufacturing site and the submission of sufficient drug product stability data to support approval of that site.

The NDA lacks sufficient finished drug product stability data to support approval of the Cadila Healthcare site proposed for drug product manufacture and control, and lacks an acceptable leachables study performed on drug product samples taken from the Cadila Healthcare 12 month stability samples. The 12 month stability samples will be available on 31 Jul 2022.

List of Deficiencies:

1. Per ICH Q1A(R2), provide at least 12 months of long term stability data on the NDA exhibit batches manufactured at the Cadila Healthcare site.
2. Provide an acceptable leachables study performed on 12 month samples taken from the long term stability study for the NDA exhibit batches manufactured at the Cadila Healthcare site.

*The Drug Product Reviewer recommended for **Inadequate**.*

PROCESS: ADEQUATE
FACILITIES: ADEQUATE

Two drug product manufacturing facilities were initially proposed: [redacted] and Cadila Healthcare Limited. [redacted] facility was proposed in the original submission on 08/27/2020. The original submission was CR-ed due to deficiencies including the incompliance status of the [redacted] facility, but the manufacturing process at [redacted] facility was found adequate. Currently [redacted] Cadila is the newly proposed manufacturing site, and it is an approved facility. The assessment in this review mainly applies to the facility and manufacturing process of the Cadila manufacturing site: the unit operations include [redacted] for the Cadila site, [redacted] The commercial batch size [redacted]

*The Process and Facilities Reviewer recommended for **Approval**.*

MICROBIOLOGY: ADEQUATE

The subject submission is a response to the Agency's Complete Response letter, dated 24 June 2021. The first cycle DMA review was adequate. However, the subject submission proposes an alternate drug product manufacturing facility. This review covers sterility assurance for the proposed alternate manufacturing facility. The applicant has met regulatory expectations with regards to:

- CCIT results demonstrate the ability of the container-closure system to maintain a sterile barrier under dynamic conditions.
- The manufacturing and sterilization processes and process controls were (b) (4) (b) (4)
- Validation data demonstrate the ability of the routine vial depyrogenation parameters to achieve a 3-log reduction in endotoxin.
- (b) (4)
- The design of the stability testing program to support the drug product's microbiological quality throughout its shelf life. In addition, the stability data submitted to date support the microbiological quality of the subject drug product.

The Microbiology Reviewer recommended for ***Approval.***

BIOPHARMACEUTICS: INADEQUATE

To address the Biopharmaceutics deficiency comment included in the CR Letter issued for the original NDA, the Applicant provided the results of the delivered dose study in the NDA Resubmission. However, because the Applicant (b) (4) which produced the proposed drug product lots evaluated in the in vitro bridging studies submitted to support the original NDA, the Applicant was requested to conduct repeat comparative in vitro physicochemical, protein binding and delivered dose studies using the drug product lots manufactured by the new drug product manufacturing site (Cadila Healthcare Limited/India).The additional data/information provided by the Applicant during the current NDA review cycle indicated that the proposed drug product is comparable, i.e., in terms of these attributes to the relied upon Listed Drug product, ALIMTA. However, the Drug Product Reviewer determined that the long-term stability data and the leachables data provided for the Cadila-manufactured drug product batches are not sufficient to support the new drug product manufacturing site, as well as the proposed drug product expiration dating period of (b) (4) months. Additionally, the labeling discussions will not be completed during the current NDA review cycle. Thus, although the comparative delivered volume/delivered dose related deficiency cited in the 6/24/2021 Complete Response Letter was addressed, there are still outstanding CMC review issues emergent from the more recent proposal to change the drug product manufacturing site at the time of the 10/14/2021 NDA Resubmission, and labeling review issues. Therefore, given the unresolved CMC and labeling deficiencies, at the current time, it cannot be concluded that an adequate scientific bridge had been established between the proposed drug product and the relied upon LD, i.e., in accordance with 21 CFR 320.24(b)(6).

List of Deficiencies:
The product quality deficiencies listed above should be resolved before the adequacy of the scientific bridge between the proposed drug product and the relied upon Listed Drug product can be established, i.e., in accordance with 21 CFR 320.24(b)(6).

The Biopharmaceutics Reviewer recommended for ***Complete Response****.*

C. Special Product Quality Labeling Recommendations

"Manufactured by" statement is no longer acceptable as the [redacted] (b) (4) was initially replaced with Cadila Healthcare Limited per amendment SN-26 dated 02/10/2022, in which name was changed to Zydus Lifesciences Limited per amendment SN-31 dated 03/28/2022.

Revise the "manufactured by" statement in the USPI to indicate the changed in manufacturing and control site from [redacted] (b) (4) to Zydus Lifesciences Limited.

No new labels or labeling have been submitted since the NDA resubmission. See the CMC comments and conclusions in CMC-DP-Labeling-Review-01 dated 05/27/2021.

Labeling comments for this review cycle are deferred due to the planned Complete Response action.

D. Risk Assessment

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

Leachable extractables	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		M	Provide an acceptable leachables study performed on 12 month samples taken from the long term stability study for the NDA exhibit batches manufactured at the Cadila Healthcare site.
Appearance (Color /turbidity)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		L	

E. List of Deficiencies for Complete Response

Quality Deficiencies:

1. Per ICH Q1A(R2), provide at least 12 months of long term stability data on the NDA exhibit batches manufactured at the Cadila Healthcare Limited/Zydus Lifesciences Limited site (FEI#3007621329, DUNS#650348852).

2. Provide an acceptable leachables study performed on 12 month samples taken from the long term stability study for the NDA exhibit batches manufactured at the Cadila Healthcare Limited/Zydus Lifesciences Limited site.

3. The product quality deficiencies listed above should be resolved before the adequacy of the scientific bridge between the proposed drug product and the relied upon Listed Drug product can be established, i.e., in accordance with 21 CFR 320.24(b)(6).

Application Technical Lead Name and Date for NDA-215179-ORIG-1-RESUB-20: Mei Ou, Ph.D. 04/01/2022

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CHAPTER VII: MICROBIOLOGY

Product Information	Solution for injection
NDA Number	215179
Assessment Cycle Number	2
Drug Product Name/ Strength	Pemetrexed Injection / 100 mg/10 mL, 500 mg/50 mL, 1 g/100 mL
Route of Administration	IV
Applicant Name	Shipla Medicare Limited
Therapeutic Classification/ OND Division	OOD/DO2
Manufacturing Site	Cadila Healthcare Limited Plot No. 1A, Pharmaceutical Special Economic Zone Sarkhej – Bavla N.H No. 8A Ta. Sanand, Dist. Ahmedabad - 382213
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary: This review covers sterility assurance for the proposed alternate manufacturing facility.

List Submissions being assessed:

Document(s) Assessed	Date Received
eCTD 0020	**10/14/2021**
eCTD 0024	**1/7/2022**

Highlight Key Issues from Last Cycle and Their Resolution: None

Remarks: The subject submission is a response to the Agency's Complete Response letter, dated 24 June 2021. The first cycle DMA review was adequate. However, the subject submission proposes an alternate drug product manufacturing facility.

Concise Description of Outstanding Issues: None

Supporting Documents: (b) (4).docx, dated 3 February 2017 is referenced for the review of (b) (4) adequate). LOA is dated 28 September 2021.

S DRUG SUBSTANCE

N/A. Drug substance is supplied non-sterile

Assessment: *Adequate*

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of container closure system –**
  - Vial: 10 mL/20 mm, 50 mL/20 mm, 100 mL/20 mm (b) (4)
  - Closure: 20 mm gray serum stopper (b) (4)
  - Seal: 20 mm aluminum flip-off seal (b) (4)

Assessment: *Adequate*

(b) (4)

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Jason God

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Julie Nemecek

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Date: 1/12/2022 02:24:14PM
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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	NDA-215179-ORIG-1-RESUB-20 NDA215179 - (0020)
Assessment Cycle Number	NDA Resubmission after Complete Response
Drug Product Name/ Strength	Pemetrexed Injection 10 mg/mL (presented as 100 mg/10 mL, 500 mg/50 mL, 1000 mg/100 mL solution in single-dose vials)
Route of Administration	For Intravenous Infusion
Applicant Name	Shilpa Medicare LLC
Therapeutic Classification/ OND Division	Anticancer: Folate analog metabolic inhibitor DO2
Listed Drug Product Relied Upon	ALIMTA® lyophilized powder for reconstitution and further dilution [NDA 21462]
Proposed Indication	Treatment of non-squamous, non-small cell lung cancer
RECOMMENDATION	**COMPLETE RESPONSE**

EXECUTIVE SUMMARY

Background:

This 505(b)(2) NDA for Pemetrexed Injection (10 mg/mL) relies for approval, at least in part, on the FDA's efficacy and safety findings for the Listed Drug (LD) product, ALIMTA® (pemetrexed) lyophilized powder for Injection (NDA 021462).The chemical composition of the proposed pemetrexed 10 mg/mL solution drug product and the relied upon Listed Drug product's final infusion solution (prepared from reconstitution of the lyophilized powder and further dilution) are the same, except for the presence of an (b) (4) (L-cysteine hydrochloride (b) (4)) in the proposed drug product's formulation (b) (4). To deliver the required pemetrexed dose (calculated based on the patient's body surface area), the appropriate volume (i.e., not necessarily 100 mL) of the proposed 10 mg/mL solution in vial product is transferred into an empty IV bag immediately prior to IV infusion that is then administered to the patient with the aid of an infusion pump.

In the Biopharmaceutics Review of the original NDA, it was concluded that the scientific bridge between the proposed drug product and the relied upon LD product could not be established completely because the Applicant was not able to provide the requested data that would demonstrate that the difference in handling and preparation between the proposed solution injectable drug product and (the final infusion of) the LD product would not result in a significant difference in "delivered dose" of pemetrexed to the patient. In the Biopharmaceutics Review, it was also acknowledged that ***i***) the proposed drug product manufacturer (b) (4) (b) (4)

(b) (4), and ***ii***) the bridging assessment will be revisited should new registration batches of the proposed drug product be manufactured for the satisfactory resolution of the outstanding manufacturing facility deficiency. Additionally, FDA recommendations related to the 'Dosage and Administration' sections and other parts of the proposed labeling were deferred for a later time.

The current Class 2 NDA Resubmission provides the Applicant's Responses to the product quality, facilities, and labeling deficiency comments cited by FDA in the Complete Response (CR) Letter issued on June 24, 2021.

Biopharmaceutics Assessment: *INCOMPLETE*

To address the Biopharmaceutics deficiency comment included in the CR Letter issued for the original NDA, the Applicant provided the results of the delivered dose study in the NDA Resubmission. However, because the Applicant (b) (4) which produced the proposed drug product lots evaluated in the *in vitro* bridging studies submitted to support the original NDA, the Applicant was requested to conduct repeat comparative *in vitro* physicochemical, protein binding and delivered dose studies using the drug product lots manufactured by the new drug product manufacturing site (Cadila Healthcare Limited/India).The additional data/information provided by the Applicant during the current NDA review cycle indicated that the proposed drug product is comparable, i.e., in terms of these attributes to the relied upon Listed Drug product, ALIMTA. However, the Drug Product Reviewer determined that the long-term stability data and the leachables data provided for the Cadila-manufactured drug product batches are not sufficient to support the new drug product manufacturing site, as well as the proposed drug product expiration dating period of (b) (4) months. Additionally, the labeling discussions will not be completed during the current NDA review cycle. Thus, although the comparative delivered volume/delivered dose related deficiency cited in the 6/24/2021 Complete Response Letter was addressed, there are still outstanding CMC review issues emergent from the more recent proposal to change the drug product manufacturing site at the time of the 10/14/2021 NDA Resubmission, and labeling review issues. .

Therefore, given the unresolved CMC and labeling deficiencies, at the current time, it cannot be concluded that an adequate scientific bridge had been established between the proposed drug product and the relied upon LD , i.e., in accordance with 21 CFR 320.24(b)(6).

List of Submissions Reviewed:

Document(s) Assessed	Date Received
SN-20 NDA Resubmission	10/14/2021
SN-21 Response to Facilities IR	11/24/2021

SN-22 Response to Drug Product IR – updated (3 months) stability data	11/30/2021
SN-23 Response to Drug Product and Process IRs	1/6/2022
SN-25 Response to Biopharm IR	1/18/2022
SN-27 Response to Follow-up Biopharm IR	2/24/2022
SN-28 Response to Drug Product IR	3/4/2022

Concise Description of Outstanding Issues:

- Resolution of Drug Product review issues related to insufficient long-term stability data and leachables data for the new registration batches, and labeling issues

B.12 BRIDGING OF FORMULATIONS USED IN THE DEVELOPMENT OF PROPOSED DRUG PRODUCT

Previously, due to current good manufacturing process (CGMP) issues, the facility at the original drug product manufacturing site, (b) (4) was not recommended for FDA approval. To address the Facilities-related deficiency in the 6/24/2021 Complete Response Letter issued for the original NDA, in the NDA Resubmission the Applicant proposed an alternate drug product manufacturing facility, Cadila Healthcare Limited/India. To support the alternate drug product manufacturing site, documentation from the alternate site were provided including analytical method validation/verification, certificates of analysis (CoA) of drug substance standards, updated batch formula with the executed batch size, description of the (similar) manufacturing process and process controls, sterility assurance documentation, excipient specifications & analytical procedures, batch analysis and stability data for *new primary registration drug product lots*, container-closure system, executed batch records. In SN-22 and SN-28, the Applicant provided the updated (3-month and 6-month) stability data for the exhibit lots manufactured by Cadila.

Per the Applicant, the drug substance supplier and DMF, as well as the manufacturing process and finished product QC specifications and analytical procedures will be the same as proposed in the original NDA submission.

In SN-21, the Applicant clarified that they (b) (4) and is currently working to address the CGMP issues in the facility. However, in a later submission (SN-26), the Applicant informed the FDA of their decision to (b) (4). Per the Facilities Reviewer (Dr. Yan Zheng), the Cadila manufacturing site is compliant.

Assessment: *Adequate*

In light of the proposal to use Cadila Healthcare/India as the lone drug product manufacturing site, per FDA request, the Applicant submitted additional *in vitro* bridging and CMC data (not already provided in the original NDA Resubmission) for the new Cadila-manufactured registration batches of the proposed drug product [i.e., 100 mg/10 mL Lot PS10012 (PS10015), 500 mg/50 mL Lot PS10011 (PS10014), 1000 mg/100 mL Lot PS10010 (PS10016)].

Specifically, to address this Reviewer's information request, the Applicant provided additional comparative physico-chemical, *in vitro* protein binding, and delivered dose study data (i.e., relative to the Listed Drug product) for the new exhibit batches (which were manufactured at the proposed commercial batch scale by the proposed new commercial drug product manufacturer using drug substance from the proposed commercial API supplier). These new set of data using the Cadila-manufactured registration batches then served as the main basis for this Reviewer's assessment of the adequacy of the scientific (*in vitro*) bridge between the proposed drug product and the LD (ALIMTA), as discussed in Section B.13 of this review document.

The ALIMTA® lots used in comparative *in vitro* physicochemical, delivered dose, and protein binding studies were not expired.

Note that the proposed to-be-marketed drug product was not evaluated in clinical studies.

B. 13 BIOWAIVER REQUEST OR CROSS-PRODUCT BRIDGING

Assessment:
BRIDGING OF PROPOSED & LISTED DRUG PRODUCTS – Inadequate

This 505(b)(2) NDA for Pemetrexed (Solution) Injection, 10 mg/mL, relies for approval on the FDA's findings of efficacy and safety for ALIMTA® (pemetrexed disodium) For Injection (NDA 021462), as well as (at least in part) the nonclinical and clinical pharmacology information in the LD's approved labeling. The noted similarities and differences between the proposed drug product and the relied upon Listed Drug are summarized in Table 1 below. 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), data/information from comparative physicochemical, comparative *in vitro* protein binding characterization studies, as well as stability testing of the proposed drug product (packaged in glass vials), and from a survey of the Inactive Ingredients Database and package inserts of CDER approved drug products were provided in the original NDA and NDA resubmissions.

Based on the provided *in vitro* bridging data, it can be concluded that the physico-chemical, *in vitro* protein binding, and delivered dose characteristics of the proposed drug product's exhibit batches manufactured by the Cadila site are similar to those provided for the relied upon Listed Drug product. For details, refer to Tables 1 and 2 of the SN-25 IR Response.

Note that during the original NDA review the Applicant was informed by FDA that the request to waive clinical BE testing of the proposed pemetrexed Ready-To-Dilute (RTD) solution injectable drug product cannot be granted via 21 CFR 320.22(b)(1) because the proposed injectable solution drug product is not qualitatively and quantitatively (Q1/Q2) the same as the relied upon Listed Drug (LD) product. Instead, the scientific bridge to ALIMTA® (Listed Drug product, LD) could potentially be established via 21 CFR 320.24(b)(6).

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

	Proposed Drug Product Pemetrexed (Solution) Injection, Shilpa Medicare, LLC	**Listed Drug Product Being Relied Upon** ALIMTA® (pemetrexed for injection); NDA 021462, Eli Lilly & Company
Dosage Form; Strength(s)/Presentation	Solution; 10 mg pemetrexed (b) (4) /mL (single-dose vials containing 100 mg/10 mL, 500 mg/50 mL, and 1000 mg/100 mL solution)#	Lyophilized Powder for Reconstitution and Further Dilution with preservative-free NSS (single dose 100 mg, and 500 mg (b) (4) /vial)
Formulation Composition	Each glass vial of 100 mg/10 mL solution contains (in addition to pemetrexed disodium hemipentahydrate equivalent to 100 mg pemetrexed+) Mannitol (100 mg) L-cysteine HCl (b) (4) (10 mg) Sodium Chloride (90 mg) Water for Injection (q.s. ad 10 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/Infusion Volume	Final drug concentration = fixed (10 mg/mL regardless of patient BSA) ***To Be Administered Undiluted*** Final Infusion Volume = variable (not necessarily 100 mL; calculated depending on the patient BSA) Sample Dosing & Administration Scenarios:	Final drug concentration = variable (calculated depending on the required pemetrexed dose based on patient BSA) ***Dilute the required volume of the reconstituted product (25 mg/mL) with 0.9% NaCl Solution*** Final Infusion Volume = fixed (100 mL regardless of patient BSA) Sample Dosing & Administration Scenarios:

	(a) For BSA = 2.0 m^2: 1000 mg/100 mL (10 mg/mL,100 mL); same final drug concentration and volume as the LD (b) For BSA = 1.0 m^2: 500 mg/50 mL (10 mg/mL, 50 mL) (c) For BSA =0.2 m^2: 100 mg/10 mL (10 mg/mL, 10 mL)	(a) For BSA = 2.0 m^2: 10 mg/mL upon dilution with NSS to 100 mL (b) For BSA = 1.0 m^2: 5 mg/mL upon dilution with NSS to 100 mL (c) For BSA =0.2 m^2: 1 mg/mL upon dilution with NSS to 100 mL
Proposed Indications/Dosing Regimen	Indications and Dosing Regimens the same as LD	
Preparation and Administration	After transferring the appropriate volume of the solution from the vial into an empty IV bag, administer *immediately* as a 10 min-IV infusion.	After dilution of the appropriate volume of reconstituted solution with 0.9% NaCl Injection (preservative-free) to a total volume of 100 mL, administer as a 10-min IV infusion.
Physico-chemical properties of the final dilution for IV infusion		
Appearance	Clear, colorless solution; free from visible particulates	
Assay	*As is: 101.6%, 98.9%, 99.9%*[a,b,c,] *(98.5% or higher during 6-month long-term and accelerated stability testing)* [Proposed ranges: (b) (4)% of label claim/LC (release); (b) (4)% (shelf-life)]	Before Reconstitution (100 mg/vial): Reconstituted/Before dilution: ND *After dilution: 102%, 95.4%*[d, e] [Approved range: (b) (4)% of LC]
pH	*As is: 7.4, 7.3, 7.3;* *7.0 – 7.4 during 6-month stability testing* [Proposed range: (b) (4) (release & shelf-life);	Reconstituted/Before dilution: ND *After dilution: 7.0, 6.9* [Approved range: (b) (4)
Osmolality (mOsm/kg)	*As is:* 407, 416, 404	Reconstituted/Before dilution: ND *After dilution: 393, 386*
Viscosity (mm^2/s)	*As is*: 1.05693, 1.06405, 1.03914	Reconstituted/Before dilution: ND *After dilution: 1.0387, 1.0317*
Specific gravity	*As is*: 1.02 – 1.02	Reconstituted/Before dilution: ND *After dilution: 1.00 – 1.00*
In Vitro Protein Binding (%, mean) 0.5 mcg/mL 10 mcg/mL 50 mcg/mL 100 mcg/mL 150 mcg/mL 200 mcg/mL pemetrexed	 83.0% 82.4% 79.5% 79.3% 77.7% 77.4%	 81.4% 82.2% 79.2% 79.0% 79.3% 77.3%
Recommended storage during product shelf-life (and upon preparation, if applicable)	– USP Controlled Room Temperature (Use solution in the IV bag immediately.)	Powder – USP Controlled Room Temperature (Use both reconstituted and diluted solution within 24 hours of preparation under refrigeration.)
Container-closure	USP Type I glass vial with (b) (4) rubber stopper with aluminium seal	

Physico-chemical & microbiological stability		
Total Impurities/ Degradants	(b) (4)%, (b) (4)%, (b) (4)% NMT (b) (4)% (during 6 months at 40°C/75%RH, and at least up to **6** months at 25°C/60%RH)	BQL
Sterility	Achieved by (b) (4) of the finished solution drug product in vials; maintained during 6 months accelerated and at least up to 6 months of long-term stability testing of the solution	-
Bacterial Endotoxins (NMT (b) (4) EU/mg of Pemetrexed)	Conforms during initial and later (up to Month 6 Accelerated and at least up to 6 months long-term) stability time points	-
Special QC specifications (tests and acceptance ranges) proposed/approved	1. Extractable Volume: NLT nominal volume (e.g., NLT (b) (4) mL for 100 mg/10 mL)	Reconstitution time = NMT (b) sec
	2. Assay of L-cysteine hydrochloride (by HPLC): At Release: NLT (b) (4)%; During Shelf-Life: NLT (b) (4)%	-
	3. Impurities: At Release / During Shelf-Life	(b) (4) NMT (b)% Largest Unspecified Impurity: NMT (b) (4)% Total Impurities NMT (b)%
	Ketopemetrexed (Pemetrexed (b) (4)): ND / ND	
	Impurity (b) (4): NMT (b) (4)% / NMT (b) (4)%	
	Impurity (b) (4): NMT (b) (4)% / NMT (b) (4)%	
	Any unspecified impurity: NMT (b) (4)% / NMT (b) (4)%	
	Total impurities: NMT (b) (4)% / NMT (b) (4)%	
	4 (b) (4): NMT (b) (4)% / NMT (b) (4)%	

[a, b, c] = unless otherwise specified, the values noted are for 10 mL, 50mL, 100 mL, respectively, of ~ 5 to 6 month old product
[d,e] = unless otherwise specified, the values noted are for 100 mg/vial and 500 mg/vial ALIMTA, reconstituted and diluted
BQL: Below Quantification Limit; ND: Not Determined
[+] Since the API is hygroscopic (i.e., gains moisture from the atmosphere when exposed to a level of about (b) (4)%), the amount of hemipentahydrate to be used (to obtain an equivalent amount of the pemetrexed (b) (4) is to be calculated using a formula that factors in the moisture content and the potency of the drug substance
[#] The proposed labeling states (b) (4)
Target fill volumes of vials: (b) (4) (based on USP recommended excess volume for non-viscous liquids)
***Tentative proposed expiration dating period = (b) (4) months (RT)

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

Justification for

1. *Difference in crystalline hydrate 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. As part of the original NDA submission, the Applicant provided the solubility data of the hemipentahydrate form of pemetrexed disodium in various aqueous media which confirmed relatively high solubility in water, and in pH 6.0 and 8.0 buffer media (50 mg/mL at 25 °C) and slightly lower solubility in pH 1.2 medium (2 mg/mL at 25 °C), as well as information that both the proposed drug product (as is) and the final dilution of the LD yielded clear, colorless solutions. Additionally, the provided stability data of the proposed solution drug product demonstrated freedom from particulates (indicative of visually complete solubility). It is also noted that the proposed pemetrexed (10 mg/mL) solution product's pH is maintained at a range of (b) (4), conditions that are favorable for maintaining the drug in solution.

NOT FOR FOIA: (b) (4)

(b) (4)

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Per the Drug Substance Reviewer (Dr. Haripada Sarker) the cross-referenced DMF (b) (4) remains adequate to support this NDA Resubmission.

2. *Difference in Formulations/Excipients – Impact on product quality*

As shown in the product comparison table above, the major difference in composition between the proposed solution product and the final infusion solution prepared from the relied upon LD powder is the presence/absence of the L-cysteine (b) (4) (as (b) (4). Previously during the original NDA review cycle, the Drug Product Reviewer determined that the amount of added L-cysteine in the formulation of the proposed RTU solution drug product is acceptable from a product stability perspective. Additionally, the Drug Product Reviewer had requested revision of the proposed residual amounts of L-cysteine from 'NLT(b) (4)%' to 'NLT(b) (4)%' of label claim to ensure sufficient levels of the (b) (4) remains during the entire proposed product's shelf-life. Refer also to the discussion below under *Justification Item #6. Difference in Pharmaceutical Dosage Form and Presentation - Impact on product quality.*

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

Based on the results of Study ALS0036, the percentage of plasma protein binding *in vitro* was comparable between the test product and the reference product (ALIMTA, 500 mg/vial Batch# S201040A) at the studied final drug concentrations ranging from 0.5 mcg/mL to 200 mcg/mL in human plasma. The test sample was produced by diluting 20 mcL volumes of the appropriate concentration pemetrexed stock solutions

in 0.9% sodium chloride solution (prepared from the Cadila-manufactured registration batches) to achieve the desired final concentrations of the active and inactive ingredients in human plasma at the same proportion as present in the proposed drug product. [Note: To support the original NDA, the Applicant performed the comparative *in vitro* protein binding study at final pemetrexed concentration of 10 mg/mL, in addition to drug concentrations ranging from 0.5 mcg/mL to 200 mcg/mL, using the (b) (4) manufactured drug product.] Based on the observed comparable *in vitro* protein binding data, a significant difference in *in vivo* drug distribution between the proposed and the reference drug products is not anticipated.

This Reviewer notes that the level of mannitol in the proposed injectable solution is almost exactly the same as that present in the final dilution of the LD, which is advantageous in terms of the assessment of comparable PK between products (since it is known that very high amounts of mannitol in a product could influence renal elimination due to this excipient's diuretic effect, and pemetrexed is excreted unchanged in the urine to a significant extent). However, it is not clear to this Reviewer why a (b) (4) like mannitol would be needed for a product that does not undergo lyophilization or freeze-drying or does not need to be filled into capsules or tableting equipment during manufacture because it is a solution drug product.

4. *Difference in Formulations/Excipients – Impact on drug product safety/tolerability*

Per the Applicant, the levels of excipients (except of the (b) (4), L-cysteine hydrochloride (b) (4) in the proposed drug product's formulation are within the IIG limits for the intravenous route of administration, as shown in the following table. The Applicant justified the level of the L-cysteine (100 mg for patient with BSA = 2.0 m^2) based on the 490 mg total daily intake of ELCYS® (cysteine hydrochloride injection) for a 70 kg stable or critically ill adult patient requiring 7 mg amino acid for total parenteral nutrition. At the time of the original NDA review, the Pharmacology/Toxicology Reviewer (Dr. M A Goheer) confirmed that the level of L-cysteine in the proposed drug product (i.e., up to 100 mg L-cysteine for a patient with BSA =2.0 m^2) is covered by levels present in intravenously administered parenteral nutrition, does not require safety qualification, and thus, is acceptable from a safety/toxicity perspective.

Additionally per the Applicant, that the proposed drug product is hypertonic should not result in any injection site reactions at the time of administration because the risk of chemical phlebitis occurs when the osmolality of the injectable solution is higher than 450 mOsm/L (Stranz, Int J Pharm Compounding, 2002). It is important to note that the proposed drug product's osmolality is only slightly higher as compared to the LD's final infusion solution which is desirable in terms of comparative systemic safety and local tolerability assessments.

Inactive ingredients quantities and IIG limits

Name of the Ingredient	10 mg/mL % w/v or % v/v	Maximum Quantity Accepted by FDA for Injectable* (%)
Mannitol	1% w/v	4.95%w/v
Sodium Chloride	0.9% w/v	0.9%w/v
(b) (4) (b) (4)	0.1% w/v	0.03 %w/v- Injection IV 15 mg- Injection IV#
Sodium Hydroxide	QS	-
Hydrochloric acid (b) (4)%	QS	-

*** eIID Database Last Updated: July 28, 2020**

5. *Difference in Dosage Form and Presentation – Impact on Clinical Outcomes (including Medication Errors)*

   All single-dose vial presentations of the proposed and Listed Drug (LD) products will have the same pharmaceutical form (solution) at the point of patient contact, the same IV administration route & rate (as 10-min IV infusion), and indications of use.

   However, whereas the LD is a powder that is reconstituted to a pemetrexed concentration of 25 mg/mL, the required volume of which is then diluted with 0.9% Sodium Chloride Injection to a final infusion volume of 100 mL, the proposed solution drug product contains a fixed pemetrexed concentration of 10 mg/mL and does not require dilution prior to administration. Thus, depending on body surface area, a patient being switched to the proposed drug product may not receive the same final drug concentration and/or total infusion volume as received when being administered the LD.

   Mainly because of the limitations posed by the selected container-closure system (glass vial) of the proposed injectable solution drug product, special preparation and handling steps for the final infusion solution are necessary. At the time of original NDA review, FDA requested the Applicant to revise the proposed labeling in order to provide clarity regarding how the proposed solution is to be administered directly from the vial as a 10-minute IV infusion, and to provide justification that use of partial vials or multiple vials to afford BSA-based dosing would not result in wrong dose medication errors. At that time, the Applicant clarified that the calculated volume of the solution will be withdrawn from the vial(s) and transferred into an empty IV bag. To minimize the risk of medication errors, the proposed drug product's labeling was revised per DMEPA recommendations. Specifically, highlighting will be added to "10 mg/mL" to emphasize the availability of the proposed product in a new pemetrexed concentration, i.e.,

different from other pemetrexed solutions currently marketed. Additionally, a "Note Concentration" banner will be added to the carton's principal display panel. Moreover, to avoid overdosage errors due to the administration of the entire content of the vial(s) when an aliquot of the solution should have been withdrawn and then transferred to an empty IV bag to deliver the correct dose, the Applicant agreed to remove the [redacted] of the container label. Refer to the DMEPA Label and Labeling Review of the original NDA for additional information.

In this NDA Resubmission, the Applicant provided the response to the following FDA information request that was conveyed on May 30, 2021:

> *In Section 2.7 of the proposed labeling, [redacted] Provide deliverable dose data to demonstrate that the transferred dose to and from the vented IV bag (when administered over 10 minutes using an infusion pump) are comparable. In performing this study, we recommend 1) positioning the pump next to the IV needle, using the smallest possible empty IV bag, and other additional specified measures to prevent delivered dose loss, 2) for patient BSA ranging from 0.5 m^2 to 2.0 m^2, and 3) ALIMTA final infusion as the internal control.*

Based on the results of the conducted delivered dose study (using the drug product lots manufactured by Cadila), the Applicant reported that for dosing of patients within a BSA range of 0.5 to 2.0 m^2, [redacted]% – [redacted]% of the nominal/target dose is retained or 'NMT [redacted]%' of the target dose is lost during transfer of drug solution from vial to the 100 mL capacity empty IV bag, (when the distance between the infusion pump and the needle output of the IV set was maintained at 15 cm). For details, refer to excerpted Table 1 below. The Applicant explained that the higher delivered dose loss measured when testing the smallest transferred volume from vial to empty infusion bag (i.e., intended for a patient with BSA of 0.5 m^2) is of lower clinical significance because the product is indicated for use in adults with higher BSA usually ranging from 1.5 to 2.0 m^2. Considering regulatory decisions made in other 505(b)(2) NDAs including those involving pemetrexed ready-to-infuse injectable products, this 'NMT [redacted]%' loss in delivered dose due to handling the product prior to IV infusion is not anticipated to result in a clinically meaningful difference in drug exposures.

Table 1: Deliverable dose study results

Sr. No	Body surface area (m^2)	Required dose to administer (mg)	Delivery from vial to IV bag		Deliverable volume collected from infusion bag (ml)	% Delivered	Delivered dose (mg)
			Withdrawn volume from the vial (ml)	Transferred volume from vial to empty infusion bag (ml)			
Test Product							
1.	0.5	250	25	25	24	96.0	240
2.	1.0	500	50	50	49	98.0	490
3.	2.0	1000	100	100	99	99.0	990
Reference (ALIMTA)- Internal control							
4.	0.5	250	10.5 ml	100 (10.5ml of ALIMTA + 89.5ml of 0.9% NaCl)	99	99.0	247.5
5.	1.0	500	20 ml	100 (20 ml of ALIMTA + 80 ml of 0.9% NaCl)	99	99.0	495
6.	2.0	1000	40 ml	100 (40 ml of ALIMTA + 60 ml of 0.9% NaCl)	99	99.0	990

Source: SN-25, Response to Biopharmaceutics IR; Deliverable Volume Study Report
Materials Used in Deliverable Volume Study: 20 mL and 50 mL (b) (4) syringes (b) (4) IV infusion bag and (b) (4) IV infusion set/tube (refer to Response to Drug Product IR in SN-28)

The latest version of the proposed labeling was provided in SN-28 (dated 3/4/2022). ***A final determination regarding the adequacy of the proposed labeling will not be made by FDA during the current NDA review cycle.***

Note that due to the absence of dedicated in-use stability data and compatibility data with various different commercially available empty IV bags, at the time of the original NDA review, the Drug Product Reviewer recommended that the proposed drug product labeling state that upon transfer of the required volume of the proposed solution drug product to the IV bag, infusion administration should be done immediately.

That the proposed drug product is to be also marketed with a 1000 mg/vial presentation (which is not commercially available for the Listed Drug product ALIMTA) is reasonable because the recommended dose of pemetrexed is 500 mg/m^2. Therefore, the 1000 mg/100 mL presentation of the proposed solution drug product would be suitable for use by patients with BSA approaching 2.0 m^2.

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

At the time of comparative *in vitro* testing, the LD had 'below quantifiable levels' of total impurities/degradants in the diluted solution prepared from the lyophilized product. On the other hand, the exhibit batches of the proposed injectable solution drug product exhibited NMT (b) (4)% total impurities during 6 months of accelerated (40 ± 2 °C/75 ±5 RH) and long-term (5 ± 3 °C, and 25°C± 2°C; RH: 60%±5%) stability testing,.

The proposed acceptance ranges for finished drug product Assay, Specific and Total Impurities are wider or more permissive during shelf-life/stability testing than at batch release of the proposed drug product. It does not appear that keto-pemetrexed impurity levels are proposed to be quantified during routine QC testing of the proposed drug product, At the time of the original NDA review, the Drug Product Reviewer requested revision of related substances to include all unspecified impurities at or above the limit of detection (LOD (b) (4)%) of the HPLC method. Additionally, the proposed tolerance limits for Total Impurities during shelf-life is slightly higher than those approved for the Listed Drug product (NMT (b) (4)% versus NMT (b) (4)%), which was deemed comparable/acceptable by the Drug Product Reviewer. Additionally, also at the time of original NDA review, the Process Reviewer (Dr. Yan Zheng) determined that the proposed drug product manufacturing process and associated in-process controls including the proposed (b) (4) (b) (4) (b) (4)

At the current time, based on the limited drug product stability data for the new registration batches that were manufactured by the Cadila site, the Drug Product Reviewer does not consider acceptable the proposed expiration dating period of (b) (4) months when the solution drug product is stored in the proposed commercial packaging configuration (glass vial) at controlled room temperature.

In an email discussion with the Microbiology Reviewer at the time of original NDA review, Dr. Amanda Buskirk indicated that no further microbiological testing is required related to the additional handling instructions (i.e., transferring the appropriate volume of the proposed drug product to an empty sterile IV bag) prior to IV infusion because of the short administration time (10 minutes). Per the NDA Resubmission's Microbiology Reviewer (Dr. Jason God), sterility assurance is adequate for the proposed new drug product manufacturing facility.

The proposed finished product QC specifications for batch release and shelf-life include control for (b) (4) NMT (b) (4)%) in the vial which is intended to (b) (4) of pemetrexed in solution. The Applicant stated that the chosen Type I clear colorless (b) (4) glass vials conformed to tests specified for Type I glass containers in USP<660> Containers-Glass which includes a test for hydrolytic resistance of the inner surface of glass containers. ***Per the Drug***

Product Reviewer the results of the studies for extractables/leachables are not adequate. There is a potential concern regarding the impact on drug product stability of the difference in the rubber stopper closure (b) (4) ***used by the original and new drug product manufacturing sites, respectively.***

R. REGIONAL INFORMATION

Post-Approval Commitments

None

Lifecycle Management Considerations

None

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None (refer to the Drug Product Reviewer's list of deficiencies)

Biopharmaceutics Assessor's Name and Date: Gerlie Gieser, Ph.D. (3/9/2022)

Gerlie Gieser

Digitally signed by Gerlie Gieser
Date: 3/09/2022 05:55:47PM
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CMC LABELING REVIEW 02

Amendment SD-020 10/14/21 (b) (4)

NDA resubmission with addition of Cadila Healthcare site (b) (4)

Responses to comments in the CR Letter dated 06/24/21.

SD-020 Comment 3: We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.[3]

SD-020 Comment 4: We reserve comment on the proposed carton and container until the application is otherwise adequate.

Responses 3,4

The comments are acknowledged.

Reviewer's Assessment: {Adequate}

No new labels or labeling have been submitted since the NDA resubmission. See the CMC comments and conclusions in CMC-DP Labeling Review 01 dated 05/23/21.

R Regional Information

1.14 Labeling

VIAL LABELS)

Reviewer's Assessment: Adequate in CMC-DP Labeling Review 01

CARTON LABELS

Reviewer's Assessment: Adequate in CMC-DP Labeling Review 01

PACKAGE INSERT

Manufactured by:

(b) (4)

Reviewer's Assessment:{Adequate}

Accepted in CMC-DP Labeling Review 01

"Manufactured by" statement is no longer acceptable as the (b) (4) was replaced with Cadila Healthcare per amendment (b) (4)

Revise the "manufactured by" statement in the USPI to indicate the changed in manufacturing and control site from (b) (4) to Cadila Healthcare.

List of Deficiencies: None

Primary Labeling Reviewer:

William Adams, CMC reviewer, ONDP

Secondary Reviewer:

Xing Wang, SPQA, ONDP

William Adams

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Date: 3/18/2022 05:47:19PM
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Xing Wang

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Date: 3/18/2022 05:55:43PM
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Mei Ou

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/s/

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Recommendation: Complete Response

NDA 215179
Review #1

Drug Name/Dosage Form	Pemetrexed Injection/ready-to-use solution for injection,
Strength(s)	10 mg/mL (presented as 100 mg/10 mL, 500 mg/50mL, 1 g/100 mL)
Route of Administration	IV infusion
Rx/OTC Dispensed	Rx
Applicant	(b) (4)

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original NDA	08/27/2020	ONDP-All
Labeling/Container Carton Draft	10/15/2020	Process and Facilities, Labeling, Microbiology
Quality Amendment	12/04/2020	Process and Facilities
Quality Amendment	01/19/2021	Biopharmaceutics
Quality Amendment	02/02/2021	Process and Facilities, Microbiology
Quality Amendment	02/19/2021	Drug Substance
Quality Amendment	02/24/2021	Biopharmaceutics
Labeling/Container Carton Draft, Package Insert	02/26/2021	Drug Product, Labeling
Labeling/Container Carton Draft	03/05/2021	Labeling
Labeling/Container Carton Draft	03/16/2021	Labeling
Clinical Pharmacology, Quality Amendment	05/10/2021	Biopharmaceutics
Quality Amendment	05/21/2021	Drug Product
Labeling/Container Carton Draft,	05/31/2021	Labeling

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER/ SECONDARY REVIEWER	BRANCH/DIVISION
Drug Substance	Katherine Windsor Ali Al Hakim	OPQ/ONDP/DNDPAPI
Drug Product	Mike (William) Adams Anamitro Banerjee	OPQ/ONDP/DNDPI
OPMA/Facility	Yan Zheng/Yiwei Li	OPQ/OPMA/DMAIV
Microbiology	Amanda Buskirk/John Metcalfe	OPQ/OPF/DMA

Biopharmaceutics	Gerlie Gieser/Banu Zolnik	OPQ/ONDP/DB/
Regulatory Business Process Manager	Kristine Leahy	OPQ/OPRO/RBPMI
Application Technical Lead	Banu Zolnik	OPQ/ONDP/DB
Laboratory (OTR)	NA	NA
ORA Lead	Caryn McNabb	ORA

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II	(b) (4)	(b) (4)	Adequate	03/11/2021 by Katherine Windsor	
	Type V			Adequate	4/25/2017 by Laura W. Moussa	MAPP 5015.5 (Rev.1)
	Type III			Adequate	6/15/2017 by Daneli Lopez Perez	

B. Other Documents: *IND or sister applications*

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

2. CONSULTS

None

Executive Summary

I. Recommendations and Conclusion on Approvability

From a Pharmaceutical Quality perspective, NDA 215179 is recommended for COMPLETE RESPONSE.

Summary of Quality Assessments

A. Product Overview

Shilpa Medicare Ltd has submitted this NDA 215179 for Pemetrexed injection, a sterile, ready-to-use solution.

This 505(b)(2) NDA for Pemetrexed Injection, 10 mg/mL relies for approval, at least in part, on the FDA's efficacy and safety findings for the Listed Drug (LD) product, ALIMTA® (pemetrexed) For Injection (NDA 021462). ALIMTA was approved on February 04, 2004 for the treatment of patients with locally advanced or metastatic nonsquamous non-small cell lung cancer as well as mesothelioma and is available as a lyophilized powder (100 mg and 500 mg per vial).

Pemetrexed Injection, 10 mg/mL is a clear, colorless to pale yellow to greenish yellow ready-to-use solution presented in a 10 mL (100 mg), 50 mL (500 mg) and 100 mL (1000 mg) single-dose glass vial. Product strength is based on Pemetrexed as the anhydrous, (b) (4) The proposed product differs from Alimta by the inclusion of L-Cysteine as an (b) (4) and in the presentation of a prepared solution which does not need to be diluted before administration.

Proposed Indication(s) including Intended Patient Population	• in combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations. (1.1) • in combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous, non-small cell lung cancer (NSCLC). (1.1) • as a single agent for the maintenance treatment of patients with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. (1.1) • as a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy. (1.1)

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

B. Quality Assessment Overview

DRUG SUBSTANCE: ADEQUATE
Pemetrexed disodium is a folate analog metabolic inhibitor. The drug substance is isolated as the hemipentahydrate, which is soluble in water. There is a USP monograph for pemetrexed disodium (listing heptahydrate, anhydrous, and free acid forms, but not the hemipentahydrate form). The Applicant cross-referenced the CMC information for pemetrexed disodium hemipentahydrate drug substance to DMF (b) (4) DMF (b) (4) was last reviewed by Katherine Windsor, Ph.D. (final signature 11-MAR-2021) and found adequate to support NDA 215179. 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) months for pemetrexed disodium (hemipentahydrate) drug substance stored at (b) (4) The Drug Substance Reviewer recommended for **Approval**.
DRUG PRODUCT: ADEQUATE
Pemetrexed Injection, 10 mg/mL is a clear, colorless to pale yellow to greenish yellow ready-to-use solution presented in a 10 mL (100 mg), 50 mL (500 mg) and 100 mL (1000 mg) single-dose glass vial. Product strength is based on Pemetrexed as the anhydrous, (b) (4). The requisite volume of drug solution is transferred from the vial(s) into an IV bag and immediately administration over 10 minutes by an infusion pump. Components: Formulation ingredients are acceptable. Forced degradation study shows acid hydrolysis and control have essentially the same degradation profile. Product is sensitive to pH and oxygen. Vial overfill is acceptable. Formulation overage is not needed. All the excipients are commonly used in the manufacture of medicinal products for human consumption. None of the excipients are novel or of human origin.

Based on the stability studies, the proposed storage statement is "Store at 20-25ºC (68-77ºF) excursions permitted to 15-30ºC (59-86ºF)

The available stability 18-month data is sufficient to support the Shilpa requested (b) (4) month initial shelf life.

The Drug Product reviewer recommended for **Approval.**

PROCESS: ADEQUATE
FACILITIES: INADEQUATE

The drug product manufacturing facility is currently in (b) (4)
The drug substance manufacturing facility is approved. The product manufacturing process includes (b) (4) the proposed manufacturing process is acceptable

The Process and Facilities Reviewer recommended for **Complete Response**.

MICROBIOLOGY: ADEQUATE

The microbiology review covers sterility assurance and microbiological quality of the drug product.

The applicant has met regulatory expectations for:

- verification of container closure integrity
- validating the temperature (b) (4) .
- validating the process used for sterilization and depyrogenation of the subject container.
- the microbiological test methods and acceptance criteria that are used to assess release specifications.
- the endotoxin test method, acceptance criteria and verification of the suitability of use of the bacterial endotoxins test that will be performed on the drug product prior to its release.
- the design of the stability testing program to support the drug product's microbiological quality throughout its shelf-life.
- post-approval stability protocol and commitment that ensures microbial quality over the proposed shelf-life of the drug product.
- adequate stability data to illustrate the drug product meets the bacterial endotoxins and sterility stability specification for at least 12 months under long-term storage conditions.

The Microbiology Reviewer recommended for **Approval.**

BIOPHARMACEUTICS: INADEQUATE

The proposed injectable drug product is already a solution that does not require dilution prior to administration. In addition to pharmaceutical form (powder/solid vs.

solution/liquid) and additional presentation (1000 mg/vial), the proposed ready-to-use (RTU) solution drug product differs mainly from the LD in terms of

i) Pemetrexed disodium polymorphic hydrate form (hemipentahydrate instead of heptahydrate);

ii) Formulation composition (contains L-cysteine hydrochloride [redacted] (b) (4) as [redacted] (b) (4) sodium chloride as [redacted] (b) (4), and water for injection as [redacted] (b) (4) in addition to mannitol and pH adjusting agents present in the LD);

iii) Slightly higher osmolality of the final infusion product as compared to the LD's final infusion solution;

iv) Although both proposed and LD products are given via the same administration route & duration/rate (IV infusion over 10 minutes), there is a difference between products with regard to the preparation/handling steps prior to administration, and (depending on the patient's body surface area or BSA), there may also be a difference in final infusion volume and final drug concentration. Specifically, the required volume of the RTU solution (proportional to the patient's BSA; not always 100 mL) is transferred to an empty sterile IV bag *immediately* prior to administration with the aid of an infusion pump, whereas in the case of the LD the required volume of the reconstituted solution is diluted further into an IV bag containing 0.9% Sodium Chloride Injection for a fixed final infusion volume of 100 mL. Additionally, unlike the LD which is diluted to a final drug concentration that varies based on the patient's BSA , the proposed solution drug product's final infusion concentration is fixed at 10 mg/mL, regardless of patient BSA.

At the time of this review's cut-off date, the Applicant was not able to provide the requested data that would demonstrate that the difference in handling and preparation between the proposed "ready-to-use" solution injectable drug product and the LD's final infusion would not result in a significant difference in delivered dose of pemetrexed to the patient. Thus, it is concluded that the submitted comparative in vitro data and additional CMC data for the proposed drug product are not sufficient to establish the scientific bridge between the proposed drug product and the relied upon LD product, i.e., in accordance with 21 CFR 320.24(b)(6).

The Biopharmaceutics Reviewer recommended for Complete Response.

C. Special Product Quality Labeling Recommendations

NA

D. **Final Risk Assessment**

FROM INITIAL RISK IDENTIFICATION			REVIEW ASSESSMENT		
Attribute	**Factors that can impact the CQA**	**Initial risk ranking**	**Risk mitigation approach**	**Final risk evaluation**	**Lifecyle consideration**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment • Site	H	(b) (4)	L	
Endotoxin Pyrogen	• Formulation • Container closure • Process parameters • Scale/equipment • Site	M	Control of components depyrogenation steps and testing of drug product	L	
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		L	
Assay (b) (4)	Formulation • Raw materials • Process parameters • Scale/equipme	L		L	

	nt • Site				
Uniformity of Dose (Fill Volume/deliverable volume)	• Formulation • Container closure • Process parameters •Scale/equipment • Site	L		**M**	Upon transferred to infusion bag, amount of delivered dose of this ready-to-use injection has not been confirmed.
Osmolality **Os**	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L		L	
pH-	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L		L	
Leachable extractables	Formulation • Container closure • Raw materials • Process parameters	L		L	

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

Banu S. Zolnik, Ph.D.
Application Technical Lead, NDA 215179

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CHAPTER III: ENVIRONMENTAL

IQA NDA Assessment Guide Reference

R REGIONAL INFORMATION

EA assessment is covered under Chapter 2 Drug Product review

LABELING
Amendment SD-013 02/26/21
Amendment SD-015 03/16/21

R Regional Information

1.14 Labeling

VIAL LABELS (SD-015)

Vial Label – Pemetrexed Injection 100 mg/10 mL (10 mg/mL
Vial Label - Pemetrexed Injection 500 mg/50 mL (10 mg/mL)
Vial Label - Pemetrexed Injection 1000 mg/100 mL (10 mg/mL)

[redacted] (b) (4)

Each mL contains 10 mg pemetrexed (equivalent to 12.1 mg pemetrexed disodium hemipentahydrate)
Recommended Dosage: See prescribing information
Store at 20-25ºC (68-77ºF); excursions permitted to 15-30ºC (59-86ºF) [See USP Controlled Room Temperature].
[redacted] (b) (4)

Rx only NDC 63759-3048; 3049; 3050-1
Pemetrexed Injection
100 mg/10 mL; 500 mg/50 mL; 1,000 mg/100 mL
(10 mg/mL)
For intravenous infusion only
Single dose vial
Discard unused portion
Administer Undiluted
[redacted] (b) (4)

[Barcode]
Lot#/Expiry date
Manufactured by
(logo)
Shilpa Medicare Limited
Jadcherla – 509301
INDIA.
Issue 0 [redacted] (b) (4)

Reviewer's Assessment: Acceptable
Except for the content statement, all CMC information is complete and correct for all 3 vial labels. Content statement is revised per the USP Salt Policy.

CARTON LABELS (SD-015)

Carton Label – Pemetrexed Injection 100 mg/10 mL (10 mg/mL
Carton Label - Pemetrexed Injection 500 mg/50 mL (10 mg/mL)
Carton Label - Pemetrexed Injection 1000 mg/100 mL (10 mg/mL)

(front/back panel)
Note Concentration:
10 mg/mL
Rx only NDC 63759-3048; 3049; 3050-1
Pemetrexed
Injection
100 mg/10 mL; 500 mg/50 mL; 1,000 mg/100 mL
(10 mg/mL)
For intravenous infusion only
Single dose vial.
Discard unused portion.
Administer undiluted
(b) (4)

(left side panel)
(b) (4)
Each mL contains 10 mg pemetrexed (equivalent to 12.1 mg pemetrexed disodium hemipentahydrate)
Recommended Dosage: See prescribing information
Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].
(b) (4)

(right panel)
[Barcode]
Manufactured by
(logo)
Shilpa Medicare Limited
Jadcherla – 509301
INDIA.
Issue (b) (4)

(top)
Rx only NDC 63759-3048; 3049; 3050-1
Pemetrexed
Injection
100 mg/10 mL; 500 mg/50 mL; 1,000 mg/100 mL
(10 mg/mL)
barcode

(bottom)
barcode

lot#, expiry date

Reviewer's Assessment: Acceptable
Except for the content statement all CMC information is complete and correct for all 3 carton labels. Content statement is revised per the USP Salt Policy.

PACKAGE INSERT (SD-013)
Highlights
(Title) **PEMETREXED INJECTION, for intravenous use**

DOSAGE FORMS AND SRENGTHS
* Injection: 100 mg/10 mL, 500 mg/50 mL, 1000 mg/100 mL in single dose vials (3)

Full Prescribing Information

(b) (4)

(b) (4)

[redacted]

3. DOSAGE FORMS AND STRENGTHS

(b) (4)

[redacted]

11. DESCRIPTION

(b) (4)

[redacted]

16. HOW SUPPLIED/STORAGE AND HANDLING

(b) (4)

[redacted]

(b) (4)

[redacted]

Reviewer's Assessment: Acceptable

Highlights: Acceptable

Section 2.7: It is presumed that the full dose will be administered from the IV bag.

Section 3: DMEPA wanted "1000 mg" expressed as "1 g" to prevent confusion.

Section 11: Except for the grammatical comments below and the content statement, the CMC information is complete and correct. "Disodium" and Hemihydrate" in the chemical name, and the ingredient names should not be capitalized since these are descriptors, not formal names. For consistency with the rest of the statement, amounts should be listed as whole numbers. "Cystine" is misspelled; should be "Cysteine. The content statement is revised per the USP Salt Policy.

Section 16: Acceptable. The CMC information is complete and correct.

'Mfg by' statement: Acceptable. Information is correct.

List of Deficiencies: None

Primary Labeling Reviewer:

William Adams, CMC reviewer, ONDP

Secondary Reviewer:

Anamitro Banerjee, Branch Chief, ONDP

William Adams

Digitally signed by William Adams
Date: 5/27/2021 09:14:53AM
GUID: 508da7220002a12c3e992e212029c42b

Anamitro Banerjee

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Date: 5/27/2021 09:22:40AM
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Yan Zheng

Digitally signed by Yan Zheng
Date: 5/04/2021 08:06:05AM
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Yiwei Li

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Date: 5/04/2021 08:07:25AM
GUID: 5424aeae00c3275e27e75fc260f140b5

CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	215179
Assessment Cycle Number	Original 505(b)(2) NDA
Drug Product Name/ Strength	Pemetrexed Injection 10 mg/mL (presented as 100 mg/10 mL, 500 mg/50 mL, 1000 mg/100 mL Ready-To-Use/RTU solution in single-dose vials)
Route of Administration	For Intravenous Infusion
Applicant Name	Shilpa Medicare LLC
Therapeutic Classification/ OND Division	Anticancer: Folate analog metabolic inhibitor DO2
Listed Drug Product Relied Upon	ALIMTA® lyophilized powder for reconstitution and further dilution [NDA 21462]
Proposed Indication	Treatment of non-squamous, non-small cell lung cancer

Assessment Recommendation: **COMPLETE RESPONSE**

Assessment Summary:

This 505(b)(2) NDA for Pemetrexed Injection, 10 mg/mL relies for approval, at least in part, on the FDA's efficacy and safety findings for the Listed Drug (LD) product, ALIMTA® (pemetrexed) For Injection (NDA 021462).

Unlike ALIMTA® which is a lyophilized powder for reconstitution and further dilution into a solution prior to IV infusion, the proposed injectable drug product is already a solution that does not require dilution prior to administration. In addition to pharmaceutical form (powder/solid vs. solution/liquid) and additional presentation (1000 mg/vial), the proposed ready-to-use (RTU) solution drug product differs mainly from the LD in terms of ***i)*** pemetrexed disodium polymorphic hydrate form (hemipentahydrate instead of heptahydrate); ***ii)*** formulation composition (contains L-cysteine hydrochloride (b) (4) as (b) (4) sodium chloride as (b) (4), and water for injection as (b) (4), in addition to mannitol and pH adjusting agents present in the LD); ***iii)*** slightly higher osmolality of the final infusion product as compared to the LD's final infusion solution; ***iv)*** a slightly higher level of measured specific and total impurities during long-term storage at controlled room temperature. ***v)*** Furthermore, although both proposed and LD products are given via the same administration route & duration/rate (IV infusion over 10 minutes), there is a difference between products with regard to the preparation/handling steps prior to administration, and (depending on the patient's body surface area or BSA), there may also be a difference in final infusion volume and final drug concentration. Specifically, the required volume of the RTU solution (proportional to the patient's BSA; not always 100 mL) is transferred to an empty sterile IV bag *immediately* prior to administration with the aid of an infusion pump, whereas in the case of the LD the required volume of the reconstituted solution is diluted further into an IV bag containing 0.9% Sodium Chloride

Injection for a fixed final infusion volume of 100 mL. Additionally, unlike the LD which is diluted to a final drug concentration that varies based on the patient's BSA , the proposed solution drug product's final infusion concentration is fixed at 10 mg/mL, regardless of patient BSA.

At the time of this review's cut-off date, the Applicant was not able to provide the requested data that would demonstrate that the difference in handling and preparation between the proposed "ready-to-use" solution injectable drug product and the LD's final infusion would not result in a significant difference in delivered dose of pemetrexed to the patient. Thus, it is concluded that the submitted comparative in vitro data and additional CMC data for the proposed drug product are not sufficient to establish the scientific bridge between the proposed drug product and the relied upon LD product, i.e., in accordance with 21 CFR 320.24(b)(6).

List of Submissions Reviewed:

Document(s) Assessed	Date Received
SDN-1 (Original)	8/27/2020
SDN-2 (Response to Drug Product Reviewer's IR – Preparation & Administration Section of Labeling)	10/16/2020
SDN-7 (Response to Biopharmaceutics IR)	1/19/2021
SDN-8 (Response to DP Manufacturing & Micro IR)	2/2/2021
SDN-9 (Response to DMEPA IR)	2/4/2021
SDN-11 (Response to DP IR – Extractables & Leachables, Elemental Impurities, Unspecified Impurities, Excipient Specifications, Drug Product Specifications	2/19/2021
SDN-12 (Response to 1st Follow-up Biopharm IR/set 2 – highest strength in vitro PB binding study, add'l data for 100 mg/vial LD product	2/24/2021
SDN-13, SDN-14, SDN-15 (Response to Labeling IRs)	2/26/2021, 3/5/2021, 3/16/2021
SDN-16 (Response to 2nd Follow-up Biopharm IR/set 2 – highest strength in vitro PB binding study, add'l data for 100 mg/vial LD product	5/10/2021
SDN-17 (Response to DP IR – L-cysteine content)	5/21/2021

Concise Description of Outstanding Issues:
-Deliverable Volume/Dose from the IV Bag

B.12 BRIDGING OF FORMULATIONS USED IN THE DEVELOPMENT OF PROPOSED DRUG PRODUCT

Assessment: *Adequate*
[***Reviewer Note***: (b) (4) .
Additionally, should new registration batches of the proposed drug product be required by FDA at the time of NDA Resubmission, this bridging assessment will be revisited.]

The comparative *in vitro* physicochemical characterization studies included in the initial NDA submission evaluated *developmental* lots of the proposed drug product.

Thus, per FDA's request, the Applicant provided additional comparative physico-chemical and in vitro protein binding data (i.e., relative to the Listed Drug product) for the exhibit batches (which were manufactured at the proposed commercial batch scale by the proposed commercial drug product manufacturer using drug substance from the proposed commercial API supplier).

The ALIMTA® lots used in comparative *in vitro* physicochemical, and protein binding studies were not expired.

Note that the proposed to-be-marketed drug product was not evaluated in clinical studies.

B. 13 BIOWAIVER REQUEST OR CROSS-PRODUCT BRIDGING

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

This 505(b)(2) NDA for Pemetrexed (Ready-To-Use Solution) Injection, 10 mg/mL, relies for approval on the FDA's findings of efficacy and safety for ALIMTA® (pemetrexed disodium) For Injection (NDA 021462), as well as (at least in part) the nonclinical and clinical pharmacology information in the LD's approved labeling. The noted similarities and differences between the proposed drug product and the relied upon Listed Drug are tabulated below. 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), comparative physicochemical, comparative in vitro protein binding characterization studies, as well as stability testing of the proposed drug product (packaged in glass vials), and survey of the Inactive Ingredients Database and package inserts of CDER approved drug products were conducted by the Applicant.

Note that during the original NDA review the Applicant was informed by FDA that the request to waive clinical BE testing of the proposed pemetrexed (b) (4)) solution injectable drug product cannot be granted via 21 CFR 320.22(b)(1) because

the proposed injectable solution drug product is not qualitatively and quantitatively (Q1/Q2) the same as the relied upon Listed Drug (LD) product. Instead, the scientific bridge to ALIMTA® (Listed Drug product, LD) could potentially be established via 21 CFR 320.24(b)(6).

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

	Proposed Drug Product Pemetrexed (Ready-To-Use Solution) Injection, Shilpa Medicare, LLC	**Listed Drug Product Being Relied Upon** ALIMTA® (pemetrexed for injection); NDA 021462, Eli Lilly & Company
Dosage Form; Strength(s)/Presentation	Ready-To-Use (RTU) Solution; 10 mg pemetrexed (b) (4) /mL (single-dose vials containing 100 mg/10 mL, 500 mg/50 mL, and 1000 mg/100 mL RTU solution)#	Lyophilized Powder for Reconstitution and Further Dilution with preservative-free NSS (single dose 100 mg, and 500 mg (b) (4) vial)
Formulation Composition	Each glass vial of 100 mg/10 mL RTU solution contains (in addition to pemetrexed disodium hemipentahydrate equivalent to 100 mg pemetrexed+) Mannitol (100 mg) L-cysteine HCl (b) (4) (10 mg) Sodium Chloride (90 mg) Water for Injection (q.s. ad 10 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/Infusion Volume	Final drug concentration = fixed (10 mg/mL regardless of patient BSA) ***To Be Administered Undiluted*** Final Infusion Volume = variable (not necessarily 100 mL; calculated depending on the patient BSA) Sample Dosing & Administration Scenarios: (a) For BSA = 2.0 m^2: 1000 mg/100 mL (10 mg/mL,100 mL); same final drug concentration and volume as the LD (b) For BSA = 1.0 m^2: 500 mg/50 mL (10 mg/mL, 50 mL) (c) For BSA =0.2 m^2: 100 mg/10 mL (10 mg/mL, 10 mL)	Final drug concentration = variable (calculated depending on the required pemetrexed dose based on patient BSA) ***Dilute the required volume of the reconstituted product (25 mg/mL) with 0.9% NaCl Solution*** Final Infusion Volume = fixed (100 mL regardless of patient BSA) Sample Dosing & Administration Scenarios: (a) For BSA = 2.0 m^2: 10 mg/mL upon dilution with NSS to 100 mL (b) For BSA = 1.0 m^2: 5 mg/mL upon dilution with NSS to 100 mL (c) For BSA =0.2 m^2: 1 mg/mL upon dilution with NSS to 100 mL
Proposed Indications/Dosing Regimen	Indications and Dosing Regimens the same as LD	

Preparation and Administration	After transferring the appropriate volume of the RTU solution from the vial into an empty IV bag, administer *immediately* as a 10 min-IV infusion.	After dilution of the appropriate volume of reconstituted solution with 0.9% NaCl Injection (preservative-free) to a total volume of 100 mL, administer as a 10-min IV infusion.
Physico-chemical properties of the final dilution for IV infusion		
Appearance	Clear, colorless solution; free from visible particulates	
Assay	*As is: 101.7%, 100.8%, 101.1%*[a,b,c,f] *(97.6% or higher during stability testing)* [Proposed ranges: (b) (4) % of label claim/LC (release); (b) (4) % (shelf-life)]	Before Reconstitution (100 mg/vial): Reconstituted/Before dilution: ND *After dilution: 106%, 104.2%*[d,e] [Approved range: (b) (4) % of LC]
pH	*As is: 7.036, 7.166, 7.171; 7.2 – 7.6 during stability testing* [Proposed range: (b) (4) (release & shelf-life);	Reconstituted/Before dilution: ND *After dilution: 6.955, 6.928* [Approved range: (b) (4)]
Osmolality (mOsm/kg)	*As is*: 445, 423, 423	Reconstituted/Before dilution: ND *After dilution: 391, 376*
Viscosity (mm^2/s)	*As is*: 1.15, 1.12, 1.13[f]	Reconstituted/Before dilution: ND *After dilution: 1.12, 1.13*
Specific gravity	As is: 1.01 – 1.01[f]	Reconstituted/Before dilution: ND *After dilution: 1.01 – 1.01*
In Vitro Protein Binding (%, mean) 0.5 mcg/mL 200 mcg/mL 10 mg/mL pemetrexed	 68.6% 63.4% 13.7%	 75.7% 68.5% 14.4%
Recommended storage during product shelf-life (and upon preparation, if applicable)	RTU – USP Controlled Room Temperature (Use solution in the IV bag immediately.)	Powder – USP Controlled Room Temperature (Use both reconstituted and diluted solution within 24 hours of preparation under refrigeration.)
Container-closure	USP Type I glass vial with (b) (4) rubber stopper with aluminium seal	
Physico-chemical & microbiological stability		
Total Impurities/ Degradants	(b) (4) %, (b) (4) %, (b) (4) % NMT (b) (4) % (during 6 months at 40°C/75%RH, and at least up to **18** months at 25°C/60%RH)	BQL
Sterility	Achieved by (b) (4) of the finished solution drug product in vials; maintained during 6 months accelerated and at least up to 12 months of long-term stability testing of the RTU solution	-
Bacterial Endotoxins (NMT (b) (4) EU/mg of Pemetrexed)	Conforms during initial and later (up to Month 6 Accelerated and at least up to 12 months long-term) stability time points	-
	1. Extractable Volume: NLT nominal volume (e.g., NLT (b) (4) mL for 100 mg/10 mL) At Release | During Shelf-Life	Reconstitution time = NMT (b) (4) sec

Special QC specifications (tests and acceptance ranges) proposed/approved	2. Assay of L-cysteine hydrochloride (by HPLC)	NLT (b) (4)%	NLT (b) (4)%	-
	3. Impurities	At Release	During Shelf-Life	
	Ketopemetrexed (Pemetrexed (b) (4)	ND	ND	(b) (4): NMT (b) (4)% Largest Unspecified Impurity: NMT (b) (4)% Total Impurities NMT (b) (4)%
	(b) (4)	NMT (b) (4)%	NMT (b) (4)%	
	Impurity-D (b) (4)	NMT (b) (4)%	NMT (b) (4)%	
	Any unspecified impurity	NMT (b) (4)%	NMT (b) (4)%	
	Total impurities	NMT (b) (4)%	NMT (b) (4)%	
	4. (b) (4)	NMT (b) (4)%	NMT (b) (4)%	

[a, b, c] = unless otherwise specified, the values noted are for 10 mL, 50mL, 100 mL RTU, respectively, at batch release
[d,e] = unless otherwise specified, the values noted are for 100 mg/vial and 500 mg/vial ALIMTA, reconstituted and diluted
[f] = 17 to 18 month old RTU sample
BQL: Below Quantification Limit; ND: Not Determined
[+] Since the API is hygroscopic (i.e., gains moisture from the atmosphere when exposed to a level of about (b) (4)%), the amount of hemipentahydrate to be used (to obtain an equivalent amount of the pemetrexed (b) (4) is to be calculated using a formula that factors in the moisture content and the potency of the drug substance
[#] The proposed labeling states (b) (4)

Target fill volumes (b) (4) based on USP recommended excess volume for non-viscous liquids)
***Tentative proposed expiration dating period = (b) (4) months (RT)

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

Justification for

1. *Difference in crystalline hydrate 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. The Applicant provided the solubility data of the hemipentahydrate form of pemetrexed disodium in various aqueous media which confirmed relatively high solubility in water, and in pH 6.0 and 8.0 buffer media (50 mg/mL at 25 °C) and slightly lower solubility in pH 1.2 medium (2 mg/mL at 25 °C), as well as information that both the proposed RTU drug product (as is) and the final dilution of the LD yielded clear, colorless solutions. Additionally, the provided stability data of the proposed RTU solution drug product demonstrated freedom from particulates (indicative of visually complete solubility). It is also noted that the proposed pemetrexed (10 mg/mL) solution product's pH is maintained at a range of (b) (4), conditions that are favorable for maintaining the drug in solution.

   NOT FOR FOIA: Based on the ALIMTA NDA data, both hemipentahydrate and heptahydrate forms of pemetrexed disodium are highly soluble in water; however, the

heptahydrate form is less hygroscopic [redacted]

The Drug Substance Reviewer (Dr. Katherine Windsor) considers the cross-referenced DMF [redacted] adequate to support this NDA.

2. *Difference in Formulations/Excipients – Impact on product quality*

As shown in the product comparison table above, the major difference in composition between the proposed ready-to-use/RTU solution product and the final infusion solution prepared from the relied upon LD powder is the presence/absence of the L-cysteine [redacted] (as [redacted]). The Drug Product Reviewer considers the amount of added L-cysteine in the formulation of the proposed RTU solution drug product acceptable from a product stability perspective. Additionally, based on the provided 6 months accelerated and 18 months long-term stability data for the proposed drug product, the Drug Product Reviewer requested revision of the proposed residual amounts of L-cysteine from 'NLT[redacted]%' to 'NLT[redacted]%' of label claim to ensure sufficient levels of the [redacted] remains during the entire proposed product's shelf-life. Refer also to the discussion below under *Justification Item #6. Difference in Pharmaceutical Dosage Form and Presentation - Impact on product quality.*

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

In Study GVK/CC/NG-2021-011, the percentage of plasma protein binding *in vitro* was comparable between the test product and the reference product (ALIMTA, 500 mg/vial Batch# S20A014C) at the studied final drug concentrations of 0.5 mcg/mL,200 mcg/mL, and 10 mg/mL in human plasma. The test product was produced by combining the appropriate volumes of the pemetrexed stock solution (25 mg/mL, Batch# PEMP1120) and the vehicle [redacted] to achieve the desired final concentrations of the active and inactive ingredients in proportions that are present in the proposed drug product. Based on the observed comparable *in vitro* protein binding data, a significant difference in *in vivo* drug distribution between the proposed and the reference drug products is not anticipated.

This Reviewer notes that the level of mannitol in the proposed ready-to-use injectable solution is almost exactly the same as that present in the final dilution of the LD, which is advantageous in terms of the assessment of comparable PK between products (since it is known that very high amounts of mannitol in a product could influence renal elimination due to this excipient's diuretic effect, and pemetrexed is excreted unchanged in the urine to a significant extent). Thus/However, it is not clear to this Reviewer why a [redacted] mannitol would be needed for a product that does not undergo lyophilization or freeze-drying or does not need to be filled into capsules or tableting equipment during manufacture because it is a solution drug product.

4. *Difference in Formulations/Excipients – Impact on drug product safety/tolerability*

Per the Applicant, the levels of excipients (except of the added (b) (4) L-cysteine hydrochloride (b) (4)) in the proposed drug product's formulation are within the IIG limits for the intravenous route of administration, as shown in the following table. The Applicant justified the level of the L-cysteine (100 mg for patient with BSA = 2.0 m^2) based on the 490 mg total daily intake of ELCYS® (cysteine hydrochloride injection) for a 70 kg stable or critically ill adult patient requiring 7 mg amino acid for total parenteral nutrition. The Pharmacology/Toxicology Reviewer (Dr. M A Goheer) confirmed that the level of L-cysteine in the proposed drug product (i.e., up to (b) (4) mg L-cysteine for a patient with BSA =2.0 m^2) is covered by levels present in intravenously administered parenteral nutrition, does not require safety qualification, and thus, is acceptable from a safety/toxicity perspective.

Inactive ingredients quantities and IIG limits

Name of the Ingredient	10 mg/mL % w/v or % v/v	Maximum Quantity Accepted by FDA for Injectable* (%)
Mannitol	1% w/v	4.95%w/v
Sodium Chloride	0.9% w/v	0.9%w/v
(b) (4) (b) (4)	0.1% w/v	0.03 %w/v- Injection IV 15 mg- Injection IV#
Sodium Hydroxide	QS	-
Hydrochloric acid (b) (4)%	QS	-

*** eIID Database Last Updated: July 28, 2020**

Additionally per the Applicant, that the proposed RTU drug product is hypertonic should not result in any injection site reactions at the time of administration because the risk of chemical phlebitis occurs when the osmolality of the injectable solution is higher than 450 mOsm/L (Stranz, Int J Pharm Compounding, 2002). It is important to note that the proposed ready-to-use drug product's osmolality is only slightly higher as compared to the LD's final infusion solution which is desirable in terms of comparative systemic safety and local tolerability assessments. As indicated above, other than to more closely match the composition (and thus, tonicity) of the relied upon Listed Drug product, it is not clear to this Reviewer what the added mannitol serves in the proposed ready-to-use solution formulation/drug product.

5. *Difference in Dosage Form and Presentation – Impact on Clinical Outcomes (including Medication Errors)*

All single-dose vial presentations of the proposed and Listed Drug (LD) products will have the same pharmaceutical form (solution) at the point of patient contact, the same IV administration route & rate (as 10-min IV infusion), and indications of use.

However, whereas the LD is a powder that is reconstituted to a pemetrexed concentration of 25 mg/mL, the required volume of which is then diluted with 0.9% Sodium Chloride Injection to a final infusion volume of 100 mL, the proposed solution drug product contains a fixed pemetrexed concentration of 10 mg/mL and does not require dilution prior to administration. Thus, depending on body surface area, a patient being switched to the proposed drug product may not receive the same final drug concentration and/or total infusion volume as received when being administered the LD.

Mainly because of the limitations posed by the selected container-closure system (glass vial) of the proposed "ready-to-use" injectable solution drug product, special preparation and handling steps for the final infusion solution are necessary. FDA requested the Applicant to revise the proposed labeling in order to provide clarity regarding how the proposed RTU solution is to be administered directly from the vial as a 10-minute IV infusion, and to provide justification that use of partial vials or multiple vials to afford BSA-based dosing would not result in wrong dose medication errors. The Applicant clarified that the calculated volume of the RTU solution will be withdrawn from the vial(s) and transferred into an empty IV bag. To minimize the risk of medication errors, the proposed drug product's labeling was revised per DMEPA recommendations. Specifically, highlighting will be added to "10 mg/mL" to emphasize the availability of the proposed product in a new pemetrexed concentration, i.e., different from other pemetrexed solutions currently marketed. Additionally, a "Note Concentration" banner will be added to the carton's principal display panel. Moreover, to avoid overdosage errors due to the administration of the entire content of the vial(s) when an aliquot of the solution should have been withdrawn and then transferred to an empty IV bag to deliver the correct dose, the Applicant agreed to (b) (4) Refer to the DMEPA Label and Labeling Review for additional information. ***Note that the Applicant's Response to the following FDA information request had not been received by the requested due date and extension date:***

In Section 2.7 of the proposed labeling, (b) (4) (b) (4) *Provide deliverable dose data to demonstrate that the transferred dose to and from the vented IV bag (when administered over 10 minutes using an infusion pump) are comparable. In performing this study, we recommend 1)positioning the pump next to the IV needle, using the smallest possible empty IV bag, and other additional specified measures to prevent delivered dose loss, 2) for patient BSA ranging from 0.5 m2 to 2.0 m2, and 3) ALIMTA final infusion as the internal control.*

Also this Biopharmaceutics Reviewer requested the assigned Medical Officer (Dr. Janice Kim) to provide clinical's assessment of whether the differences between the proposed and the LD products in terms of final infusion volume, drug concentration, manner of administration, and handling prior to dosing/administration is not anticipated to pose significant differences in clinical outcomes; refer to the Medical Reviewer's memo for additional information.

Note that due to the absence of dedicated in-use stability data and compatibility data with various different commercially available empty IV bags, the Drug Product Reviewer will recommend that the proposed drug product labeling state that upon transfer of the required volume of the proposed solution drug product to the IV bag, infusion administration should be done immediately.

That the proposed drug product is to be also marketed with a 1000 mg/vial presentation (which is not commercially available for the Listed Drug product ALIMTA) is reasonable because the recommended dose of pemetrexed is 500 mg/m^2. Therefore, the 1000 mg/100 mL presentation of the proposed RTU solution drug product would be suitable for use by patients with BSA approaching 2.0 m^2.

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

At the time of comparative *in vitro* testing, the LD had 'below quantifiable levels' of total impurities/degradants in the diluted solution prepared from the lyophilized product. On the other hand, the exhibit batches of the proposed Ready-To-Use Injectable Solution drug product, during 6 months of accelerated (40 ± 2 °C/75 ±5 RH) and 12 months of long-term (5 ± 3 °C, and 25°C± 2°C; RH: 60%±5%) stability testing, exhibited NMT (b) (4)% total impurities.

The proposed acceptance ranges for finished drug product Assay, Specific and Total Impurities are wider or more permissive during shelf-life/stability testing than at batch release of the proposed drug product. It does not appear that keto-pemetrexed impurity levels are not proposed to be quantified during routine QC testing of the proposed drug product; however, the Drug Product Reviewer requested revision of related substances to include all unspecified impurities at or above the limit of detection (LOD (b) (4)%) of the HPLC method. Additionally, the proposed tolerance limits for Total Impurities during shelf-life is slightly higher than those approved for the Listed Drug product (NMT (b) (4)% versus NMT (b) (4)%), which was deemed comparable/acceptable by the Drug Product Reviewer. Per the Process Reviewer (Dr. Yan Zheng) the proposed drug product manufacturing process and associated in-process controls including the proposed (b) (4) Based on the provided 18 months long-term stability data, the Drug Product Reviewer considers the proposed expiration dating period of (b) (4) months when

stored in the proposed commercial packaging configuration (glass vial) at controlled room temperature acceptable.

In an email discussion with the Microbiology Reviewer, Dr. Amanda Buskirk indicated that no further microbiological testing is required related to the additional handling instructions (i.e., transferring the appropriate volume of the proposed drug product to an empty sterile IV bag) prior to IV infusion because of the short administration time (10 minutes).

The proposed finished product QC specifications for batch release and shelf-life include control for [redacted] (NMT [redacted]%) in the vial which is intended to [redacted] of pemetrexed in solution. The Applicant stated that the chosen Type I clear colorless [redacted] glass vials conformed to tests specified for Type I glass containers in USP<660> Containers-Glass which includes a test for hydrolytic resistance of the inner surface of glass containers. Per the Drug Product Reviewer the results of the requested new studies for elemental impurities and extractables/leachables are acceptable. Note that like the LD, [redacted] rubber stopper is used for the packaging of the proposed RTD solution drug product.

The Applicant reported that the photostability of the proposed solution drug product in a clear glass vial is the same with and without a secondary (opaque carton) packaging. The Drug Product Reviewer confirmed that the forced degradation studies showed no light sensitivity for pemetrexed or L-cysteine.

R. REGIONAL INFORMATION

Post-Approval Commitments

None

Lifecycle Management Considerations

None

BIOPHARMACEUTICS LIST OF DEFICIENCIES

Response to Biopharmaceutics Information Request to address the issue related to deliverable dose

Primary Biopharmaceutics Assessor's Name and Date: Gerlie Gieser, Ph.D. (6/7/2021)

Secondary Assessor Name and Date (and Secondary Summary, as needed): Banu Zolnik, Ph.D. (06/07/2021)

Banu Zolnik

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Gerlie Gieser

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	215179
Assessment Cycle Number	1
Drug Product Name/ Strength	Pemetrexed Injection, 100 mg/10 mL, 500 mg/50 mL, and 1 g/100 mL
Route of Administration	Intravenous injection
Applicant Name	Shilpa Medicare Limited
Therapeutic Classification/ OND Division	OOD/DO2
Manufacturing Site	(b) (4)
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Original Submission	**8/27/2020**
Filing IR Response	**10/15/2020**
IR Response	**2/2/2021**

Highlight Key Issues from Last Cycle and Their Resolution: None

Remarks: Pemetrexed Injection is a new drug product submitted to OOD/DO2 (now known as OODP) intended for use as a first line therapeutic in patients with malignant pleural mesothelioma (b) (4) or metastatic non-small cell lung cancer. The reference listed drug (RLD) for the subject drug product is ALIMTA®, which is manufactured by Lilly USA, LLC. An information request was sent to the applicant on 1/19/2021 and the response was received on 2/2/2021. Responses are reviewed below.

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

Supporting Documents:
D11648M40R01.docx, dated 1/29/2020

S DRUG SUBSTANCE

The final drug product is subjected to [redacted] and [redacted]. Therefore, the drug substance will not be reviewed for sterility assurance.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- Description of drug product – Section 3.2.P.1, "Description and Composition of the Drug Product," pg. 2 of 8, Section 1.14.1.1, "Draft Carton and Container Labels"
  The drug product is a sterile, clear, colorless to pale yellow/greenish yellow solution for injection packaged in single dose vials.
- Drug product composition – Section 3.2.P.1, "Description and Composition of the Drug Product," pg. 3 of 8.
  The following table is adapted from the application:

Ingredient	Standard	mg/mL	Quality/Vial				Function
			100 mg/10 mL	500 mg/50 mL	1 g/100 mL	% w/v	
Pemetrexed disodium hemipentahydrate	IH	10	100 mg	500 mg	1000 mg	1%	[redacted]
Mannitol	USP – NF/Ph. Eur.	10	100 mg	500 mg	1000 mg	1%	
Sodium chloride		9	90 mg	450 mg	900 mg	0.9%	
L-cysteine hydrochloride [redacted]		1	10 mg	50 mg	100 mg	0.1%	
Sodium hydroxide		*q.s. to adjust pH					pH adjusting agent
Hydrochloric acid [redacted]%							
Water for Injection		q.s to 1 mL	q.s. to 10 mL	q.s. to 50 mL	q.s. to 100 mL	q.s. to 100%	[redacted]
[redacted]							

* q.s = quality sufficient

- Description of container closure system – Section 3.2.P.1, "Description and Composition of the Drug Product," pg. 4 of 8.

Component	10 mL fill volume	50 mL fill volume	100 mL fill volume
Container	10 mL/20 mm [redacted] glass vial	50 mL/ 20 mm [redacted] glass vial	100 mL/20 mm [redacted] glass vial
Closure	20 mm [redacted] rubber stopper		
Seal	20 mm light blue aluminum flip off seals		

Assessment: *Adequate*

The description of the drug product, drug product composition, and container closure system meets regulatory expectation.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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Amanda Buskirk

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John Metcalfe

Digitally signed by John Metcalfe
Date: 2/10/2021 12:54:13PM
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Comments: I concur with the primary reviewer's assessment.

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/

BANU S ZOLNIK
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