CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208746Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 10, 2022
From	Yang Nan, Ph.D. OPQ/ONDP/DNDP1
Subject	Cross-Discipline Team Leader Review
NDA	208746
Type of Application	505(b)(2)
Applicant	Hospira, Inc., a Pfizer company
Date of Receipt	December 22, 2021
PDUFA Goal Date	June 22, 2022
Proposed Proprietary/Established Name	NA/ pemetrexed for injection
Dosage forms/Strength	Powers for injection: 100 mg/vial, 500 mg/vial, and 1 gram/vial
Route of Administration	Intravenous
Proposed Indication(s)	1. Non-Squamous Non-Small Cell Lung Cancer (NSCLC) Pemetrexed for Injection is indicated: • In combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous, non-small cell lung cancer (NSCLC). • As a single agent for the maintenance treatment of patients with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. • As a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy. Limitations of Use: Pemetrexed for Injection is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer. 2. Mesothelioma Pemetrexed for Injection is indicated, in combination with cisplatin, for the initial treatment of patients with malignant pleural mesothelioma whose disease is unresectable or who are otherwise not candidates for curative surgery.
Recommended:	**Approval**

This cross-discipline team leader review is based on Integrated Quality Assessment (DARRTS, May 09, 2022), legal input from the 505(b)(2) committee, and interdisciplinary labeling review.

1. Introduction

The proposed Pemetrexed (as ditromethamine) for Injection is a sterile lyophilized powder (100 mg/vial, 500 mg/vial, and 1 g/vial presentations), intended to be reconstituted and then diluted with 0.9% Sodium Chloride Injection solution for intravenous administration. The submission is a 505(b)(2) application, relying on the listed drug (LD) Alimta (NDA 021462) for safety and efficacy. Alimta is available in 100 mg and 500 mg single-dose vials; the proposed drug product is available in three strengths: 100 mg, 500 mg and 1 gram in single-dose vials. The therapeutic active moiety (pemetrexed), dosage form and route of administration of the proposed drug product are identical to the listed drug product. However, the proposed drug product differs from LD in salt form of the active moiety. Alimta contains the drug substance pemetrexed in *disodium salt form*, mannitol, and hydrochloric acid or sodium hydroxide as pH adjuster; the proposed drug product contains pemetrexed in *ditromethamine salt form* and mannitol but does not contain pH adjuster.

In support of the equivalence of the LD and the proposed drug product, the Applicant provided comparative physicochemical properties and a bio-waiver request. Clinical data was not submitted in the application.

The original NDA submission was dated on September 15, 2016; the agency issued Complete Response Letter on July 10, 2017, citing Facility deficiency. The resubmission was received on July 10, 2020 and assessed as adequate. A tentative approval letter was issued to the Applicant on January 8, 2021. In the current submission, the Applicant seeks full approval of the NDA.

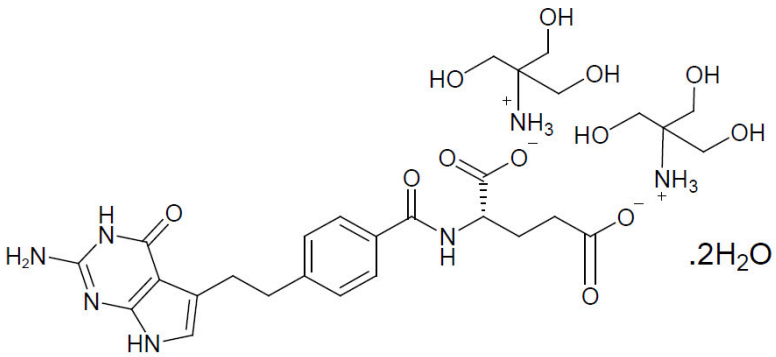
2. Background

The current application relies on the Agency's determination of human safety and efficacy for the pemetrexed lyophilized powder for injection (Alimta), which has been previously approved for marketing under NDA 021462 and NDA 021677. The original patents for Alimta expire in 2021 and 2022.

The Applicant is seeking approval of a lyophilized powder form of pemetrexed ditromethamine for the same indication granted for Alimta. Alimta is indicated for the initial treatment of non-squamous non-small cell lung cancer in combination with cisplatin, as a single agent treatment for nonsquamous non-small cell lung cancer after prior chemotherapy, and for the treatment of mesothelioma in combination with cisplatin.

3. Chemistry, Manufacturing and Controls (CMC)

Drug Substance



Molecular Formula: $C_{28}H_{47}N_7O_{14}$ Molecular Weight: 705.68

The previous drug substance quality review dated August 17, 2020 concluded the drug substance was adequate. In this amendment, multiple drug substance changes were made in the referenced DMF (b) (4) for Pemetrexed ditromethamine dihydrate. DMF (b) (4) has been reviewed and found adequate in support of NDA 208746.

Drug Product

The drug product sections of the application were found adequate in last review cycle. In this amendment, the Applicant provided the following updates:

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

The drug product remains adequate after review.

Process and Facilities

In the last review cycle, manufacturing process and facilities were found acceptable. In this amendment, the Applicant proposed the following process changes:

- (b) (4)

These proposed process changes were assessed as acceptable. All facilities remain adequate.

Biopharmaceutics

No change. Refer to the CDTL review dated June 28, 2017 for details.

Microbiology

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

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

- (b) (4)
- (b) (4)

Microbiology review team found the proposed changes acceptable.

Overall CMC recommendation:
The Office of Pharmaceutical Quality recommends NDA 208746 for ***Approval***.

4. Pharmacology/Toxicology
No additional information was provided in this submission. Refer to the CDTL review dated June 28, 2017 for approval recommendation.

5. Clinical
No additional information was provided in this submission. Refer to the CDTL review dated June 28, 2017 for approval recommendation.

6. Clinical Pharmacology
No additional information was provided in this submission. Refer to the CDTL review dated June 28, 2017 for details.

7. Advisory Committee Meeting
N/A

8. Pediatrics
Full waiver from the pediatric studies request under IND 131252 was reviewed by the PeRC and it was granted on September 08, 2016

9. Other Relevant Regulatory Issues
None

10. Labeling
Minor edits were made on the labeling in this review cycle. The Applicant accepted FDA's edits (b) (4)

(b) (4)

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**
  The cross disciplinary team lead recommendation: **Approval** to NDA 208746.

- **Risk Benefit Assessment**

Please refer to NDA 21462

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/s/

YANG N NAN
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ERIN A LARKINS
05/11/2022 10:38:52 AM

Cross-Discipline Team Leader Review

Date	December 9, 2020
From	Xing Wang, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA	208746
Type of Application	505(b)(2)
Applicant	Hospira, Inc., a Pfizer company
Date of Receipt	July 10, 2020
PDUFA Goal Date	January 10, 2021
Proposed Proprietary/Established Name	NA/ pemetrexed for injection
Dosage forms / Strength	For Injection: 100 mg/vial, 500 mg/vial, and 1 gram/vial
Route of Administration	Intravenous
Proposed Indication(s)	Pemetrexed for injection is a folate analog metabolic inhibitor indicated for: • Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer: • Initial treatment in combination with cisplatin. • Maintenance treatment of patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. • After prior chemotherapy as a single-agent. •Mesothelioma: in combination with cisplatin.
Recommended:	**Tentative Approval**

This cross-discipline team leader review is based on Integrated Quality Assessment (DARRTS, October 20, 2020), legal input from the 505(b)(2) committee, and NDA 208746 labeling review.

1. Introduction

The proposed Pemetrexed (as ditromethamine) for Injection is a sterile lyophilized powder (100 mg/vial, 500 mg/vial, and 1 g/vial presentations), intended to be reconstituted and then diluted with a suitable intravenous solution prior to administration. The submission is a 505(b)(2) application, referencing the lyophilized cake formulation, Alimta (NDA 021462). The listed drug (LD) Alimta is available in 100 mg and 500 mg single dose vials. The therapeutic active moiety (pemetrexed), dosage form, strength, route of administration, and drug content of the proposed drug product is identical to the listed drug product. However, the listed and the proposed drug product differ in salt form of the active moiety (b) (4). In support of the equivalence of the LD and the proposed drug product, the applicant provided comparative physicochemical properties and a bio-waiver request. Clinical data was not submitted in the application. Other than the pemetrexed in disodium salt form, Alimta contains mannitol, and hydrochloric acid or sodium hydroxide for pH adjustment to form a lyophilized cake formulation (b) (4). Alimta is reconstituted with 0.9% sodium chloride injection solution followed by further dilution prior to administration. The proposed drug product contains pemetrexed in ditromethamine salt form and mannitol (b) (4) but does not contain pH adjusters. The proposed drug product is recommended to be reconstituted in 0.9% Sodium

Chloride Injection solution [redacted] (b) (4). The proposed Hospira product may be further diluted using 0.9% Sodium Chloride Injection [redacted] (b) (4).

The original NDA submission was dated on September 15, 2016; the agency issued Complete Response Letter on July 10, 2017, citing Facility deficiency. The resubmission was received on July 10, 2020.

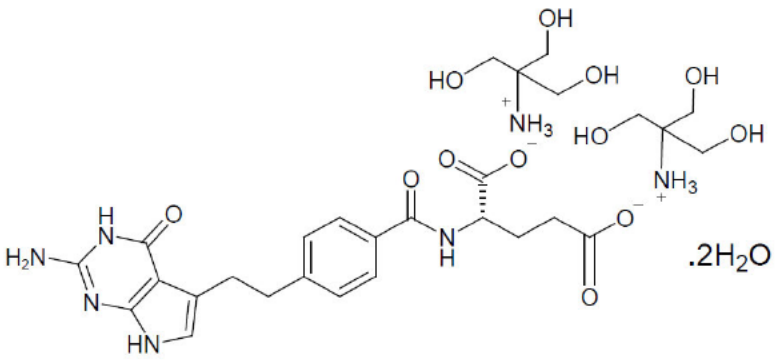
2. Background

The current application relies on the Agency's determination of human safety and efficacy for the pemetrexed lyophilized powder for injection (Alimta), which has been previously approved for marketing under NDA 021462 and NDA 021677. The original patents for Alimta expire in 2021 and 2022.

The applicant is seeking approval of a lyophilized powder form of pemetrexed ditromethamine for the same indication granted for Alimta. Alimta is indicated for the initial treatment of nonsquamous non-small cell lung cancer in combination with cisplatin, as a single agent treatment for nonsquamous non-small cell lung cancer after prior chemotherapy, and for the treatment of mesothelioma in combination with cisplatin.

3. Chemistry, Manufacturing and Controls (CMC)

Drug Substance



Molecular Formula: $C_{28}H_{47}N_7O_{14}$ Molecular Weight: 705.68

The previous drug substance quality review, performed on June 1, 2017, recommended approval of the drug substance. In this resubmission, multiple drug substance changes were made by the referenced DMF [redacted] (b) (4) for Pemetrexed ditromethamine dihydrate and proposes [redacted] (b) (4) from the drug substance specification. DMF [redacted] (b) (4) was found adequate in support of NDA 208746.

Drug Product

The drug product sections of the application were found adequate in last review cycle. In this resubmission, the applicant submitted

(1) an amendment to previously submitted elemental impurity risk assessment report ((b) (4) testing result), and accordingly updated drug product specifications;
(2) updated stability data to extend the proposed shelf-life of the drug product to 36 months when stored at controlled room temperature (20 – 25°C; 68 – 77°F).
The application remains adequate from a drug product perspective.

Facilities
(b) (4) is responsible for Manufacturer of drug substance (b) (4), release and stability testing. In the previous review back to may, 2017, this site was "withhold" due to OAI and warning letter issued, which triggered Complete Response to NDA 208746. All the other facilities were found acceptable. This site was inspected in (b) (4) and was "approve", based on file review and DFR recommendation. All facilities are found adequate in current review. There is no change to the previous adequate assessment of Manufacturing Process.

Biopharm
No updates in this resubmission. Remain adequate

Microbiology
No updates in this resubmission. Remain adequate

Overall CMC recommendation: ***Approval***

4. Pharmacology/Toxicology
No new information was provided in this resubmission. Refer to CDTL review dated on June 28, 2017 for approval recommendation.

5. Clinical
No new information was provided in this resubmission. Refer to CDTL review dated on June 28, 2017 for approval recommendation.

6. Clinical Pharmacology
No new information was provided in this resubmission. Refer to CDTL review dated on June 28, 2017 for NAI recommendation.

7. Advisory Committee Meeting
N/A

8. Pediatrics
Full waiver from the pediatric studies request under IND 131252 was reviewed by the PeRC and it was granted on September 08, 2016

9. Other Relevant Regulatory Issues
Per email by Mary Ann Holovac dated on November 10, 2020, NDA 208746 is cleared for ****tentative approval at best**** by the 505(b)(2) committee. This is because the applicant lost their patent litigation and converted their patent certification from paragraph IV to paragraph III. As

the application will not be fully approved this cycle, clearance from the 505(b)(2) committee will be needed for any future cycle.

10. Labeling

Labeling is found acceptable after revision.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

The cross disciplinary team lead recommendation: **Tentative Approval** to NDA 208746.

- **Risk Benefit Assessment**

Please refer to NDA 21462

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/s/

XING WANG
12/09/2020 09:47:51 AM

Cross-Discipline Team Leader Review

Date	June 28, 2017
From	Anamitro Banerjee, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA	208746
Type of Application	505(b)(2)
Applicant	Hospira, Inc., a Pfizer company
Date of Receipt	September 15, 2016
PDUFA Goal Date	July 15, 2017
Proposed Proprietary/Established Name	N/A/ pemetrexed for injection
Dosage forms / Strength	Injection/ 25 mg/mL in 100 mg/vial, 500 mg/vial, and 1 g/vial
Route of Administration	Intravenous injection
Proposed Indication(s)	Pemetrexed for injection is a folate analog metabolic inhibitor indicated for: • Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer: • Initial treatment in combination with cisplatin. • Maintenance treatment of patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. • After prior chemotherapy as a single-agent. •Mesothelioma: in combination with cisplatin.
Recommended:	**Complete Response**

This cross-discipline team leader review is based on the primary reviews, memos and documented review input of:

- Drug Substance (Sharon Kelly), dated June 01, 2017
- Drug Product (Xing Wang), dated May 23, 2017
- Microbiology (Yeissa Chabrier Rosello), dated May 01, 2017
- Manufacturing Facilities (Wenzheng Zhang), dated June 02, 2017
- Manufacturing Process (Zhaoyang Meng), dated May 24, 2017
- Quality Biopharmaceutics (Om Anand), dated May 26, 2017
- Clinical (Barbara Scepura); in DARRTS, dated June 21, 2017

- Pharmacology/Toxicology (Stephanie L. Aungst); in DARRTS, dated June 16, 2017
- DMEPA (Otto Townsend), dated March 01, 2017
- DMPP (Sharon R. Mills); in DARRTS, dated June 18, 2017
- Clinical Pharmacology (Safaa Burns), dated April 06, 2017

1. Introduction

The proposed Pemetrexed (as ditromethamine) for Injection is a sterile lyophilized powder (100 mg/vial, 500 mg/vial, and 1 g/vial presentations), intended to be reconstituted and then diluted with a suitable intravenous solution prior to administration. The submission is a 505(b)(2) application, referencing the lyophilized cake formulation, Alimta (NDA 021462). The listed drug (LD) Alimta is available in 100 mg and 500 mg single dose vials. The therapeutic active moiety (pemetrexed), dosage form, strength, route of administration, and drug content of the proposed drug product is identical to the listed drug product. However, the listed and the proposed drug product differ in salt form of the active moiety (b) (4). In support of the equivalence of the LD and the proposed drug product, the applicant provided comparative physicochemical properties and a bio-waiver request. Clinical data was not submitted in the application. Other than the pemetrexed in disodium salt form, Alimta contains mannitol, and hydrochloric acid or sodium hydroxide for pH adjustment to form a lyophilized cake formulation (b) (4). Alimta is reconstituted with 0.9% sodium chloride injection solution followed by further dilution prior to administration. The proposed drug product contains pemetrexed in ditromethamine salt form and mannitol (b) (4), but does not contain pH adjusters. The proposed drug product is recommended to be reconstituted in 0.9% Sodium Chloride Injection solution (b) (4). The proposed Hospira product may be further diluted using 0.9% Sodium Chloride Injection (b) (4).

2. Background

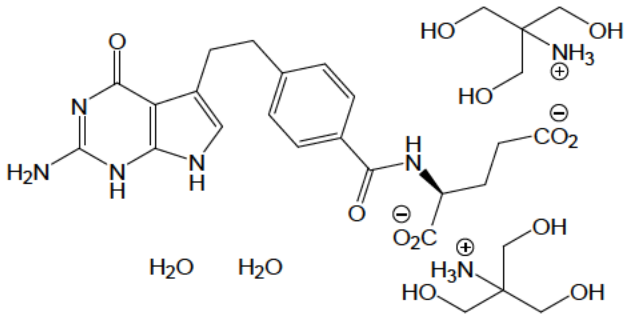
The current application relies on the Agency's determination of human safety and efficacy for the pemetrexed lyophilized powder for injection (Alimta), which has been previously approved for marketing under NDA 021462 and NDA 021677.

The applicant is seeking approval of a lyophilized powder form of pemetrexed ditromethamine for the same indication granted for Alimta. Alimta is indicated for the initial treatment of nonsquamous non-small cell lung cancer in combination with cisplatin, as a single agent treatment for nonsquamous non-small cell lung cancer after prior chemotherapy, and for the treatment of mesothelioma in combination with cisplatin.

3. Chemistry, Manufacturing and Controls (CMC)

The drug substance for NDA 208476 is pemetrexed ditromethamine dihydrate. Labeling and strength designation is on the basis of the pemetrexed free acid, consistent with the listed product, Alimta. The FDA salt nomenclature policy is adopted for labeling purposes.

Chemical Name: Ditromethamine (2S)-2-[[4-[2-(2-amino-4-oxo-4,7 -dihydro-1H -pyrrolo[2,3-d]-pyrimidin-5-yl) ethyl] benzoyl] amino]-pentanedioate dihydrate.



Chemical Formula: $C_{28}H_{47}N_7O_{14}$
Molecular Weight: 705 (b) (4)

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

(b) (4)

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

(b) (4)

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

The drug product specifications include testing for description of the powder as well as the reconstituted solution, identification, pH, color and clarity of solution, assay, related substances, water content, reconstitution time, uniformity of dosage units, particulate matter, bacterial endotoxin, sterility, extractable volume, and [redacted]. The applicant reported a new impurity [redacted] and proposed a specifications limit of NMT [redacted]%.
Bsed on the input from the nonclinical reviewer, the proposed limit was found acceptable.
The applicant provided 12 months stability data under long term and intermediate storage conditions, and 6 months stability data under accelerated storage conditions for three representative batches for each presentation. Based on the data presented, [redacted] months of expiration dating period may be granted for the drug product when stored at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (59°F and 86°F). Based on in-use stability data provided in the application, the reconstituted and further diluted solution may be stored under refrigerated conditions (2°C to 8°C) for 24 hours [redacted].
The applicant is requesting categorical exclusion for EA as per 21 CFR 25.15(d)

Facilities
The drug substance manufacturer ([redacted]) has an unresolved facility risk (OAI and Warning Letter) that prevents approval of this application. All the other facilities are currently acceptable.

Biopharmaceutics
The biopharmaceutics review assessed the adequacy of the Applicant's biowaiver request for the proposed drug product, pemetrexed ditromethamine. Per 21 CFR 320.24(b)(6), the supporting data and information for the biowaiver request were evaluated to determine if the proposed drug product was adequately bridged to the LD (pemetrexed disodium). The proposed and LD products contain different salts, which are predominantly dissociated in solution prior to infusion. The use of the ditromethamoine salt (by the Applicant) as a pharmaceutical alternative to the disodium salt would not therefore be expected to impact the disposition kinetics of pemetrexed. In addition to the different salt forms, the proposed drug product [redacted]
The Applicant submitted data and information to demonstrate that diluted solutions of the proposed and LD products were similar in their physicochemical properties (osmolality, pH) and protein binding. The intracellular akalinizing effect of tromethamine in the proposed drug product was also assessed in interdisciplinary discussions and found to be inconsequential in the disposition kinetics of pemetrexed.
The totality of the data submitted in the Application demonstrates that the proposed drug product has been adequately bridged to the listed drug; therefore an in vivo pharmacokinetic study is not needed.

Overall CMC recommendation
The Office of Pharmaceutical Quality recommends a Complete Response action for NDA 208746 on the basis of inadequate status of the manufacturing and testing facility. The Facilities Reviewer recommends the following language for the CR letter: **"During a recent inspection of the [redacted] manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved".**

4. Pharmacology/Toxicology

The applicant is relying on the findings described in the label for Alimta to support the nonclinical requirements for evaluation of pemetrexed as tromethamine. The nonclinical data submitted to support this NDA was limited to qualification of any novel impurities or high levels of excipients or degradants and the comparability of the proposed Hospira product to the LD.

The applicant conducted a single dose intravenous study to qualify (b) (4) (newly identified degradant in the proposed Hospira product). In the dog study, administration of up to (b) (4)% of this impurity (resulting in a dose of ~(b) (4) µg/kg, (b) (4)mg/m^2) resulted in no mortality or treatment related effects noted in ophthalmology, urinalysis, organ weights, and macroscopic assessments. There were no clear differences in hematology and clinical chemistry or histopathological findings in the proposed Hospira pemetrexed with impurities versus Hospira pemetrexed or Alimta.

Comparative toxicokinetic assessment of Alimta and the proposed Hospira product show increases in mean C_{max} (~200%) and AUC (~60%) for the proposed Hospira product without impurities. C_{max} values for the Hospira product with impurities remained elevated; however the AUC values were comparable with Alimta.

The information provided in this submission supports the proposed impurity levels and suggests comparable safety between the LD and the proposed Hospira product though the toxicokinetic data is unclear to fully support this comparability.

Labeling for this product was not evaluated from the nonclinical perspective due to manufacturing issues identified (*vide supra*).

The Pharmacology/Toxicology Reviewer recommends approval of the application.

5. Clinical

No clinical safety or efficacy data were submitted in this NDA application. Labeling was not completed for this product.

The clinical team recommends approval of this product contingent upon satisfactory reviews by other FDA disciplines.

6. Clinical Pharmacology

This NDA does not contain any clinical or clinical pharmacology studies as the Applicant requests a biowaiver.

A bio-waiver will be granted for this 505(b)(2) application when it can be approved.

No action indicated from the clinical pharmacology perspective.

7. Advisory Committee Meeting

N/A

8. Pediatrics

Full waiver from the pediatric studies request under IND 131252 was reviewed by the PeRC and it was granted on September 08, 2016

9. **Other Relevant Regulatory Issues**
The application may not be approved for marketing until patent/s for the listed drug expires or the current patent infringement lawsuit is settled in Hospira's favor. In addition, Hospira is under a 30 month marketing stay that will expire on June 06, 2019.

10. Labeling
The Division will harmonize the label with the Alimta label once the LD label is updated. Labeling comments will not be sent to applicant in this review cycle.

14. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

This drug product differs with the listed drug, Alimta, in the salt form of active moiety and in the composition of the product (absence of pH adjusters). Pre-clinical studies were conducted to qualify the proposed salt form and a new degradant identified in this product. No clinical studies were conducted to assure safety and efficacy and a bio-waiver request will be granted for this 505(b)(2) application when it can be approved. The cross disciplinary team lead recommendation is for a **Complete Response** to the application based on deficiencies identified by Quality Review staff, related to inadequate facilities inspections. Also, the drug product may not be approved for marketing until pertinent patents for the listed drug "Alimta" expire or the current patent infringement lawsuit is settled in Hospira's favor.

- **Risk Benefit Assessment**

Please refer to NDA 021462

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/s/

ANAMITRO BANERJEE
06/28/2017