CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208746Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	July 9, 2017
From	Joseph E. Gootenberg, M.D.
Subject	Deputy Division Director Summary Review
NDA	208746
Type of Application	505(b)(2)
Applicant	Hospira, Inc., a Pfizer company (Hospira)
Date of Submission	September 15, 2016
PDUFA Goal Date	July 15, 2017
Proposed Proprietary Name	Pemetrexed for injection
Dosage Form(s) / Strength(s)	Injection/ 25 mg/mL in 100 mg/vial, 500 mg/vial, and 1 g/vial
Applicant Proposed Indications	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 Action	**Complete Response**

Material Reviewed/Consulted	**Names of discipline reviewers**
Clinical Review	Barbara Scepura
Clinical Team Leader	Erin Larkins
Nonclinical Review	Stephanie Aungst
Nonclinical Team Leader	Whitney Helms
Clinical Pharmacology Review	Safaa Burns
DMPP	Sharon R. Mills
OPQ ATL Review	Amit K. Mitra Anamitro Banerjee?
Drug Substance Review	Sharon Kelly
Drug Product Review	Xing Wang
Manufacturing Facilities Review	Wenzheng Zhang
Manufacturing Process Review	Zhaoyang Meng
Microbiology Review	Yeissa Chabrier Rosello
Quality Biopharmaceutics Review	Om Anand and Okpo Eradiri
OSE/DMEPA	Otto Townsend
CDTL Review	Anamitro Banerjee

1. Introduction

This New Drug Application, NDA 208746, for Pemetrexed for injection was submitted by Hospira under the provisions of section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The application relies on FDA's previous findings of safety and efficacy for the listed drug, Alimta (Pemetrexed for injection) manufactured by Eli Lilly and Company (Lilly). The listed drug, Alimta, was originally approved on February 4, 2004 under NDA 021462 and is marketed as a lyophilized powder available in sterile single-use vials containing 100 mg or 500 mg pemetrexed as pemetrexed disodium. Alimta is administered by reconstituting and diluting the lyophilized powder with 0.9% NaCl. Hospira's proposed presentation is a lyophilized powder available in sterile single-use vials containing 100 mg, 500 mg or 1000 mg pemetrexed as pemetrexed ditromethamine, and is reconstituted by dilution with (b) (4) solution. Although 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, the listed and the proposed drug product differ in salt form of the active moiety, quantitative and qualitative composition of the excipients, (b) (4).

This application is limited to non-clinical, chemistry, manufacturing and controls information, and proposed product labeling. A waiver of bioequivalence studies is requested and the application relies on FDA's findings of safety and effectiveness of the listed drug, Alimta, for non-clinical, clinical pharmacology, and clinical safety and efficacy data. The proposed indication, dose, and route and duration of administration of Hospira's Pemetrexed for injection are the same as the listed drug, Alimta.

An inspection in (b) (4) of one of the manufacturing facilities, (b) (4), conducted to ensure compliance with GMPs and implementation of actions to address items on previous FDA-483s, identified significant deviations from GMPs. An FDA-483 with 9 observations was issued at the end of the inspection and an "Official Action Indicated" classification ensued. (b) (4) responded twice to the observations; however, the Office of Compliance review determined that the responses lacked sufficient corrective actions. A Warning Letter dated (b) (4) was issued (see CMS case # (b) (4)) citing significant deviations from CGMP. A review by the Facilities Reviewer of the application, manufacturing capability, and inspectional history of (b) (4) has determined that this facility is not considered acceptable to manufacture the drug substance for NDA (b) (4). Therefore, the Facilities Reviewer has given an overall "withhold" recommendation for the facilities during this review cycle.

A Complete Response letter will be issued requesting resolution of the GMP issues at that facility which preclude approval.

2. Background

Pemetrexed is a folate analog metabolic inhibitor indicated for the treatment of locally advanced or metastatic non-squamous non-small cell lung cancer (1) as initial treatment in combination with cisplatin, (2).as maintenance treatment of patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy, (3) after prior chemotherapy as a single-agent, and for the treatment of Mesothelioma in combination with cisplatin.

Pemetrexed is chemically similar to folic acid and is in the class of chemotherapy drugs called folate antimetabolites. It works by inhibiting three enzymes used in purine and pyrimidine synthesis—thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT). By inhibiting the formation of precursor purine and pyrimidine nucleotides, pemetrexed prevents the formation of DNA and RNA, which are required for the growth and survival of both normal cells and cancer cells. Pemetrexed has broad antitumor activity in a wide variety of solid tumors. The most common and serious toxicities of pemetrexed, myelosuppression and mucositis, appear to be mitigated by folic acid and vitamin B12 supplementation, which has not been shown to adversely affect efficacy in some tumor types.

The current application relies on the Agency's determination of safety and efficacy for the Pemetrexed lyophilized powder for injection (Alimta), which has been previously approved for marketing under NDA 021462 and NDA 021677. Hospira is seeking approval of a lyophilized powder form of pemetrexed ditromethamine for the same indications granted for Alimta

3. Product Quality

I concur with the conclusions reached by the CDTL and Product Quality Lead Anamitro Banerjee that a Complete Response action is recommended due to a withhold recommendation from the Office of Process and Facilities reviewer, Wenzheng Zhang. An inspection in (b) (4) conducted to ensure compliance with GMPs at the Drug Substance manufacturing facility (under DMF (b) (4), LOA provided), (b) (4), identified significant deviations from GMPs. An FDA-483 with 9 observations was issued at the end of the inspection and an "Official Action Indicated" classification ensued. Although (b) (4) responded twice to the observations, the Office of Compliance review determined that the responses lacked sufficient corrective actions. A Warning Letter dated (b) (4) was issued (see CMS case # (b) (4)) citing significant deviations from CGMP. A review by the Facilities Reviewer of the application, manufacturing capability, and inspectional history of (b) (4) has determined that this facility is not considered acceptable to manufacture the drug substance for NDA (b) (4). Therefore, the Facilities Reviewer has given an overall "withhold" recommendation for the facilities during this review cycle.

Hospira requested a bio-waiver for this drug product. The biopharmaceutics review assessed the adequacy of the Hospira's bio-waiver request for the proposed drug product, pemetrexed

ditromethamine. Per 21 CFR 320.24(b)(6), the supporting data and information for the bio-waiver 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 Hospira as a pharmaceutical alternative to the disodium salt would not therefore be expected to impact the disposition kinetics of pemetrexed. In addition to the different salt forms, the proposed drug product (b) (4) . Hospira 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. The Biopharmaceutics Reviewer recommends approval of the requested bio-waiver for this drug product at the time of approval of the application.

The following items were reviewed by Product Quality and found to be adequate:

- The synthesis of the bulk drug substance, pemetrexed ditromethamine
- The formulation of the Drug Product
- In-process manufacturing controls
- Drug Product impurity levels
- Drug Product stability, including long-term stability, under real-time and accelerated conditions
- The overall microbiological control and sterility assurance
- Container closure system compatibility with the Drug Product
- The proposed expiratory dating period of (b) (4) months
- Labelling of the product's strength consistent with FDA salt nomenclature policy

I agree that, other than the "withhold" recommendation for the facilities, there are no additional Product Quality issues that would preclude approval of this Application.

A Complete Response action will be issued 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 (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this NDA may be approved".**

4. Nonclinical Pharmacology/Toxicology

This application relies on FDA's previous findings of safety and efficacy for the listed drug, Alimta (Lilly). 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.

Hospira conducted a single dose intravenous study to qualify [redacted] (b) (4) (newly identified degradant in the proposed Hospira product). In the dog study, administration of up to [redacted] (b) (4) % of this impurity 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 compared to Alimta.

Comparative toxicokinetic assessment of Alimta and the proposed Hospira product demonstrated increases in mean Cmax (~200%) and AUC (~60%) for the proposed Hospira product without impurities. Cmax 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.

I concur with the conclusions of the Nonclinical Pharmacology/Toxicology reviewer that there are no nonclinical pharmacology/toxicology issues that would preclude approval of this product.

5. Clinical Pharmacology

This NDA does not contain any clinical or clinical pharmacology studies as Hospira requested a biowaiver.

I concur with the conclusions of the Clinical Pharmacology reviewer that there are no clinical pharmacology issues that would preclude approval of this product.

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

6. Clinical Microbiology

See Section 3 "Product Quality".

7. Clinical/Statistical-Efficacy

The application relies on FDA's previous findings of safety and efficacy for the listed drug, Alimta (Lilly). No Clinical Safety or Efficacy data were submitted in the Application. I concur with the conclusions of the clinical reviewer that no clinical issues were identified that would preclude approval, contingent upon agreement upon labeling. The Clinical Reviewer notes the deficiencies identified by the Product Quality review staff, and provides a recommendation not to approve based on those deficiencies.

8. Safety

The application relies on FDA's previous findings of safety and efficacy for the listed drug, Alimta (Lilly). No safety data were submitted in the Application. I concur with the conclusions of the clinical reviewer that no clinical issues, including safety issues, were identified that would preclude approval, contingent upon agreement upon labeling.

9. Advisory Committee Meeting

This 505(b)(2) application was not referred to an advisory committee because it has the same active ingredient, same route of administration, and same proposed indications as the listed drug and relies on FDA's finding of safety and efficacy for the listed drug, Alimta (pemetrexed) for Injection.

10. Pediatrics

A request for a full waiver from the pediatric studies was reviewed by the PeRC and was granted on September 8, 2016.

11. Other Relevant Regulatory Issues

As discussed in the Introduction and in Section 3 of this review, the Office of Process and Facilities Reviewer has recommended that approval be withheld until the applicant has satisfactorily addressed the deficiencies identified at (b) (4), one of the manufacturing facilities identified in the NDA

In addition, the application may not be approved for marketing until certain patents and exclusivity granted for the listed drug, Alimta, expire, or the current patent infringement lawsuit brought by Lilly on December 22, 2016 is settled in Hospira's favor. At this time Hospira is under a 30 month marketing stay that will expire June 6, 2019.

12. Labeling

The internal review of the labeling was completed to a great extent; however, the revised labeling will not be sent to applicant in this review cycle.

The Division plans to request Hospira to harmonize the label with the proposed updated Alimta label now under review as NDA 0021462, Supplement 50, once an updated Alimta label is approved.

13. Decision/Action/Risk Benefit Assessment

- **Recommended Regulatory Action**

This product is nearly identical to the listed product, Alimta, when the listed product is reconstituted and diluted for administration, differing only 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 new clinical studies were provided with this submission, as no clinical studies were conducted for this 505(b)(2) application. A bio-waiver request will be granted for this 505(b)(2) application when it can be approved.

However, the drug product may not be approved for marketing until pertinent patents for the listed drug "Alimta" expire or the current patent infringement lawsuit brought by Lilly on December 22, 2016 is settled in Hospira's favor. My recommendation is that a **Complete Response** to the application be issued based on deficiencies identified by Quality review staff, related to inadequate facilities inspections.

The Office of Process and Facilities reviewer recommends the following language be used in the Complete Response Letter:

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

- **Risk Benefit Assessment**

The application relies on FDA's previous findings of safety and efficacy for the listed drug, Alimta (Lilly). There are no new efficacy or safety concerns that would preclude approval of this product.

Joseph E. Gootenberg -S

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/s/

JOSEPH E GOOTENBERG
07/09/2017