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APPLICATION NUMBER:

215179Orig1s000

CLINICAL REVIEW(S)

File Memorandum

NDA/SDN	215179/34
Memo Date	05/17/2023
Submission Date	08/23/2022
Product	Pemetrexed Injection 10 mg/ml (100 mg/10 mL, 500 mg/50 mL, 1000 mg/100 mL)
PDUFA Goal Date	May 23, 2023
Sponsor/Applicant	Shilpa Medicare LTD
Clinical Reviewer	Satinder Choudhary
Clinical Team Lead	Paz Vellanki

Action Recommended: No clinical studies have been conducted under the submitted NDA and no clinical issues need to be addressed related to this NDA. The clinical team recommends approval upon satisfactory review from other FDA disciplines.

Background: This is a 505(b) (2) application by Shilpa Medicare ltd. for Pemetrexed for Injection. Shilpa is not proposing a proprietary name for their product. The reference drug product is Eli Lilly and Company's Alimta (pemetrexed disodium) for injection (NDA 021462). Alimta was granted traditional approval on February 4, 2004.

Alimta has the following indications:

- in combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations.
- 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.
- 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.

Shilpa proposes the same indications for Pemetrexed for Injection as described for Alimta.

Shilpa's proposed drug product has the same amount of active ingredient and route of administration as Alimta. The differences between the products are:

- Alimta is a lyophilized powder for injection and requires initial reconstitution with 0.9% sodium chloride solution for injection resulting in a 25 mg/mL pemetrexed solution. Further dilution is required prior to administration by intravenous infusion. Shilpa's product, Pemetrexed Injection, is a "ready-to-use" 10 mg/mL solution for injection requiring no

further dilution to be withdrawn from the vial(s) and then transferred to the empty sterile IV bag in the same volume of the solution required to deliver the recommended dose calculated based on the patient's body surface area (BSA) (500 mg/m^2) to deliver an equivalent pemetrexed solution for infusion.

- The formulation for Shilpa's product contains mannitol 100 mg compared to mannitol 106 mg for Alimta and Shilpa's product contains additional L-cysteine HCl (b) (4) (10 mg) sodium chloride (90 mg) water for injection (q.s. ad 10 mL).

Product labeling has been updated to align with the listed drug Alimta.

Summary of Findings: No clinical safety or efficacy data were submitted in this NDA application. For further information regarding this NDA, please refer to reviews by other disciplines.

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/s/

SATINDER K CHOUDHARY
05/22/2023 10:05:03 AM

PAZ J VELLANKI
05/22/2023 10:11:48 AM

File Memorandum

NDA/SDN	215179/34
Memo Date	05/17/2023
Submission Date	08/23/2022
Product	Pemetrexed Injection 10 mg/ml (100 mg/10 mL, 500 mg/50 mL, 1000 mg/100 mL)
PDUFA Goal Date	May 23, 2023
Sponsor/Applicant	Shilpa Medicare LTD
Clinical Reviewer	Satinder Choudhary
Clinical Team Lead	Paz Vellanki

Action Recommended: No clinical studies have been conducted under the submitted NDA and no clinical issues need to be addressed related to this NDA. The clinical team recommends approval upon satisfactory review from other FDA disciplines.

Background: This is a 505(b) (2) application by Shilpa Medicare ltd. for Pemetrexed for Injection. Shilpa is not proposing a proprietary name for their product. The reference drug product is Eli Lilly and Company's Alimta (pemetrexed disodium) for injection (NDA 021462). Alimta was granted traditional approval on February 4, 2004.

Alimta has the following indications:

- in combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations.
- 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.
- 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.

Shilpa proposes the same indications for Pemetrexed for Injection as described for Alimta, with the exception of use 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 (patent protected).

Shilpa's proposed drug product has the same amount of active ingredient and route of administration as Alimta. The differences between the products are:

- Alimta is a lyophilized powder for injection and requires initial reconstitution with 0.9% sodium chloride solution for injection resulting in a 25 mg/mL pemetrexed solution. Further dilution is required prior to administration by intravenous infusion. Shilpa's product, Pemetrexed Injection, is a “ready-to-use” 10 mg/mL solution for injection requiring no further dilution to be withdrawn from the vial(s) and then transferred to the empty sterile IV bag in the same volume of the solution required to deliver the recommended dose calculated based on the patient’s body surface area (BSA) (500 mg/m^2) to deliver an equivalent pemetrexed solution for infusion.
- The formulation for Shilpa's product contains mannitol 100 mg compared to mannitol 106 mg for Alimta and Shilpa's product contains additional L-cysteine HCl (b) (4) (10 mg) sodium chloride (90 mg) water for injection (q.s. ad 10 mL).

Product labeling has been updated to align with the listed drug Alimta (with the exception of use in combination with pembrolizumab and platinum chemotherapy).

Summary of Findings: No clinical safety or efficacy data were submitted in this NDA application. For further information regarding this NDA, please refer to reviews by other disciplines.

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/s/

SATINDER K CHOUDHARY
05/18/2023 05:45:09 PM

PAZ J VELLANKI
05/18/2023 05:46:49 PM

File Memorandum

NDA/SDN	215179/20
Memo Date	March 24, 2022
Submission Date	October 14, 2021
Product	Pemetrexed Injection 10 mg/ml (100 mg/10 mL, 500 mg/50 mL, 1000 mg/100 mL)
PDUFA Goal Date	April 14, 2022
Sponsor/Applicant	Shilpa Medicare LTD
Clinical Reviewer	Satinder Choudhary
Clinical Team Lead	Nicole Drezner

Action Recommended: No clinical studies have been conducted under the submitted NDA and no clinical issues need to be addressed related to this NDA. The clinical team recommends approval upon satisfactory review from other FDA disciplines. However, a complete response (CR) will be issued due to insufficient finished drug product stability data to support approval of the Cadila Healthcare site proposed for drug product manufacture and control and lack of 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.

Background: This is a 505(b) (2) application by Shilpa Medicare ltd. for Pemetrexed for Injection. Shilpa is not proposing a proprietary name for their product. The reference drug product is Eli Lilly and Company's Alimta (pemetrexed disodium) for injection (NDA 021462). Alimta was granted traditional approval on February 4, 2004.

Alimta has the following indications:

- in combination with pembrolizumab and platinum chemotherapy, for the initial treatment of patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations.
- 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.
- 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.

Shilpa proposes the same indications for Pemetrexed for Injection as described for Alimta, with the exception of use 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 (patent protected).

Shilpa's proposed drug product has the same amount of active ingredient and route of administration as Alimta. The differences between the products are:

- Alimta is a lyophilized powder for injection and requires initial reconstitution with 0.9% sodium chloride solution for injection resulting in a 25 mg/mL pemetrexed solution. Further dilution is required prior to administration by intravenous infusion. Shilpa's product, Pemetrexed Injection, is a "ready-to-use" 10 mg/mL solution for injection requiring no further dilution to be withdrawn from the vial(s) and then transferred to the empty sterile IV bag in the same volume of the solution required to deliver the recommended dose calculated based on the patient's body surface area (BSA) (500 mg/m^2) to deliver an equivalent pemetrexed solution for infusion.
- The formulation for Shilpa's product contains mannitol 100 mg compared to mannitol 106 mg for Alimta and Shilpa's product contains additional L-cysteine HCl (b) (4) (10 mg) sodium chloride (90 mg) water for injection (q.s. ad 10 mL).

Product labeling has been updated to align with the listed drug Alimta (with the exception of use in combination with pembrolizumab and platinum chemotherapy).

Summary of Findings: No clinical safety or efficacy data were submitted in this NDA application. For further information regarding this NDA, please refer to reviews by other disciplines.

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SATINDER K CHOUDHARY
03/25/2022 05:30:41 PM

NICOLE L DREZNER
03/25/2022 09:54:41 PM

MARTHA B DONOGHUE
03/26/2022 11:51:04 AM

Memo Date: June 8, 2021
For: NDA 215179
Submission Date: August 27, 2020
PDUFA Date: June 27, 2021
Product: Pemetrexed Injection 100 mg/10 mL, 500 mg/50 mL, and 1000 mg/100 mL
Indication(s):

- In combination with pembrolizumab and platinum chemotherapy, in patients with metastatic non-squamous NSCLC, with no EGFR or ALK genomic tumor aberrations.
- In combination with cisplatin for the initial treatment of patients with locally advanced or metastatic, non-squamous, non-small cell lung cancer (NSCLC).
- As a single agent for the maintenance treatment of patients with locally advanced or metastatic, non-squamous NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy.
- As a single agent for the treatment of patients with recurrent, metastatic non-squamous, NSCLC after prior chemotherapy. Limitations of Use: pemetrexed injection is not indicated for the treatment of patients with squamous cell, non-small cell lung cancer.
- 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.

Sponsor: Shilpa Medicare Ltd.
From: Nicole Drezner, MD, Clinical Team Leader, Thoracic and Head and Neck Malignancies, DO2
Reference Drug: Alimta® (NDA 021462)

Shilpa submitted NDA 215179 via the 505(b)(2) pathway relying on FDA's previous findings of safety and efficacy for Reference Listed Drug (RLD), Alimta.

Recommendation:

No clinical studies have been conducted under the submitted NDA and no clinical issues need to be addressed related to this NDA. The clinical team recommends approval upon satisfactory review from other FDA disciplines. However, this application will be (b) (4)

Background:

Shilpa requested a waiver of in-vivo bioavailbility studies to demonstrate the bioequivalence of pemetrexed injection to the listed drug Alimta. The proposed drug product differs from Alimta in

the following ways: 1) Pemetrexed Injection is a “ready to use” solution (Alimta is a lyophilized powder); 2) Pemetrexed Injection includes an additional strength (1 g/100 mL); and 3) Pemetrexed Injection includes L-cysteine hydrochloride as (b) (4) which is not present in Alimta. The safety and efficacy data are primarily based on data from Alimta’s NDA 021462 as well as published literature.

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NICOLE L DREZNER
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