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APPLICATION NUMBER:

214408Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	214408
Supporting document/s:	10
Applicant's letter date:	November 17, 2021
CDER stamp date:	November 17, 2021
Product:	Pemetrexed injection
Indication:	Non-squamous non-small cell lung cancer (NSCLC) and mesothelioma
Applicant:	Accord Healthcare, Inc. 1009 Slater Road, STE 210-B Durham, NC 27703
Review Division:	Division of Oncology 2
Reviewer:	Melissa A. Pegues, PhD
Acting Team Leader:	Claudia P. Miller, PhD
Division Director:	John K. Leighton, PhD (DHOT) Harpreet Singh, MD (DO2)
Project Manager:	Idara E. Ojofeitimi

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

On January 27, 2020, the Applicant submitted NDA 214408 for Pemetrexed Injection under the 505(b)(2) pathway and is relying primarily on FDA's prior findings of safety and effectiveness for the listed drug Alimta® to support the pharmacology and toxicology requirements for a new drug application. Pemetrexed Injection is a ready-to-dilute formulation of pemetrexed with different excipients than the listed drug, Alimta®. After review of the application, FDA issued a Complete Response letter on November 23, 2020 due to insufficient information provided to support the safety of the amount of the citric acid excipient in the proposed formulation. The Applicant resubmitted NDA 214408 on November 17, 2021 and included new nonclinical data to address deficiencies regarding the proposed use of large amounts of citric acid excipient described in the Complete Response letter dated November 23, 2020.

1.2 Brief Discussion of Nonclinical Findings

The amount of citric acid excipient in the proposed formulation is high with up to (b) (4) (b) (4) citric acid at the clinical dose of 500 mg/m^2 pemetrexed. Additionally, the Applicant proposed IV administration over a 10 minute infusion period, resulting in an infusion rate of approximately (b) (4) mg/kg/minute citric acid; the proposed infusion rate was not supported considering known risks of citric acid intoxication and metabolic alkalosis and the lack of data to mitigate safety concerns.

To address this potential safety risk, the Applicant performed a GLP-compliant study to evaluate acute toxicity of intravenous administration of citric acid in rats. Rats were administered a single 10 minute intravenous infusion of vehicle (saline), 75, 150, or 300 mg/kg citric acid, 75 mg/kg Pemetrexed Injection, or 75 mg/kg reference listed drug (Alimta; Pemetrexed disodium for Injection); a sham (untreated) group was also included. Clinical signs of dullness, tremors, and clonic convulsions occurred in animals administered 300 mg/kg citric acid (1800 mg/m^2), but there were no clinical signs or changes in hematology or clinical chemistry, including calcium levels, in rats administered citric acid doses ≤150 mg/kg (900 mg/m^2) or 75 mg/kg pemetrexed injection or reference product. In male rats administered 300 mg/kg citric acid (approximately 6-times the amount of citric acid at the recommended 500 mg/m^2 pemetrexed dose), serum calcium levels were 5.59% and 5.29% higher than vehicle-treated and sham animals, respectively, at 1 hour post-dose on Day 1 but improved by Day 14. Considering that IV administration of citric acid was well tolerated at dose levels approximately three times higher than citric acid levels at the clinical dose based on body surface area, there is sufficient coverage of the citric acid excipient at a relevant infusion rate at the proposed clinical dose.

1.3 Recommendations

1.3.1 Approvability

The nonclinical team recommends approval.

1.3.2 Additional Non Clinical Recommendations

None

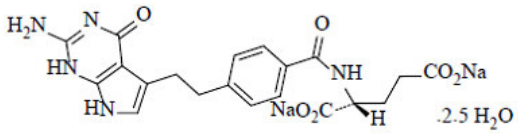
1.3.3 Labeling

The nonclinical recommendation to the Applicant's proposed labeling are primarily based on the listed drug, were discussed internally, and will be communicated to the Applicant.

2 Drug Information

2.1 Drug

CAS Registry Number (Optional): 150399-23-8, pemetrexed disodium anhydrous
Generic Name: Pemetrexed Injection
Code Name: None
Chemical Name : *N*-{*4*-[2-(2-amino-oxo-4,7-dihydro-1*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]phenyl]carbonyl}-L-glutamic acid disodium, hemipentahydrate
Molecular Formula/Molecular Weight: $C_{20}H_{19}N_5Na_2O_6 \bullet 2.5H_2O$; 516.41 g/mol
Structure or Biochemical Description



(Excerpted from Applicant's NDA)

Pharmacologic Class: Folate antimetabolite

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 142070 for Pemetrexed Injection and NDA 021462 for pemetrexed sodium (Alimta®), the referenced listed drug.

2.3 Drug Formulation

Pemetrexed Injection is supplied at a concentration of 25 mg/mL in a sterile, clear, colorless to pale yellow solution for intravenous infusion available in single-dose 4 mL, 20 mL, 34 mL, and 40 mL vials.

Figure 1: Formulation for Pemetrexed Injection

Ingredients	RLD [ALIMTA (pemetrexed disodium) for injection of Eli Lilly]				Applicant's Pemetrexed Injection	
	RLD lyophilized formulation		RLD after re-constitution & before dilution (25 mg/mL)	RLD After dilution (b) (4)	Before dilution (25 mg/mL) [proposed formulation]	After dilution (b) (4)
	100 mg	500 mg				
Pemetrexed	100	500	25 mg/mL		25 mg/mL	
Mannitol	106	500	25 mg/mL (approx.)		--	
Citric Acid Anhydrous	--	--	--	--	15 mg/mL	
L-Methionine	--	--	--	--	0.5 mg/mL	
Monothioglycerol	--	--	--	--	4.4 mg/mL	
Sodium hydroxide and /or Hydrochloric acid (for pH adjustment)	q.s. for pH adjustment	q.s. for pH adjustment	q.s. for pH adjustment	q.s. for pH adjustment	q.s. for pH adjustment	q.s. for pH adjustment
(b) (4)						

**concentration (b) mg/mL is with respect to the administration of recommended/maximum daily dose of drug substance (i.e. (b) (4) mg).

Excipients	Per mL quantity of excipients in Pemetrexed Injection 25 mg/mL	Max. daily intake of excipients as per drug substance maximum daily dose (b) (4) mg
Anhydrous Citric Acid	15 mg/mL	(b) (4)
L-Methionine	0.50 mg/mL	
Monothioglycerol	4.40 mg/mL	

(Excerpted from Applicant's NDA)

2.4 Comments on Novel Excipients

The amount of citric acid excipient in the proposed formulation is high with up to (b) (4) (b) (4) citric acid at the clinical dose of 500 mg/m^2 pemetrexed. The proposed IV infusion period of 10 minutes results in an infusion rate of approximately (b) (4) mg/kg/minute citric acid; potential safety risks at this infusion rate include citric acid intoxication and metabolic alkalosis. To mitigate safety concerns the Applicant conducted a toxicity in rats to evaluate potential acute toxicity of the infusion of high amounts of citric acid. Considering that IV administration of ≤150 mg/kg citric acid (approximately three times higher than citric acid levels at the clinical dose) was well tolerated in rats, there is sufficient coverage of the citric acid excipient at a relevant infusion rate at the proposed clinical dose.

2.5 Comments on Impurities/Degradants of Concern

None

2.6 Proposed Clinical Population and Dosing Regimen

Pemetrexed injection is indicated for the initial treatment of non-squamous NSCLC in combination with pembrolizumab and platinum chemotherapy, initial treatment of non-squamous NSCLC in combination with cisplatin, as a single-agent for the treatment of non-squamous NSCLC after prior chemotherapy, and for the treatment of mesothelioma

in combination with cisplatin. The recommended dose of Pemetrexed injection is 500 mg/m^2 administered as an IV infusion over 10 minutes on Day 1 of each 21-day cycle.

2.7 Regulatory Background

The referenced listed drug, pemetrexed disodium (Alimta®) was approved on 2/4/2004 (NDA 021462). The Applicant submitted a 505(b)(2) NDA for Pemetrexed Injection on January 27, 2020. After review of the application, FDA issued a complete response letter on November 23, 2020 due to insufficient information provided to support the safety of the amount of the citric acid excipient in the proposed pemetrexed formulation in the context of the standard 10-minute infusion time for pemetrexed. The nonclinical team recommended that the Applicant conduct an acute animal toxicity study showing that the amount of citric acid present in the proposed formulation for Pemetrexed Injection is not acutely toxic. The Applicant submitted a proposed protocol for an acute toxicity study in rats to IND 142070 on December 21, 2020; the nonclinical team agreed that the proposed study design appeared sufficient provided that the dose levels for Pemetrexed Injection and the listed drug were at least 75 mg/kg, a dose which is approximately the human equivalent. The completed acute toxicity study in rats included in the re-submission of NDA 214408 is sufficient to address the safety issue of the amount of citric acid excipient detailed in the complete response letter.

3 Studies Submitted

3.1 Studies Reviewed

- Study #VLL/0721/G/T113: Acute Toxicity Study of Citric Acid in Wistar Rats by Slow Intravenous Administration

3.3 Previous Reviews Referenced

A memorandum from Dr. Whitney Helms for NDA 214408 was referenced for the initial review of Pemetrexed Injection.

6 General Toxicology

6.1 Single-Dose Toxicity

Study title: Acute Toxicity Study of Citric Acid in Wistar Rats by Slow Intravenous Administration

Study no.:	VLL/0721/G/T113
Study report location:	4.2.3.1
Date of study initiation:	July 24, 2021
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Citric acid: ASPXDP11042 (98.7%), ASPXD11042A (98.4%), ASPXDP11042B (99.1%) Test article: Pemetrexed Injection, P2103500 (102.5%) Reference product: Pemetrexed (Alimta ®), S20G041A

Key Study Findings

- There were no clinical signs or changes in body weight, hematology, clinical chemistry, calcium levels, urinalysis, or gross pathology after IV administration of citric acid doses ≤150 mg/kg (~3- times the citric acid levels at the clinical dose of 500 mg/m^2 Pemetrexed Injection).
- Clinical signs of dullness, tremors, and clonic convulsions occurred in animals administered 300 mg/kg citric acid (1800 mg/m^2), a dose approximately 6-times higher than the amount of citric acid excipient in the proposed formulation at the recommended clinical dose of 500 mg/m^2 based on body surface area.
- Potassium levels were increased 16.67% in females administered 300 mg/kg citric acid compared to vehicle-treated controls on Day 15.

Methods

Doses:	0, 75, 150, or 300 mg/kg citric acid; 75 mg/kg test article; 75 mg/kg reference product; a sham (untreated) group was also included
Frequency of dosing:	Single dose
Route of administration:	Intravenous infusion over 10 minutes
Dose volume:	5 mL/kg
Formulation/Vehicle:	Sodium chloride injection
Species/Strain:	Wistar rat
Number/Sex/Group:	10/sex/group
Age:	<9 weeks old
Weight:	Males: 165.11-222.64 g; Females: 126.68-180.76 g
Satellite groups:	None
Unique study design:	None
Deviation from study protocol:	None

Observations and Results

Mortality

No mortalities

Clinical Signs

Dullness, tremors, and clonic convulsions occurred in animals administered 300 mg/kg citric acid, 1-4 hours post-dose, but resolved by Day 2.

Table 1: Clinical Signs in Rats

		Male						Female					
Clinical sign	Time point	0 mg/kg	75 mg/kg CA	150 mg/kg CA	300 mg/kg CA	75 mg/kg Test	75 mg/kg Ref	0 mg/kg	75 mg/kg CA	150 mg/kg CA	300 mg/kg CA	75 mg/kg Test	75 mg/kg Ref
Dullness	Immediately post-dose										8		
	1h post-dose				5								
Tremors	1h post-dose										2		
	4h post-dose										3		
Clonic convulsions	4h post-dose										2		

CA=citric acid; Test=pemetrexed test article; Ref=pemetrexed reference product

Body Weights

Unremarkable

Feed Consumption

Unremarkable

Hematology

Hematology parameters were measured on Day 15. Findings were unremarkable.

Clinical Chemistry

Serum calcium measurements were collected pre-dose, 10 minutes and 1 hour post-dose on Day 1, and on Day 14. Serum calcium levels were increased at all dose levels immediately post-dose compared to vehicle-treated animals; however, this finding is not considered treatment-related as values were similar to sham animals. In males administered 300 mg/kg citric acid, calcium levels were also slightly higher (5.29%) 1 hour post-dose on Day 1 compared to sham animals. All other clinical chemistry parameters were measured on Day 15; potassium levels were increased 16.67% (not statistically significant) in females administered 300 mg/kg citric acid compared to vehicle-treated controls.

Table 2: Changes in Serum Calcium Levels Compared to Vehicle-Treated Control Rats

	Male					Female				
	75 mg/kg CA	150 mg/kg CA	300 mg/kg CA	75 mg/kg Test	75 mg/kg Ref	75 mg/kg CA	150 mg/kg CA	300 mg/kg CA	75 mg/kg test	75 mg/kg Ref
Pre-dose	-1.66%	-2.40%	-1.39%	-0.92%	1.39%	-0.90%	-0.18	0.36%	-1.26%	-1.08%
Immediately post-dose	3.61%	3.21%	*7.33%*	2.61%	*4.12%*	0.20%	2.63%	2.05%	0.29%	-0.98%
1h post-dose	0.66%	1.89%	*5.59%*	1.89%	9.50%	1.72%	2.48%	2.87%	1.53%	1.43%
Day 14	1.08%	0.79%	-0.10%	0.00%	-0.29%	-1.83%	-0.10%	0.48%	0.38%	1.15%

CA=citric acid; Test=test article (pemetrexed injection); Ref=reference product
Bold: p<0.05; bold and italic: p<0.01

Urinalysis

Unremarkable

Gross Pathology

Unremarkable

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/s/

MELISSA A PEGUES
03/10/2022 09:38:37 AM

CLAUDIA P MILLER
03/10/2022 10:32:37 AM

MEMORANDUM

Date: November 5, 2020
From: Whitney S. Helms, PhD
Supervisory Pharmacologist
Division of Hematology Oncology Toxicology for Division of Oncology 2
To: NDA 214408 (Pemetrexed Injection)
Re: Pharmacology and Toxicology

On January 27, 2020 Accord submitted a New Drug Application (NDA) for Pemetrexed Injection (pemetrexed disodium hemipentahydrate) under the 505(b)(2) pathway, identifying the listed drug as ALIMTA® under NDA 021462 held by Eli Lily, approved on February 4, 2004. No new nonclinical information was included in the current submission; however, the Applicant has proposed a specification for the (b) (4) impurity of NMT (b) (4)% and included a justification for this specification in Module 3. While only a minor metabolite identified in urine in multiple species (mouse, dog, and human), detected levels in urine were as high as (b) (4)% of the parent exposure. Considering that (b) (4) is a known metabolite of pemetrexed present at higher levels than the proposed (b) (4)% limit, there is sufficient data to support this specification and the proposed limit does not represent a significant safety risk from a toxicological perspective.

The CMC team also consulted the pharmacology/toxicology team on two additional issues: the levels of 2 leachables and the acceptability of the excipients. The two leachables were (b) (4) detected at (b) (4) ppm and (b) (4) at up to (b) (4) ppm. There is sufficient data to support the safety of (b) (4) at this level in the current product. For (b) (4) the Applicant suggested an analytical evaluation threshold of (b) (4) µg/mL (ppm), based on a threshold of toxicological concern (TTC) of (b) (4) µg/g. The Applicant appears to have based on the TTC on an oral LD50 of (b) (4) mg/kg in rats included in the material safety data sheet. FDA disagrees with the Applicant's calculation of the TTC for (b) (4) Based on publicly available data, (b) (4) has some carcinogenic potential, therefore, a lower TTC is appropriate. At the actual detected levels of (b) (4) the exposure would be ≤ (b) (4) µg. Given the indications for pemetrexed in patients with advanced cancer, the fact that pemetrexed itself is genotoxic, and the recommended dosing schedule of once every 3 weeks, the ≤ (b) (4) µg level does not represent a significant safety risk. The nonclinical team conveyed concerns regarding the AET proposed by the Applicant to the CMC team in case these concerns impacted the Applicant's plan for testing but stated that the current levels were acceptable.

Finally, amount of citric acid in the proposed formulation is high: up to (b) (4) (b) (4) at the 500 mg/m^2 pemetrexed dose. The Applicant included a justification for this amount of citric acid based on its presence in another drug in the inactive ingredient database, however the other product is infused over an hour vs a 10-minute infusion for pemetrexed. There is a long history of use of citric acid in humans, including as an

excipient and as an anticoagulant in infused blood products and the literature includes a known risk of citric acid intoxication and metabolic alkalosis. Acute toxicity data identify LD_{50}s for citric acid given as an intravenous injection of as low as 42 mg/kg (126 mg/m^2) in mice though lethal doses were higher in larger species given slower infusions[1]. Given the long history of human use of citric acid, the justification for this level of citric acid was discussed with the clinical team which concluded that, clinically, the infusion rate for citric acid is based on a study in rats with a maximum infusion rate of 1 mmol/kg/hr [2] or 0.02 mmol/kg/min as the maximum due to citrate metabolism. With a molecular weight of 192 g/mol, the 0.02 mmol/kg/min maximum infusion rate of citric acid in mg/kg is approximately 3.84 mg/kg/min. At (b) (4) mg with an infusion of 10 minutes and considering a body weight of 50 kg, the rate of citric acid given with Pemetrexed Injection would be approximately (b) (4) mg/kg/minute, suggesting that proposed amount of citric acid may be acceptable; however, there was residual uncertainty that the level of citric acid was reasonably supported by the available data. As a result, FDA sent the following information request for any additional support for the amount and infusion rate of citric acid:

> While we acknowledge the justification for the total daily dose of citric acid at the proposed concentration of this excipient for Pemetrexed Injection, the justification appears to be based on a product with a slow infusion of citric acid over 24 hours. Published data suggests that faster infusion of large amounts of citric acid can have acute toxicity that includes convulsions and EKG changes due to changes in calcium concentrations and that the threshold for the risk these toxicities increases as infusion time increases with an LD50 of around 126 mg/m^2 in mice following IV infusion (compared to up to (b) (4) mg/m^2 of citric acid in the proposed 10 minute infusion of pemetrexed). Please provide any additional data, including clinical data, to justify the safety of administration of the proposed amount of citric acid over the rapid infusion time of 10 minutes.

The Applicant's response consisted of cited data from Bunker et. al 1955[3] which described the potential for citric acid toxicity as a part of large volume blood infusion with citric acid used as an anticoagulant. The Applicant calculates the citric acid infusion rate at which patients didn't have issues in this paper as 783 mg/10 ml (around 1.1 mg/kg/min) but the authors of paper state that the while rate of 0.5 mg/kg/min did not have any effects, "as the rate of infusion was increased to 1 mg per kilogram per minute (or approximately 500 cc. of blood in 15 minutes) for a patient who weighed 70 kg. (154 lb.) the concentration of serum citrate rose above 9 mg per 100 cc. in half of the normal patients and in all but an occasional patient with liver disease. Correspondingly, there

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[1] PubChem [Internet]. Bethesda (MD): National Library of Medicine (US), National Center for Biotechnology Information; 2004-. PubChem Compound Summary for CID 311, Citric acid; [cited 2020 Sept. 22]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Citric-acid

[2] Toyoshima S, Fukuda T, Masumi S, Nakashima Y, Kawaguchi Y, Nakayama M. Maximum acceptable infusion rate of citrate: relationship between blood ionized calcium levels and cardiovascular effects in anesthetized rats. Clin Nutr. 2006 Aug;25(4):653-60

[3] Bunker J.P., Stetson J.B., Coe R.C., Grillo H.C., Murphy A.J. (1955), Citric acid intoxication, The Journal of the American Medical Association, Vol. 157, No. 16, p 1361-1367

was an increasing tendency for the calculated ionized calcium level to fall, although in some cases this was prevented or corrected by the intravenous administration of calcium, usually as the chloride salt." The clinical team did not consider this data robust enough to mitigate the levels of citric acid in the current formulation.

The safety of the proposed rate of citric acid infusion in the Applicant's pemetrexed product is, at least potentially, a rate that could be toxic. Furthermore, trying to address the potential safety issue by amending the product label to recommend changing the infusion rate of pemetrexed for this single pemetrexed product appears insufficient to address this specific formulation-related toxicity. In the absence of additional data, the infusion rate of citric acid in Pemetrexed Injection is not supported from a safety perspective. To address this data gap, the Applicant plans to conduct an acute animal toxicity study and will submit a protocol for FDA comment prior to initiating a study. A single dose animal toxicology study designed to compare infusion of Pemetrexed Injection and the listed drug at dose levels that result in sufficient coverage of the citric acid at a relevant infusion rate that includes an assessment of acute mortality and electrolyte levels during and immediately following infusion could address this safety concern. In the absence of the proposed animal study or other additional data to support the infusion rate of citric acid, the pharmacology/toxicology team does not recommend approval at this time.

Table 1: Formulation of Pemetrexed Injection

Ingredients	RLD [ALIMTA of Eli Lilly]				Applicant's Pemetrexed Inj.	
	RLD lyophilized formulation		RLD after re-constitution & before dilution (25 mg/mL)	RLD After dilution (b) (4)	Before dilution (25 mg/mL) [proposed formulation]	After dilution (b) (4)
	100 mg	500 mg				
Pemetrexed	100	500	25 mg/mL		25 mg/mL	
Mannitol	106	500	25 mg/mL (approx.)		--	
Anhydrous Citric Acid	--	--	--	--	15 mg/mL	
L-Methionine	--	--	--	--	0.5 mg/mL	
Monothioglycerol	--	--	--	--	4.4 mg/mL	
Sodium hydroxide and /or Hydrochloric acid (for pH adjustment)	q.s. for pH adjustment	q.s. for pH adjustment	q.s. for pH adjustment	q.s. for pH adjustment	q.s. for pH adjustment	q.s. for pH adjustment

(b) (4)

Excipients	Per mL quantity of excipients in Pemetrexed Injection 25 mg/mL	Max. daily intake of excipients as per drug substance maximum daily dose (b) mg
Anhydrous Citric Acid	15 mg/mL	(b) (4)
L-Methionine	0.50 mg/mL	
Monothioglycerol	4.40 mg/mL	

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/s/

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