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APPLICATION NUMBER:

208746Orig1s000

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:	208746
Supporting document/s:	4
Applicant's letter date:	September 15, 2016
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Product:	Pemetrexed (as ditromethamine) for injection
Indication:	NSCLC
Applicant:	Hospira Inc 275 North Field Dr Dept 0392 BLDG H1-2N LAKE FOREST, ILLINOIS 60045 UNITED STATES
Review Division:	DHOT (DOP2)
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1 Executive Summary

1.1 Introduction

On September 15, 2016 Hospira, Inc., submitted a New Drug Application (NDA) for Pemetrexed (as ditromethamine) for injection under the 505(b)(2) pathway, identifying the reference listed drug as ALIMTA® under NDA 021462 held by Eli Lily, approved on February 4, 2004. Pemetrexed is a folate analog metabolic inhibitor.

1.2 Brief Discussion of Nonclinical Findings

Hospira is relying on the findings described in the label for ALIMTA to support the nonclinical requirements for evaluation of pemetrexed (as ditromethamine). The Hospira drug is a change in the salt form of pemetrexed from a disodium salt to a ditromethamine salt. Other changes include the use of mannitol as (b) (4) for the lyophilized product. The nonclinical data submitted to support NDA 208746 was limited to the qualification of any novel impurities or high levels of excipients or degradants and the comparability of the Hospira product to the reference listed drug.

The Applicant conducted a single dose intravenous study to qualify the (b) (4) impurity identified in Hospira's Pemetrexed (as ditromethamine) under accelerated storage conditions. Four groups of dogs received 25 mg/kg (500 mg/m^2; the recommended clinical dose of pemetrexed) of Alimta or Hospira Pemetrexed with or without the added impurity. The Applicant used pemetrexed (as ditromethamine) with (b) (4) at levels of (b) (4)% (resulting in a (b) (4) dose of ~ (b) (4) µg/kg) in one group and (b) (4)% (resulting in a (b) (4) impurity dose of ~ (b) (4) µg/kg, (b) (4) mg/m^2) in another group. No mortalities or treatment-related effects were noted in ophthalmology, urinalysis, organ weights, and macroscopic assessments. Transient decreased food consumption occurred beginning on Day 2 and continuing through Day 5 in all pemetrexed treated groups. Concurrently, a transient, minimal decrease in body weight was noted through Day 11 in all pemetrexed-treated groups. All changes in body weight and food consumption were comparable between Alimta-treated and Hospira Pemetrexed (with or without impurity)-treated animals. Clinical observations in all treatment groups included gastric toxicity (soft/mucoid/watery feces), emesis/vomitus, and inappetence in 1-3 animals per treatment group; all signs recovered by the end of the recovery period. Hematology findings of decreased leukocytes and increased fibrinogen occurred in all pemetrexed-treated animals. Microscopic histopathology findings were limited to the GI tract and consisted of minimal to mild necrosis/degeneration. There were no clear differences in hematology and clinical chemistry or histopathological findings in Hospira pemetrexed with impurities versus Hospira pemetrexed or Alimta.

The Applicant also conducted a toxicokinetic assessment of pemetrexed in each of the dosing groups. While the Applicant states that there were no statistical differences in the exposure (Cmax and AUC) to pemetrexed for Alimta versus the Hospira products, there were clear increases in the mean Cmax (~2x) and AUC (~60%) for Hospira pemetrexed without impurities versus Alimta. The Cmax values for Hospira pemetrexed

with impurities (both dose levels) remained elevated compared to Alimta; however, the AUC values for the high impurity products were within a comparable range (<10%) of the listed drug exposure.

Overall this study supported the safety of the [redacted] impurity at levels of up to [redacted] mg/m^2, approximately [redacted] times the delivered dose of [redacted] mg/m^2 at the 500 mg/m^2 recommended clinical dose of pemetrexed and the proposed [redacted] shelf-life specification of [redacted]%. In addition, the study suggests comparable safety between the listed drug, Alimta, and the Hospira products, though the toxicokinetic data is too unclear to fully support comparability to the listed drug.

1.3 Recommendations

1.3.1 Approvability

There were no pharmacology/toxicology issues that arose during the review period that would prevent approval of Hospira Pemetrexed. The Applicant plans to rely on nonclinical findings for the listed drug, Alimta, to support nonclinical sections of the label.

1.3.2 Additional Non Clinical Recommendations

None

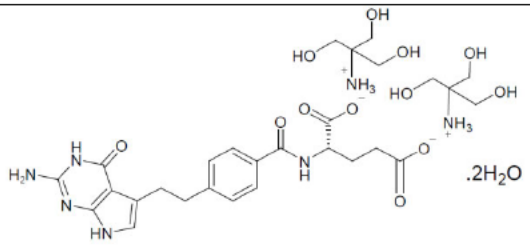
1.3.3 Labeling

Labeling was not completed for this application due to manufacturing issues that would prevent the approval of Hospira pemetrexed during the current review cycle.

2 Drug Information

2.1 Drug

CAS Registry Number	1851348-04-3
Generic Name	Pemetrexed ditromethamine
Code Name	Pemetrexed ditromethamine dehydrate, RA034
Chemical Name	Ditromethamine (2S)-2-[[4-[2-(2-amino-4-oxo-4,7 - dihydro-1H -pyrrolo[2,3-dipyrimidin-5-yl)ethyl]benzoyl] amino]-pentanedioate dehydrate OR L-Glutamic acid, N-[4-[2-(2-amino-4,7-dihydro-4- oxo-lH-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-.ditromethamine dihydrate
Molecular Formula/Molecular Weight	$C_{28}H_{47}N_{7O}14$ / 705.68

Structure or Biochemical Description	
Pharmacologic Class	Folate analog metabolic inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 131252 for Hospira pemetrexed

2.3 Drug Formulation

Component	Quantity per Milliliter (mL)	Strength: 25 mg/mL Presentations					
		100 mg/vial		500 mg/vial		1 g/vial	
		Nominal Quantity per unit	Quantity per unit (includes (b) (4) overfill)[3]	Nominal Quantity per unit	Quantity per unit (includes (b) (4) overfill)[3]	Nominal Quantity per unit	Quantity per unit (includes (b) (4) overfill)[3]
Pemetrexed ditromethamine[1] (*as pemetrexed base*)	39.17 mg (25.0 mg[5])	156.68 mg (100 mg[4])	(b) (4)	783.4 mg (500 mg[4])	(b) (4)	1566.8 mg (1000 mg[4])	(b) (4)
Mannitol	(b) (4)	(b) (4)	106 mg[4]	(b) (4)	500 mg[4]	(b) (4)	1000 mg[4]
Water for Injection[2]							(b) (4) (b) (4) (b) (4)

[1] Factored to 100% basis. Refer to *Section 3.2.P.2* for the formulation development.

[2] Once reconstituted, the strength of the active pharmaceutical ingredient, Pemetrexed, is 25 mg/mL for all presentations.

[3] Each vial of Pemetrexed (as ditromethamine) for Injection contains a sufficient excess to allow withdrawal of the labelled quantity of drug substance. The quantity per unit values presented are inclusive of this excess. The target excess compared to labelled quantity pemetrexed is (b) (4). Refer to *Section 3.2.P.2.2.1 Formulation Development* for discussion on overfills.

[4] These amounts refer to the label claim.

[5] Removed during lyophilization.

[6] (b) (4)

(Excerpted from Applicant's submission)

2.4 Comments on Novel Excipients

No novel excipients were included in the current formulation. The maximum amount of mannitol delivered at the recommended clinical dose of 500 mg/m^2 is approximately (b) (4) mg assuming a human body surface area of 2. This dose is significantly lower than the approved dose of mannitol for the prevention of renal failure of 50-100g. The safety of mannitol at this level is, therefore, reasonably covered by clinical experience.

2.5 Comments on Impurities/Degradants of Concern

Hospira conducted a single dose intravenous administration study for qualification of a (b) (4) impurity identified in Hospira's Pemetrexed (as ditromethamine) under accelerated storage conditions. (Study reviewed below). With the (b) (4) impurity included in the Hospira product and delivered to dogs at concentrations of up to ~ (b) (4) µg/kg ((b) (4) mg/m^2), there was no clear difference in toxicity between Hospira pemetrexed with impurities or with the listed drug. At the proposed shelf-life specification of no more than (b) (4)%, patients would receive no more than (b) (4) mg/m^2 at the recommended pemetrexed dose of 500 mg/m^2 given once every 3 weeks. The safety of this impurity at the proposed limit is reasonably supported by the nonclinical data.

2.6 Proposed Clinical Population and Dosing Regimen

Hospira Pemetrexed for Injection has the same route of administration, indications, and method of use as the reference listed drug, Alimta. This included intravenous administration of 500 mg/m^2 once every 3 weeks in combination with cisplatin for NSCLC and mesothelioma and single agent use at 500 mg/m^2 once every 3 weeks for NSCLC.

2.7 Regulatory Background

A preNDA meeting occurred on November 30, 2015.

6 General Toxicology

6.1 Single-Dose Toxicity

Study title: Hospria Pemetrexed (as ditromethamine): A Single Dose Intravenous Infusion Toxicity Study with a 14-Day Recovery Period in Beagle Dogs

Study no.:	1203-019
Study report location:	EDR 4.2.3.7.6
Conducting laboratory and location:	(b) (4) [redacted] USA
Date of study initiation:	September 30, 2015
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Hospira Pemetrexed/PD11501/98.2%

Key Study Findings

- No mortalities occurred during study
- There was no clear difference in toxicity between the listed drug and the Hospira product with or without spiked impurity
- Findings were ascribed to both Alimta and Hospira Pemetrexed and included
  - GI toxicity as shown by clinical signs
  - Histopathology findings of minimal and mild degeneration and necrosis along the GI tract
  - Hematology findings of decreased leukocytes typically associated with pemetrexed treatment

Methods

Doses:	25 mg/kg; See Table 1
Frequency of dosing:	Single dose on Day 1; 14 day recovery
Route of administration:	Intravenous infusion over 10 minutes

Dose volume:	2 mL/kg
Formulation/Vehicle:	Saline (0.9% sodium chloride)
Species/Strain:	Beagle dogs
Number/Sex/Group:	5/sex/group
Age:	6-7 months
Weight:	Males 7.9-11 kg; Females 6.6-8.7 kg
Satellite groups:	None
Unique study design:	Impurity qualification study
Deviation from study protocol:	None that impacted study outcome

Table 1: Doses used in single dose IV study in dogs

Group Number	Test Article	Dose Level (mg/kg)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	Number of Animals	
					Male	Female
1	Control Saline	0	2.0	0	5[a]	5[a]
2	Hospira Pemetrexed (without impurity)	25	2.0	12.5	5[a]	5[a]
3	Alimta®	25	2.0	12.5	5[a]	5[a]
4	Hospira Pemetrexed[b]	25	2.0	12.5	5[a]	5[a]
5	Hospira Pemetrexed[c]	25	2.0	12.5	5[a]	5[a]

[a]Two animals remained on study for the 14-day untreated recovery period.
[b]Low dose impurity exposure at approximately (b) (4) µg/kg
[c]Mid dose impurity exposure at approximately (b) (4) µg/kg

(Excerpted from Applicant's submission)

The positive control article, Alimta, and test article, Hospira Pemetrexed as ditromethamine for Injection (without impurity), and Hospira Pemetrexed as ditromethamine for Injection containing the (b) (4) impurity at a targeted content of approximately (b) (4) % (Group 4) and (b) (4) % (Group 5) were used as received. When pemetrexed is dosed at the human equivalent dose of 500 mg/m^2 in the beagle dog (25mg/kg) this equates to an approximate (b) (4) impurity dose of (b) (4) µg/kg in the low dose, and (b) (4) µg/kg in the mid dose treatment groups, respectively.

Observations and Results

Mortality

Monitored twice daily

- Unremarkable

Clinical Signs

Monitored twice daily with detailed examinations twice weekly

Clinical signs in Alimta and Hospira (with and without impurity) treated animals included:

- Watery/soft/mucoid feces occurred from Day 3 to Day 7 (1-2 animals per group)
- Emesis occurred Day 2 to Day 4 (3 animals per group)
- Inappetence occurred on Day 3 (1-2 animals per group)

- One male treated with (b) (4) µg/kg of impurity showed decreased activity on Day 4 which correlated with decreased food consumption on Days 3-5. No other animals showed decreased activity

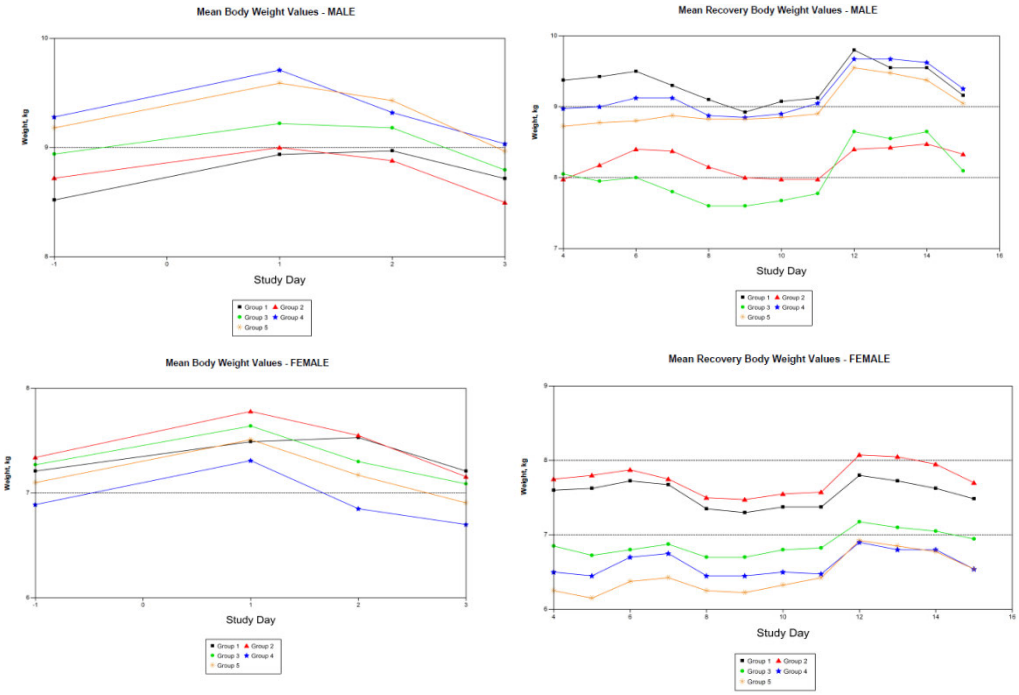
- All clinical signs fully resolved by the end of the recovery period

Body Weights

Recorded daily

- Decreased body weight in all treated groups through Day 3 to terminal necropsy
- Recovery animals showed a reversal toward controls by Day 11

Figure 1: Mean body weight changes in male (upper panels) and female (lower panels) dogs up to terminal and recovery necropsies



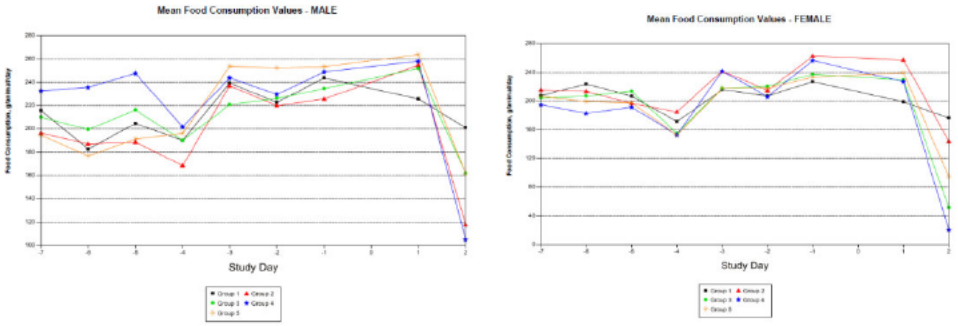
(Excerpted from Applicant's submission)

Feed Consumption

Recorded daily

- Decreased food consumption began on Day 2 and continued through terminal necropsy on Day 3
- Recovery animals continued to exhibit decreased food consumption with a trend toward controls occurring by the end of recovery period
- No difference occurred between Alimta treated and Hospira treated animals

Figure 2: Food consumption trends in dogs treated with Alimta or Hospira with or without impurity



(Excerpted from Applicant's submission)

Ophthalmoscopy

Performed pre dosing and prior to necropsy

- Unremarkable

ECG

Not conducted

Hematology

Collected on Days -1, 2, 3, 7, and 15, coagulation conducted on all on Days -1, 3, and 15

- Decreased leukocyte including neutrophils, lymphocytes, eosinophils, basophils
  - Recovered by end of recovery period
- Increased fibrinogen
  - Still present at recovery
- No significant differences in hematology changes between Hospira pemetrexed without impurities versus with impurities

Table 2: Hematology effects of Alimta or Hospira with and without impurity

Table I. Summary of Effects on Leukocytes[a]

		Reference Listed Drug		25 mg/kg Hospira Pemetrexed					
		25 mg/kg Alimta[c]		Without impurity		(b) (4) µg/kg impurity		(b) (4) µg/kg impurity	
		Group 3		Group 2		Group 4		Group 5	
	Interval	M	F	M	F	M	F	M	F
WBC	Day 2	--	--	--	--	--	--	--	--
	Day 3	--	--	--	--	-25%	--	--	--
	Day 7	-25%	-41%	-31%	-42%	-40%	-39%	-48%	-34%
	Recovery[b]	--	--	--	--	--	--	--	--
Neut	Day 2	--	--	--	--	--	--		--
	Day 3	--	--	--	--	--	--		--
	Day 7	-22%	-60%	-37%	-47%	-61%	-53%	-58%	-49%
	Recovery[b]	--	--	--	--	--	--	--	--
Lymph	Day 2	--	--	-22%	--	--	--	--	--
	Day 3	-26%	-28%	-25%	-29%	-29%	-30%	-29%	-28%
	Day 7	-46%	-29%	-51%	-43%	[redacted]	-19%	[redacted]	-16%
	Recovery[b]	--	--	--	--	--	--	-18%	--
Eosino	Day 2	-37%	--	-27%	-42%	--	--	-37%	--
	Day 3	-41%	-34%	-50%	-67%	-37%	-48%	-42%	-64%
	Day 7	-73%	--	--	-71%	--	--	--	--
	Recovery[b]	--	--	--	--	--	--	--	--
Baso	Day 2	-85%	-88%	-92%	-85%	[redacted]	-77%	[redacted]	-87%
	Day 3	-85%	-86%	-92%	-88%	-89%	-91%	-94%	-83%
	Day 7	-71%	-64%	-47%	--	-100%	-32%	--	--
	Recovery[b]	--	--	--	--	--	--	--	--

Table I. Summary of Effects on Leukocytes[a]

		Reference Listed Drug		25 mg/kg Hospira Pemetrexed					
		25 mg/kg Alimta[6]		Without impurity		(b) (4) µg/kg impurity		(b) (4) µg/kg impurity	
		Group 3		Group 2		Group 4		Group 5	
	Interval	M	F	M	F	M	F	M	F
Other	Day 2	-70%	-53%	-75%	-62%	-74%	-39%	-67%	-64%
	Day 3	-41%	-50%	-47%	-41%	-44%	--	--	--
	Day 7	--	-53%	--	-71%	-100%	--	--	--
	Recovery[b]	--	--	--	--	--	--	--	--

[a] Percent change relative to pretest mean; [b] Recovery collection on Day 15
M – Male; F – Female
--No meaningful change
WBC – Total leukocyte count; Neut – Neutrophil count; Lymph – Lymphocyte count; Eosino – Eosinophil count; Baso – Basophil count; Other – "Other cells" count

		Reference Listed Drug		25 mg/kg Hospira Pemetrexed					
		25 mg/kg Alimta[6]		Without impurity		(b) (4) µg/kg impurity		(b) (4) µg/kg impurity	
		Group 3		Group 2		Group 4		Group 5	
	Interval	M	F	M	F	M	F	M	F
Fibrinogen	Day 3	+20%	+20%	+15%	+36%	+25%	+19%	+20%	+28%
	Recovery[b]	+37%	+16%	+19%	+31%	+11%	+22%	--	+22%

[a] Percent change relative to pretest mean; [b] Recovery collection on Day 15
M – Male; F – Female
--No meaningful change

(Excerpted from Applicant's submission)

Clinical Chemistry

Collected on Days -1, 2, 3, 7, and 15

- Decreased albumin up to -18% compared to pretest values occurred in all treatment groups
- On Day 15 one female in the Hospira Pemetrexed without impurity had a 5.9-fold increase in ALT compared to pretest value; however there were no histopathological correlates or acute findings following injection suggesting that it was clearly drug related.

Urinalysis

Conducted on all on Days -1, 3, and 15

- Unremarkable

Gross Pathology

- Unremarkable

Organ Weights

- Unremarkable

Histopathology

Adequate Battery yes

Peer Review no

Histological Findings
No impurity-related microscopic observations occurred and all observations were ascribed to the test articles. All histologic findings occurred in the GI tract and had reversed by the recovery necropsy.

Table 3: Histopathology findings in dogs treated with Alimta or Hospira Pemetrexed with or without impurity

Group	1		2		3		4		5	
Sex	M	F	M	F	M	F	M	F	M	F
Number Examined	3	3	3	3	3	3	3	3	3	3
Tongue										
Degeneration/necrosis, epithelial										
-minimal	0	0	3	1	2	1	2	3	3	3
Esophagus										
Degeneration/necrosis, epithelial										
-minimal	0	0	3	3	3	3	3	3	3	3
Stomach, cardia										
Degeneration/necrosis, epithelial										
-minimal	0	0	2	3	3	3	2	3	2	3
Stomach, pylorus										
Degeneration/necrosis, mucosal	0	0	3	3	3	3	3	3	3	3
-minimal	0	0	3	2	0	3	2	0	1	1
-mild	0	0	0	1	3	0	1	3	2	2
Small intestine, duodenum										
Degeneration/necrosis, mucosal	0	0	3	2	3	3	3	3	3	3
-minimal	0	0	2	1	1	0	1	0	0	0
-mild	0	0	1	1	2	2	2	3	2	2
-moderate	0	0	0	0	0	1	0	0	1	1
Small intestine, ileum										
Degeneration/necrosis, mucosal	0	0	3	2	3	3	3	3	3	3
-minimal	0	0	3	2	2	0	2	3	2	0
-mild	0	0	0	0	1	3	1	0	1	3
Small intestine, jejunum										
Degeneration/necrosis, mucosal	0	0	3	2	3	3	3	3	3	3
-minimal	0	0	2	2	2	0	1	1	1	0
-mild	0	0	1	0	1	2	2	2	2	2
-moderate	0	0	0	0	0	1	0	0	0	1
Large intestine, cecum										
Degeneration/necrosis, mucosal	0	0	3	2	3	3	3	3	3	3
-minimal	0	0	3	1	3	1	0	2	1	0
-mild	0	0	0	1	0	2	3	1	2	3
Large intestine, colon										
Degeneration/necrosis, mucosal	0	0	3	0	3	3	3	3	3	3
-minimal	0	0	3	0	2	0	0	2	0	0
-mild	0	0	0	0	1	3	3	1	3	3
Large intestine, rectum										
Degeneration/necrosis, mucosal	0	0	2	2	3	3	3	3	3	3
-minimal	0	0	2	2	3	2	1	2	0	1
-mild	0	0	0	0	0	1	2	1	3	2

M: Male; F: Female
Group 1: Control Saline 0 mg/kg
Group 2: Pemetrexed (as ditromethamine) for Injection, 25 mg/kg (without impurity)
Group 3: Alimta® 25 mg/kg
Group 4: Pemetrexed (as ditromethamine) for Injection, 25 mg/kg. Low dose impurity exposure at approximately (b) (4) mg/kg
Group 5: Pemetrexed (as ditromethamine) for Injection, 25 mg/kg. Mid dose impurity exposure at approximately (b) (4) mg/kg

(Excerpted from Applicant's submission)

Special Evaluation

None

Toxicokinetics

Samples were collected predose, within 2 minutes of the end of infusion, and at 0.25, 0.5, 1, 2, 4, 8, 16, and 24 hours from the start of infusion on Day 1

- Cmax for Hospira Pemetrexed was consistently higher than Alimta
- Mean AUC for Hospira Pemetrexed without impurities was ~60% higher than Alimta; however the AUCs for the Hospira pemetrexed with impurities were within 10% of that of the listed drug
- No differences in exposure occurred between sexes
- Pre dose samples did not contain measurable levels of any test article

Table 4: Toxicokinetic data from Beagle dogs dosed with Alimta and Hospira Pemetrexed with and without added impurity

Group Number	Test Article	C_{max} (ng/mL)[c]	$AUC_{0\text{-}24hr}$ (hr*ng/mL)[c]
2	Hospira Pemetrexed (without impurity)	243000	160000
3	Alimta®	104000	97900
4	Hospira Pemetrexed[a]	138000	107000
5	Hospira Pemetrexed[b]	119000	103000

[a]Low dose impurity exposure at approximately (b) (4) µg/kg.
[b]Mid dose impurity exposure at approximately (b) (4) µg/kg.
[c]Numbers presented are the alternative mean.

(Excerpted from Applicant's submission)

Considering there were no differences in exposure between sexes, the data was combined.

Dosing Solution Analysis

Dosing solutions fell within the acceptance criteria ((b) (4) % of theoretical dose level; relative standard deviation ≤ 5%).

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/s/

STEPHANIE L AUNGST
06/16/2017

WHITNEY S HELMS
06/16/2017

I concur with Dr. Aungst's conclusions that the limited nonclinical data submitted are sufficient to qualify the proposed specification for [redacted] (b) (4) and demonstrate reasonable comparability between the toxicity of Hospira Pemetrexed and the listed drug, Alimta. As the Applicant is relying on the FDA's previous findings from the summary basis of approval of the listed drug, I also concur that there are no outstanding issues identified from a pharmacology/toxicology perspective during this review cycle that would prevent its approval and no deficiencies from a pharmacology/toxicology perspective that need to be addressed as a part of the complete response.