Clinical Pharmacology Review

NDA	21-462
Submission Date:	17 Sept., 2010
Brand Name:	Alimta™
Generic Name:	Pemetrexed disodium injection
Formulation:	100 mg and 500 mg Powder, Lyophilized, For Solution for Intravenous (iv) Use
OCP Reviewer:	Jeanne Fourie Zirkelbach, PhD
OCP Team Leader:	Qi Liu, PhD
OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Drug Oncology Products
Sponsor:	Eli Lilly Company
Submission Type; Code:	0065 - Efficacy Supplement, Pediatric Exclusivity
Dosing regimen:	500 mg/m^2 i.v. on Day 1 of each 21-day cycle.
Approved Indication:	Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer and Mesothelioma as a single agent or in combination with cisplatin.

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1 EXECUTIVE SUMMARY

Pemetrexed disodium injection (Alimta®) is currently indicated for locally advanced or metastatic nonsquamous non-small cell lung cancer and mesothelioma as a single agent or in combination with cisplatin (NDA 21-462). The current efficacy supplement was submitted to FDA for pediatric exclusivity determination. The applicant submitted proposed labeling and pediatric study results from two clinical trials to address the Pediatric Written Request.

Protocol H3E-US-JMFC was a phase 1 dose-escalation trial of pemetrexed in children and adolescents with recurrent solid tumors. Pediatric patients (n = 32) received pemetrexed given as 10-minute intravenous (iv) infusion every 21 days. The maximum tolerated dose (MTD) of pemetrexed was determined to be 1910 mg/m^2. The single dose plasma pemetrexed pharmacokinetics were characterized in pediatric patients (13 male and 9 female) aged 4 to 18 years over the dose range of 400 to 2480 mg/m^2. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration (C_{max}) increased proportionally with dose. The body surface adjusted clearance and mean terminal elimination half-life ($t1/2_\beta$) of pemetrexed appeared constant over the dose range from 400 to 2480 mg/m^2. In addition, the observed body surface area adjusted clearance of pemetrexed in pediatric patients was comparable to that in adults.

Protocol H3E-MC-JMHW was a phase 2 multi-center open-label trial in children with recurrent malignancies. The primary objectives were to examine the response rate and to further define the toxicities. Pediatric patients (n = 72) received 1919 mg/m^2 (or 60 mg/kg if patient < 12 months old) pemetrexed given as a 10-minute iv infusion every 21 days. Pharmacokinetic data were not obtained in this phase 2 trial. Results indicated that pemetrexed was not efficacious in the pediatric tumors studied.

From a Clinical Pharmacology perspective, the results from the two clinical trials submitted are acceptable, and the pediatric written request is fulfilled.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 21-462. This submission is considered acceptable from a clinical pharmacology perspective.

Labeling Recommendations

Please refer to Section 3 - Detailed Labeling Recommendations.

1.2 PHASE IV COMMITMENTS

None.

1.3 REGULATORY BACKGROUND

The applicant submitted proposed labeling and pediatric study results from two clinical trials to address the Pediatric Written Request first issued by the Division of Drug Oncology Products (DDOP) on 5 October, 2001, with amendments made on 9 July 2001, 3 July 2002, 7 may 2004, 16 April, 2007 and 2 July 2010.

1.4 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Pemetrexed disodium injection (Alimta®) is a novel antimetabolite that inhibits thymidylate synthase, dihydro folate reductase and glycinamide ribonucleotide formlyl transferase, and mediates cell death by inhibition of NDA synthesis.

The applicant submitted results from two clinical trials in pediatric patients for pediatric exclusivity determination. A phase 1 dose-escalation trial (Protocol H3E-US-JMFC) entitled "A phase 1 study of pemetrexed (LY231514, Alimta) in Children and Adolescents with Recurrent Solid Tumors" was conducted in 32 pediatric and adolescent patients. Pemetrexed was administered as 10-minute iv infusion every 21 days for at least one cycle. The single dose plasma pemetrexed pharmacokinetics were characterized over the dose range of 400 to 2480 mg/m^2 in 22 pediatric patients (13 male and 9 female) aged 4 to 18 years. Pemetrexed total systemic exposure (AUC) and maximum plasma concentration (C_{max}) increased proportionally with dose. Across all doses the geometric mean body surface area adjusted clearance of pemetrexed was 2.30 $L/h/m^2$ (39% CV), and the mean elimination half-life ($t1/2_{\beta}$) was 2.3 hours. In addition, the observed body surface area adjusted clearance of pemetrexed in pediatric patients was comparable to that in adults.

Protocol H3E-MC-JMHW was a phase 2 multi-center open-label trial in children with recurrent malignancies. The primary objectives were to examine the response rate and to further define the toxicities. Pediatric patients (n = 72) received 1919 mg/m^2 (or 60 mg/kg if patient < 12 months old) pemetrexed given as a 10-minute iv infusion every 21 days. Pharmacokinetic data were not obtained in this phase 2 trial. Results indicated that pemetrexed was not efficacious in the pediatric tumors studied.

Signatures:

Reviewer: Jeanne Fourie Zirkelbach, PhD
Division of Clinical Pharmacology 5

Team Leader: Qi Liu, PhD
Division of Clinical Pharmacology 5

Cc: DDOP: CSO - D Hanner; MTL - J Johnson; MO - A McKee,
DCP-5: Reviewers - J Fourie Zirkelbach,
DDD - B Booth
PM TL -
PG TL -
DD - A Rahman

2 QUESTION BASED REVIEW

Note: Only relevant sections were completed.

2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

2.1.3 What are the proposed dosage(s) and route(s) of administration?

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

2.2.4 Exposure-response

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

2.3.2.1 Pediatric patients

Study Design:

The applicant conducted a phase 1 dose-escalation trial (Protocol H3E-US-JMFC) in 32 pediatric and adolescent patients (21 males and 11 females). Inclusion criteria included adequate renal function (creatinine clearance $\geq$ 70 mL/min/m^2) and hepatic function (total bilirubin $\leq$ 1.5 x the upper limit of normal (ULN) for age, serum ALT $\leq$ 2.5 x ULN for age and albumin $\geq$ 2 g/dL).

The primary objectives were:

- To estimate the MTD of pemetrexed administered as a 10-minute iv infusion every 3 weeks;
- To determine the dose-limiting toxicities on this schedule;
- To characterize the plasma pharmacokinetics (PK) of pemetrexed in children with refractory cancer.

Pemetrexed was administered as 10-minute iv infusion every 21 days for at least one cycle. The starting dose was pemetrexed 400 mg/m^2 (approximately 80% of the original adult MTD), with subsequent dose escalations occurring in increments of 30%. Escalations were planned in groups of three patients, with an additional 3 patients to be added at the first indication of dose-limiting toxicity (DLT). No intrapatient dose escalations were allowed. All patients were required to take a daily oral multivitamin supplement containing 400 µg of folic acid, and intra-muscular (im) injections of cyanocobalamine (B12) were administered prior to the first dose of pemetrexed and after every third cycle (every 9 weeks). The dose was 500 µg im for children <12 years old and 1000 µg im for children and adolescents ≥12 years old.

Pharmacokinetic Data:

In Cycle 1, blood samples were collected for pharmacokinetic analysis prior to drug infusion, at the end of infusion, and 15 minutes, 30 minutes, 2 hours, 4 hours, 6 to 8 hours, and 24 hours following infusion. The single dose plasma pemetrexed pharmacokinetics were characterized using non-compartmental analysis.

Single Dose Pemetrexed Pharmacokinetic Results:

The single dose pharmacokinetics of pemetrexed were characterized in 22 pediatric patients (13 male and 9 female) over the dose range of 400 to 2480 mg/m^2. The age range of patients in the pharmacokinetic dataset was 4 to 18 years (median 12 years) (see Table 1).

Results from the FDA non-compartmental analysis showed that the body surface area adjusted clearance and mean terminal elimination half-life ($t1/2_\beta$) of pemetrexed appeared constant over the dose range from 400 to 2480 mg/m^2 (see Table 2). The geometric mean body surface adjusted clearance of pemetrexed was 2.30 L/h/m^2 (39% CV) across all doses and the mean elimination half-life was 2.3 h (range 1.2 to 4.0 h) (see Table 2).

Based on the sponsor's non-compartmental analysis, the geometric mean systemic clearance of premetrexed was reported as 2.59 L/h/m^2 (34% CV). Overall, the single dose pharmacokinetic parameters reported by the sponsor were similar to those obtained in the FDA analysis over the 400 to 2480 mg/m^2 dose range.

Table 1 Demographics of patients for pharmacokinetic evaluation:

	Age (Years)	Weight (kg)	BSA (m^2)	CrCLCG, STD (mL/min)
N	22	22	22	22
Arithmetic Mean (CV%)	11.8 (40.7)	50.2 (56.8)	1.4 (36.7)	133 (39.1)
Minimum	4	15	0.66	48.3
Maximum	18	127	2.56	247

Abbreviations: BSA = body surface area; CrCLCG = creatinine clearance by Cockcroft-Gault formula; CV% = coefficient of variation; N= number of patients; STD = standard deviation.

Table 2. Summary of Pemetrexed Single Dose Pharmacokinetics in Pediatric Patients after a single 10 min iv infusion (dose range 400 to 2480 mg/m^2). Data are from the phase 1 trial: H3E-US-JMFC and are summarized from the FDA non-compartmental pharmacokinetic analysis (Geometric Mean (CV%). Results were similar to those reported by the sponsor.

	Geometric mean (%CV)							
	400 mg/m^2	**520 mg/m^2**	**670 mg/m^2**	**870 mg/m^2**	**1130 mg/m^2**	**1470 mg/m^2**	**1910 mg/m^2**	**2480 mg/m^2**
	(N=1)	**(N=3)**	**(N=2)**	**(N=2)**	**(N=3)**	**(N=5)**	**(N=2)**	**(N=2)**
AUC0-∞ µg.h/mL	110	207 (21)	301 (6)	420 (7)	358 (15)	692 (58)	1029 (85)c	1586 (35)c
Cmax µg/mL	92 6	144 (22)	237 (10)	416 (24)	241 (3)	387 (20)	403 (17)c	766 (11)c
Tmax (h)a	0 22	0 25 (0 25-0 30)	0 24 (0 22-0 25)	0 17 (0 17-0 17)	0 25 (0 17 -0 25)	0 18 (0 17-0 33)	0 28 (0 17-0 38)c	0 18 (0 18-0 18)c
T1/2 (h)b	2 58	2 56 (2 47-2 66)	1 80 (1 26-2 57)	2 81 (2 70-2 92)	1 65 (1 18-2 40)	2 58 (2 37-2 88)	3 17 (2 53-3 99)c	1 99 (1 66-2 39)c
CL ($L/h/m^2$)	3 63	2 51 (21)	2 23 (6)	2 07 (7)	3 16 (15)	2 12 (58)	1 86 (85)c	1 56 (35)c
Vss (L/m^2)	8 26	6 20 (25)	4 25 (16)	4 48 (10)	5 88 (14	5 24 (45)	5 84 (24)c	4 30 (25)c

Abbreviations: AUC0-∞ = area under the curve from time zero to infinity; _Cmax = maximal observed concentration; CL = systemic clearance; CV = coefficient of variation; N = number of patients; t1/2 = half-life; tmax = time to maximal observed concentration; Vss = volume of distribution at steady state

a Median (range)

b Geometric mean (range)

c Patients whose AUC(tlast-∞) accounted for greater than 20% of the total AUC were omitted from the calculation, thus resulting in a sample size reduction from N=3 to N=2

Figure 1 shows that following a single iv administration, the pharmacokinetics of pemetrexed was linear and drug exposure was dose proportional within the dose range of 400 to 2480 mg/m^2.

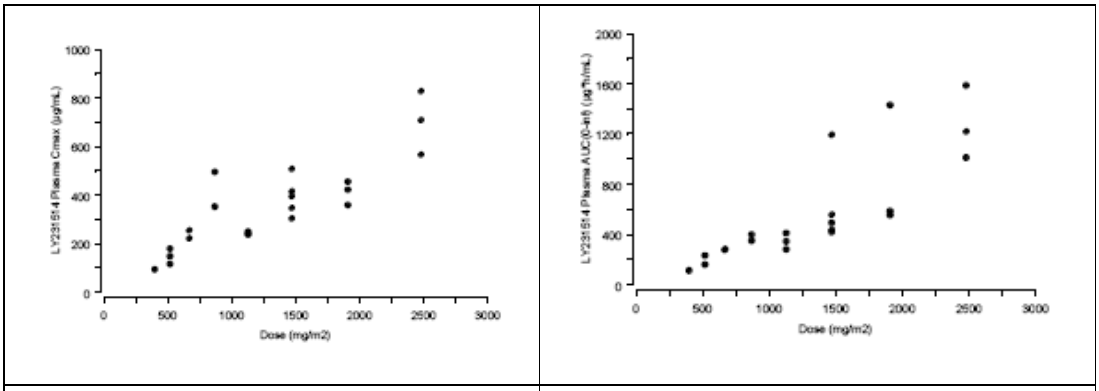

Figure 1. Relationship between individual Cmax (Left panel) and individual AUC0-∞ (Right panel) and dose level after a single 10 min iv infusion (dose range 400 to 2480 mg/m^2). Data from the phase 1 trial: H3E-US-JMFC

Pharmacokinetic data from the study were separated into age categories to investigate if there were any obvious differences in pharmacokinetics among age groups for pemetrexed. The observed body surface area adjusted clearance was comparable among the pediatric age groups and adults (adult data from a dose escalation Phase 1 study ranging from 600 to 1400 mg/m^2 in adult patients (H3E-MC-JMAS) (see Table 3).

Table 3. Sponsor's Figure Summarizing Pemetrexed Pharmacokinetics in Patients with different age groups.

	JMFC			JMAS
	Children (≥2 to <12 years) (N=11)	Adolescents (≥12 to <16 years) (N=3)	Adults (≥16 years) (N=8)	Adults (≥18 years) (N=99)
Absolute dose (mg)	1000 (442 - 2450)	988 (871 - 1760)	3460 (850 - 5100)	1590 (888 - 2740)
C_{max} (µg/mL)	346.18 (147.24 - 506.71)	221.36 (177.6 - 395.34)	437.39 (92.56 - 827.72)	N/A
C_{max} (µg/mL, normalized to 500 µg/m^2)	141 (93.6 - 284)	165 (134 - 171)	115 (103 - 167)	N/A
AUC(0-∞) (µg·h/mL)	395 (158 - 1190)	280 (229 - 436)	796 (110 - 1580)	287 (120 - 672)
AUC(0-∞) (µg·h/mL, normalized to 500 µg/m^2)	181 (123 - 405)	209 (148 - 220)	178 (138 - 374)	182 (99.8 - 302)
CL (L/h/m^2)	2.77 (1.23 - 4.06)	2.4 (2.27 - 3.37)	2.87 (1.34 - 3.63)	2.75 (1.66 - 5.01)
$t_{1/2}$ (h)	2.64 (1.18 - 3.12)	2.47 (1.26 - 2.63)	2.37 (1.15 - 3.95)	N/A
V_{ss} (L/m^2)	6.09 (4.35 - 7.82)	5 (4.08 - 6.91)	6.18 (4.72 - 8.33)	8.07 (5.32 - 12.6)

Abbreviations: $AUC_{0-\infty}$ = area under the curve from time zero to infinity; C_{max} = maximal observed concentration; CL = systemic clearance; CV = coefficient of variation; N = number of patients; $t_{1/2}$ = half-life; t_{max} = time to maximal observed concentration; V_{ss} = volume of distribution at steady state.

Determination of the maximum tolerated dose and efficacy in pediatric patients:
In the current phase 1 trial the maximum tolerated dose (MTD) was defined as the dose level at

which 0 of 6 or 1 of 6 patients experienced DLT, with at least 2 of 3 patients or 2 of 6 patients encountering a DLT at the next higher dose. Based on this definition, the MTD of pemetrexed was determined to be 1910 mg/m^2, and this dose was the dose was used in the subsequent phase 2 efficacy trial (H3E-MC-JMHW).

Protocol H3E-MC-JMHW was a phase 2 multi-center open-label trial in children with recurrent malignancies. This trial did not collect pharmacokinetic data. The primary objectives were to examine the response rate and to further define the toxicities. Pediatric patients (n = 72) received 1919 mg/m^2 (or 60 mg/kg if patient < 12 months old) pemetrexed given as a 10-minute iv infusion every 21 days. Results indicated that pemetrexed was not efficacious in the pediatric tumors studied.

2.3.2.2 Renal impairment

2.3.2.3 Hepatic impairment

2.3.2.4 What pregnancy and lactation use information is there in the application?

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

2.4.2 Drug-drug interactions

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

2.5.2 What is the composition of the to-be-marketed formulation?

2.5.3 What moieties should be assessed in bioequivalence studies?

2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?

2.6 ANALYTICAL SECTION

2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

In the current phase 1 trial (H3E-US-JMFC), plasma concentrations of pemetrexed were

determined using a validated liquid chromatography tandem mass spectroscopy (LC/MS/MS) method at the (b) (4). This was appropriate as pemetrexed is not metabolized to an appreciable extent and is primarily eliminated in the urine, with 70% to 90% of the dose recovered unchanged within the first 24 hours following administration (current package insert).

2.6.2 Which metabolites have been selected for analysis and why?

No active metabolites were measured in human plasma as pemetrexed does not have major active metabolites.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

In vitro studies indicate that pemetrexed is approximately 81% bound to plasma proteins. The total concentration of pemetrexed in plasma was measured, and this was appropriate.

2.6.4 What bioanalytical methods are used to assess concentrations? (Refer to the guidance for industry on Bioanalytical Method Validation, http://www fda.gov/cder/guidance/4252fnl.pdf)

Pemetrexed, plasma concentrations were assessed using a LC/MS/MS based bioanalytical method.

(b) (4)

2.6.4.1 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The method for measuring pemetrexed concentrations in human plasma was validated over the ranges of 10 – 2,000 and 1,000 – 200,000 ng/mL using a 100 µL sample volume. Standard curves were linear ($r^2 > 0.99$) over the specified range for both standard curves. The coefficient of variation for standard values at the lower limit of quantitation (10 ng/mL) was 4.1%. The coefficient of variation for the slope of standard curves was 9.3%. For the low concentration range standard curve, coefficients of variation for the low (30 ng/mL), medium (300 ng/mL) and high (1600 ng/mL) QC samples were 12%, 5.2% and 6.3%, respectively. For the high concentration range standard curve, coefficients of variation for the low (1600 ng/mL), medium (16000 ng/mL) and high (160000 ng/mL) QC samples were 2.2%, 0.9% and 1.2%, respectively.

Standard curves were analyzed by linear least-squares regression analysis weighted by the inverse of the ALIMTA concentration to obtain an equation of the form, $y = mx + b$, where y is the response ratio, x is the drug concentration, m is the slope of the standard curve and b is the y-intercept. Concentrations of drug in the patient plasma samples were calculated from regression parameters using the rearranged form of the equation, $x = (y-b)/m$.

2.6.4.2 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

The method was validated over 2 ranges. The lower limit of quantitation was 10 ng/mL for the low range assay and 1000 ng/mL for the high range assay, and the upper limit of quantitation was 2000 ng/mL for the low range assay and 200,000 ng/mL for the high range.

2.6.4.3 What are the accuracy, precision, and selectivity at these limits?

Accuracy: The interassay accuracy (% relative error) during validation ranged from 1.5% to 11.5%, and the intra-assay accuracy (% relative error) ranged from 3.3% to 6.1% for the low range assay. The intra-assay accuracy (% relative error) ranged from 1.6% to 6.4% for the high range assay.

Precision: The interassay precision (% relative standard deviation [STD]) during validation ranged from 5.2% to 12%, and the intra-assay precision (% relative STD) ranged from 0.2% to 8.3% for the low range assay. The intra-assay precision (% relative STD) ranged from 0.9% to 2.2% for the high range assay.

2.6.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

Pemetrexed has been shown to be stable for up to 36 months when stored at approximately -20°C.The recovery of pemetrexed from plasma was determined at 3 concentrations (30, 750 and 1600 ng/mL) after 3 freeze thaw cycles by measuring the (b) (4) peak area ratio in samples before and after the freeze-thaw cycles. Mean recoveries for 30, 750 and 1600 ng/mL were 96.9%, 99.9 and 99.2%, respectively.

2.6.4.5 What is the QC sample plan?

Quality control samples were prepared in the low (30 ng/mL), medium (750 ng/mL) and high (1600 ng/mL) concentration ranges. Duplicate or triplicate aliquots of each were used in each standard curve each day.

3 DETAILED LABELING RECOMMENDATIONS

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4 APPENDICES

4.1 NDA FILING AND REVIEW FORM

General Information About the Submission

NDA Number	21462	**Brand Name**	Alimta®
DCP Division (I, II, III, IV, V)	V	**Generic Name**	Pemetrexed disodium Injection
Medical Division	Oncology	**Drug Class**	Folate analog metabolic inhibitor
OCP Reviewer	Jeanne Fourie Zirkelbach, PhD	**Indication(s)**	Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer and Mesothelioma.
OCP Team Leader	Qi Liu, PhD	**Dosage Form**	100 mg and 500 mg Powder, Lyophilized, For Solution for Intravenous (i.v.) Use
Date of Submission	09/17/2010	**Dosing Regimen**	500 mg/m^2 i.v. on Day 1 of each 21-day cycle.
Due Date of OCP Review		**Route of Administration**	Intravenous infusion over 10 minutes
Standard PDUFA Due Date	3/17/2010	**Sponsor**	Eli Lilly Company

Clinical Pharmacology Information

	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**1**	**1**	Alimta-Assay-Val: Method + Validation for Alimta in human plasma
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	**x**	**x**		H3E-US-JMFC –single dose plasma PK Alimta – pediatric dose escalation trial
multiple dose:				
Dose proportionality -				
fas ing / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				

Subpopulation studies -				
ethnicity:				
gender:				
geriatrics:				
renal impairment:				
hepatic impairment:				
pediatrics:	**x**	**2**	**2**	H3E-US-JMFC – Phase 1 pediatric dose escalation trial. H3E-MC-JMHW -A Phase 2 Study of Pemetrexed in Children wi h Recurrent Malignancies
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
QTC studies:				
In-Vitro Release BE				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Biliary Elimination				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments

	"X" if yes	**Comments**
Application filable?	**X**	
Comments sent to firm?		
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date	**J Fourie Zirkelbach, Ph.D.**	
Secondary reviewer Signature and Date	**Q Liu, Ph.D.**	

CC: HFD-150 (CSO – **D Hanner;** MTL– J Johnson**;** MO –**A McKee**)

HFD-860 (Reviewer – J Fourie Zirkelbach; TL – Q Liu; DDD - B Booth; DD - A Rahman)

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/s/

JEANNE FOURIE
03/03/2011

QI LIU
03/03/2011