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RESEARCH**

APPLICATION NUMBER:

21-677

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-667

Drug: ALIMTA

Generic name: Pemetrexed; N-[4-[2-(2-amino-3,4-dihydro-4-oxo-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]-benzoyl]-L-glutamic acid; MTA; LY231514;

Formulation: 40 ml aqueous solution of 200 or 1000 mg for intravenous infusion; lyophilized powder of 20, 100 and 500 mg for reconstitution and intravenous infusion.

Indications: ALIMTA as a single agent for the treatment of patients with locally advanced or metastatic non-small cell lung cancer.

Applicant: Eli Lilly and Company
Indianapolis, IN 46285

OCPB Division: Division of Pharmaceutical Evaluation 1 (HFD-860)

OND Division: Division of Oncology Drug Products (HFD-150)

Submission Dates: 03-NOV-2003

Primary/Pharmacometric Reviewer: Brian Booth, Ph.D.

Pharmacometric Team Leader: Joga Gobburu, Ph.D.

Team Leader: N.A.M. Atiqur Rahman, Ph.D.

Type of Submission: NDA-New Molecular Entity

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II. Executive Summary

The applicant is seeking marketing approval for Alimta as a single-agent for the treatment of patients with locally advanced or metastatic non-small lung cell cancer. Non-inferiority of Alimta to docetaxel could not be determined, but the Oncologic Drugs Advisory Committee agreed with the FDA that the 9.1 % response rate and better toxicity profile warranted accelerated approval of Alimta as a single-agent for NSCLC. The applicant demonstrated that cancer type did not alter the pharmacokinetics of Alimta.

Recommendation: The Alimta NDA 21-677 is acceptable to the Office of Clinical Pharmacology and Biopharmaceutics.

Phase 4 Commitments:

No phase 4 commitments are recommended.

Reviewer: Brian Booth, Ph.D.

Team Leader: NAM Atiqur Rahman, Ph.D.

Pharmacometrics Team Leader: Jogarao Gobburu, Ph.D.

CC: NDA 21-462
HFD-150/Division File
HFD-150/PGarvey, MCohen, JohnsonJ
HFD-860/MehtaM, RahmanNAM, GobburuJ, BoothB
CDR/Biopharm

III. Summary of Clinical Pharmacology Findings

Alimta is a novel antimetabolite that inhibits thymidylate synthase, dihydro folate reductase and glycinamide ribonucleotide formyl transferase, and mediates cell death by inhibiting DNA synthesis. Alimta induced a 9.1 response rate in non-small cell lung cancer (NSCLC) in patients who had failed previous treatments. The main toxicity of Alimta is neutropenia, but leukopenia, thrombocytopenia, stomatitis, vomiting diarrhea and nausea were also noted. The pharmacokinetics of Alimta follow a 2-compartment model, and excretion is predominantly renal. Alimta was not metabolized by any cytochrome P-450, nor did it inhibit any cytochrome P-450 isozyme. Total systemic clearance of Alimta is 91.8 ml/min and is well correlated with glomerular filtration rate and creatinine clearance (CLcr) calculated using the Cockcroft-Gault formula. The elimination half-life is 3.5 hours, and no accumulation was noted. The pharmacokinetics of Alimta were not affected by sex, age or ethnicity. In the current application, the applicant used the previously described and reviewed population pharmacokinetic model and databases to assess whether the pharmacokinetics of Alimta were affected by NSCLC. The results indicated that the CL and central and peripheral volumes of distribution of Alimta were not significantly affected. The sponsor also assessed protein binding at higher concentrations of Alimta. Protein binding decreased to 58% at 1100 ug/ml. However, this concentration corresponds to a dosage that is approximately ten-fold higher than the currently indicated dosage, and does not represent anything that is clinically meaningful. No changes have been made to the pharmacokinetics section of the Alimta label.

IV. Question Based Review

A. General Attributes

What are the highlights of the chemical properties of drug substance and formulation of the drug product?

Alimta (pemetrexed;MTA;LY231514) is antifolate antineoplastic agent similar to methotrexate. The chemical name for ALIMTA is N-[4-[2-amino-4,7-dihydro-4-oxo-1H-pyrrolo [2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid disodium salt, which has a molecular weight of 597.49. The chemical structure is shown in Figure 1.

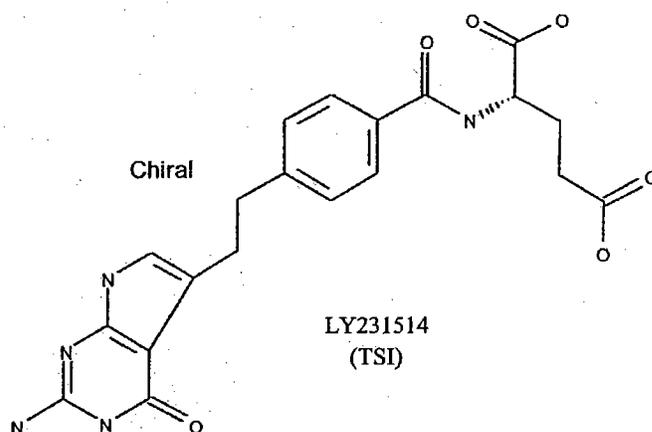


Figure 1. The chemical structure of Alimta

Alimta is available as a lyophilized powder containing 500 mg of Alimta and 500 mg of mannitol. Vials are reconstituted with 20 ml of 0.9% saline (USP) and pH may be adjusted with hydrochloric acid or sodium hydroxide.

What is the putative mechanism of action of Alimta?

Alimta inhibits thymidylate synthase (TS), which is essential for with DNA synthesis, and thereby mediates its cytotoxic activity. Alimta also inhibits dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyl transferase (GARFT).

B. General Clinical Pharmacology

What is the effectiveness endpoint?

The primary clinical endpoint in the pivotal trial of Alimta vs docetaxel was overall survival. Response rate, response duration and progression-free survival were the secondary endpoints for this study. Responses were defined as complete response (CR),

partial response (PR), stable disease (SD) or progressive disease (PD) based on tumor size assessed by CAT scan. The applicant proposed a non-inferiority analysis, but the interpretation of this analysis was confounded for two reasons. The survival effect of docetaxel from a historical study was believed to be too small (104 patients) to adequately quantify the docetaxel effect, and in the current study 32% of the Alimta patients crossed over to docetaxel following progression. The Oncology Drugs Advisory Committee (July 27, 2004) agreed with the FDA that the secondary endpoint of response rate and the better toxicity profile of Alimta (compared to docetaxel) warranted accelerated approval.

What are the characteristics of the exposure-response relationships of Alimta?

Effectiveness

In the pivotal phase 3 trial, only one dose of Alimta was administered. Consequently, no concentration-effect relationships could be determined because of the narrow range of doses and AUCs available in this study.

Toxicity

Neutropenia

The main toxicity associated with Alimta was hematological. Neutropenia was the most significant toxicity.

Are the pharmacokinetics of Alimta affected by the NSCLC?

No. In order to address this possibility, the applicant used the population pharmacokinetic model and databases of Alimta already described and reviewed in original NDA submission (refer to the Clinical Pharmacology review of NDA 21-462 for details). To determine the effect of disease on Alimta pharmacokinetics, the sponsor used the following function

$$P = [TVP(1-IND) + TVP \cdot \Theta_7 \cdot IND] e^{\eta}$$

Where P is the pharmacokinetic parameter that was tested (CL, V1 or V2), and TVP is the typical value of that parameter. IND is an indicator variable that is set to "1" if the cancer being is present, "0" otherwise. Θ_7 is the cancer effect factor. If the cancer has no effect, Θ_7 equals 1. Increases or decreases indicate the effect on the parameter tested.

A change in the minimum objective function (MOF) of 3.841 was considered statistically significant, however, only CL changes of >20 % or V changes of >40 % were considered clinically significant.

Thirty-five Australian patients were excluded from the study because a different method of serum creatinine measurement was used in these patients, and the subsequent creatinine clearance and Alimta systemic clearance were demonstrated to be significantly different from the remaining 252 patients by 20 %.

The analysis indicated that CL of Alimta was unaffected by NSCLC (change in MOF was -2.486). These results are presented graphically below

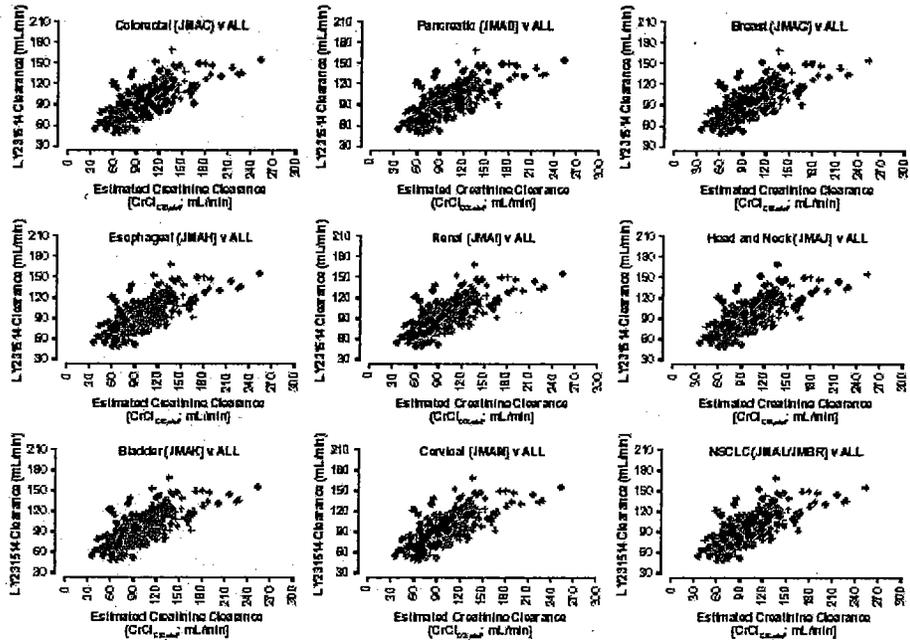


Figure 9.2. Overlay plots: LY231514 CL versus CrCl_{std}.

Grey crosshairs: All cancer types
 Black circles: Particular cancer type

NSCLC reduced the MOF on V1 by -32.321. Θ_7 was 0.75 (95% CI 0.683 to 0.831), indicating approximately 25 % reduction in volume, which according to the predefined criteria, was not considered significant. NSCLC had no significant effect on V2 (change in MOF of -0.319).

Is there additional information regarding protein binding?

Yes. Previous protein binding studies for Alimta indicate 80% binding at the dosage indicated for malignant pleural mesothelioma and NSCLC (500 mg/m²). The sponsor conducted a phase 1 study in Japanese patients, who were treated with dosages of Alimta up to 1200 mg/m². Maximal Alimta concentrations at this dose were 212 ug/ml, whereas maximal plasma concentrations at the 500 mg/m² are approximately 100 ug/ml. The applicant investigated the protein binding of Alimta at higher concentrations to assess protein binding at dosages of Alimta greater than 500 mg/m². The applicant studied protein binding at 220, 440, 660, 880 and 1100 ug/ml of Alimta, by incubating radiolabeled compound in plasma for 1 hour at 37°C. The extent of protein binding was determined by ultracentrifugation, and liquid scintillation counting. These studies indicated that protein binding decreased from 77 % at 220 ug/ml, to 58% at 1100 ug/ml. However, the decrease in protein binding (20 %) is not likely to be clinically significant. In patients with moderate renal impairment, the Alimta AUC increased by 100 % without any corresponding increase in toxicity. Therefore the small change in protein binding that occurs from increasing the dose from 500 to 1200 mg/m² (80% at C_{max} 100 ug/ml compared to 77% at 220 ug/ml) is not significant. Furthermore, the dosage of Alimta indicated for NSCLC is the same as for malignant pleural mesothelioma (500 mg/m²). Therefore, labeling changes for protein binding also appear unwarranted.

V . Detailed labeling Recommendations

None.

20 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

X § 552(b)(5) Deliberative Process

B. NDA Filing Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	21677	Brand Name	ALIMTA	
OCPB Division (I, II, III)	1	Generic Name	pemetrexed	
Medical Division	Oncology (HFD-150)	Drug Class	Antimetabolite, antineoplastic	
OCPB Reviewer	Brian Booth	Indication(s)	NSCLC	
OCPB Team Leader	Atik Rahman/Joga Gobburu	Dosage Form	solution	
		Dosing Regimen	500 mg/m2 q21days	
Date of Submission	04-NOV-2003	Route of Administration	iv	
Estimated Due Date of OCPB Review		Sponsor	Eli Lilly	
PDUFA Due Date	04-SEP-2004	Priority Classification	s	
Division Due Date				
Clin. Pharm. and Biopharm. 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				
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
I. Clinical Pharmacology				
Mass balance:	na			
Isozyme characterization:	na			
Blood/plasma ratio:	na			
Plasma protein binding:	x	1		
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	na			
multiple dose:	na			
Patients-				
single dose:	x	3		
multiple dose:	x	10		
Dose proportionality -				
fasting / non-fasting single dose:	na			
fasting / non-fasting multiple dose:	na			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	na			
In-vivo effects of primary drug:	na			
In-vitro:	na			
Subpopulation studies -				
ethnicity:	na			
gender:	Na			
pediatrics:	Na			
geriatrics:	Na			
renal impairment:	Na			
hepatic impairment:	na			
PD:				
Phase 2:				
Phase 3:				
PK/PD:				

Phase 1 and/or 2, proof of concept:			
Phase 3 clinical trial:			
Population Analyses -			
Data rich:	x	1	
Data sparse:	no		
II. Biopharmaceutics			
Absolute bioavailability:	na		
Relative bioavailability -			
solution as reference:	na		
alternate formulation as reference:	na		
Bioequivalence studies -			
traditional design; single / multi dose:	na		
replicate design; single / multi dose:	na		
Food-drug interaction studies:	na		
Dissolution:	na		
(IVIVC):	na		
Bio-wavier request based on BCS	na		
BCS class	na		
III. Other CPB Studies			
Genotype/phenotype studies:	na		
Chronopharmacokinetics	na		
Pediatric development plan	na		
Literature References	x	12	
Total Number of Studies			
<i>Fileability and QBR comments</i>			
	"X" if yes	Comments	
Application fileable ?	x	Reasons if the application is <u>not</u> fileable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?	
Comments sent to firm ?	no	Comments have been sent to firm (or attachment included). FDA letter date if applicable.	
QBR questions (key issues to be considered)	Are the pharmacokinetics of Alimta in NSCLC the same as the Alimta kinetics in mesothelioma?		
Other comments or information not included above			
Primary reviewer Signature and Date			
Secondary reviewer Signature and Date			

CC: NDA XX-XXX, HFD-850(P. Lee), HFD-860 (M. Mehta), HFD-XXX(CSO), HFD-8XX(TL, DD, DDD), CDR

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/s/

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