CLINICAL REVIEW

Application Type	Commercial
Application Number(s)	NDA 21-462 S-(b) (4)
Priority or Standard	Priority
Submit Date(s)	09/17/10
Received Date(s)	09/17/10
PDUFA Goal Date	
Division / Office	OODP/DDOP
Reviewer Name(s)	Amy McKee, M.D.
Review Completion Date	
Established Name	Pemetrexed
(Proposed) Trade Name	Alimta®
Therapeutic Class	Antifolate
Applicant	Eli Lilly and Company
Formulation(s)	Lyophilized powder for reconstitution for intravenous injection
Dosing Regimen	Not applicable
Indication(s)	None
Intended Population(s)	None

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend that the Pediatric Exclusivity be granted for Alimta and the pediatric information be included in the Alimta labeling.

My recommendation is based on the review finding that the Applicant completely responded to all the elements in the Pediatric Written Request (PWR).

1.2 Risk Benefit Assessment

The risk profile of Alimta in pediatric population appears to be similar to that of adult population. However, this submission provided no evidence of efficacy for Alimta in the pediatric population. Therefore, the risks associated with Alimta use in the pediatric population are without benefit and such a use is not recommended.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable.

1.4 Recommendations for Postmarket Requirements and Commitments

Not applicable.

2 Introduction and Regulatory Background

2.1 Product Information

Established Name: Pemetrexed
Proprietary Name: Alimta®
Applicant: Eli Lilly and Company
Pharmacological Class: antifolate
Proposed Indication: There is no proposed pediatric indication.
Proposed Dosage and Administration: There is no proposed dose or route of administration in pediatric patients

2.2 Tables of Currently Available Treatments for Proposed Indications

There is no proposed indication in pediatric patients.

2.3 Availability of Proposed Active Ingredient in the United States

Pemetrexed is supplied as a sterile lyophilized powder for intravenous infusion available in single-dose vials. The product is a white to either light yellow or green-yellow lyophilized solid. Each 500-mg vial of pemetrexed contains pemetrexed disodium equivalent to 500 mg pemetrexed and 500 mg of mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.

2.4 Important Safety Issues With Consideration to Related Drugs

Not applicable.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Pemetrexed is approved for the following indications in adults: maintenance therapy of advanced/metastatic NSCLC other than predominantly squamous cell histology, locally advanced or metastatic NSCLC after prior chemotherapy and malignant pleural mesothelioma. There is no approved indication for the pediatric population.

Table 1 includes a brief regulatory history regarding the proposed pediatric development plan, Proposed Pediatric Study Request (PPSR), and issued Pediatric Written Request (PWR) for use of Alimta in children with cancer.

Table 1: Pediatric Regulatory History

October 5, 2001	Initial Pediatric Written Request Issued
July 3, 2002	Pediatric Written Request Re-Issued under the Best Pharmaceuticals for Children Act
May 7, 2004 April 16, 2007 July 2, 2010	Minor revisions to Pediatric Written Request
September 17, 2010	Submission of Supplemental New Drug Application to NDA 21462 to provide pediatric study reports for pediatric exclusivity determination.

2.6 Other Relevant Background Information

This submission contains a Phase 1, dose-finding study in pediatric solid tumors and a single-arm, Phase 2 trial to evaluate the response rate in patients with recurrent

osteosarcoma, Ewing sarcoma/peripheral neuroendocine tumor (PNET) and neuroblastoma.

The pediatric solid tumors noted above represent a heterogeneous group of tumors with differing incidences, genetic aberrations, median age at diagnosis and initial treatment strategies. However, the commonality with these solid tumors is that recurrent disease is difficult to treat and most often leads to mortality. Multiple chemotherapeutic regimens have been investigated in recurrent pediatric solid tumors; however, few have demonstrated a survival advantage to date. This submission represents an exploratory investigation to determine whether pemetrexed has activity in any of these solid tumors.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contains the debarment certificate, sufficient datasets, and relevant CRFs. The overall quality and integrity of the submission is adequate.

3.2 Compliance with Good Clinical Practices

According to the ethics sections of the submission:
1) The studies used as a basis for clinical data presented in the submission were conducted in compliance with Good Clinical Practices (GCP), as required by the International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice.
2) The studies also meet the requirements of the Declaration of Helsinki, standard operating procedures for clinical investigations and documentation of the Applicant, applicable national laws and regulations and the ethical principles of the Directive 2001/20/EC.

3.3 Financial Disclosures

The clinical investigators did not participate in any financial arrangement with the applicant whereby the value of the compensation for conducting the study could be affected by the outcome of the study as defined in 21 CFR 54.2(a), had no proprietary interest in this product or significant equity interest in the applicant as defined in 21 CFR 54.2(b) and were not the recipients of significant payments of other sorts as defined in 21 CFR 54.2(f).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Not applicable.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Not applicable.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Pemetrexed for injection is an antifolate antineoplastic agent that exerts its action by disrupting folate-dependent metabolic processes essential for cell replication. In vitro studies have shown that pemetrexed inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are folate-dependent enzymes involved in the de novo biosynthesis of thymidine and purine nucleotides. Pemetrexed is taken into cells by membrane carriers such as the reduced folate carrier, membrane folate binding protein transport systems. Once in the cell, pemetrexed is converted to polyglutamate forms by the enzyme folylpolyglutamate synthetase. The polyglutamate forms are retained in cells and are inhibitors of TS and GARFT. Polyglutamation is a time- and concentration-dependent process that occurs in tumor cells and, is thought to occur to a lesser extent, in normal tissues. Polyglutamated metabolites are thought to have an increased intracellular half-life resulting in prolonged drug action in malignant cells.

4.4.2 Pharmacodynamics

Please see Clinical Pharmacology Review.

4.4.3 Pharmacokinetics

Please see Clinical Pharmacology Review.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical trials submitted in support of NDA S-(b) (4) are shown in Table 2.

Table 2: Pemetrexed Pediatric Clincial Trials

Study	Primary Objective	Treatment Plan	Number of patients	Diagnosis
H3E-US-JMFC(JMFC): A Phase 1, dose-escalation trial	Determine the maximum tolerated dose and pharmacokinetics in pediatric patients with refractory solid tumors	Pemetrexed on day 1 of 21-day cycles'; planned dose levels of 400, 520, 670, 870, 1130, 1470, 1910 and 2480 mg/m^2	33	Refractory solid tumors
H3E-MC-JMHW(JMHW): A phase 2, open-label trial	Estimate response rates in relapsed or refractory solid tumors	Pemetrexed 1910 mg/m^2 as a 10-minute infusion on day 1 of 21-day cycles up to 17 cycles or until disease progression, death or unacceptable toxicity	72	Relapsed or refractory osteosarcoma, Ewing sarcoma/PNET, rhabdomyosarcoma, neuroblastoma, enpendymoma, medulloblastoma/supratentorial PNET or high-grade glioma

5.2 Review Strategy

The main focus of this review is to evaluate whether the Applicant has successfully fulfilled the requirement set forth in the issued PWR for the eligibility determination on the pediatric exclusivity. To that end, both studies submitted in this supplement, were fully. To perform this review, the dossier, previous meeting minutes, the Proposed Pediatric Study Request (PPSR), PWR, and published literature were reviewed.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Protocol JMFC

Study Title
A Phase 1 Study of Pemetrexed in Children and Adolescents with Recurrent Solid Tumors

Protocol Milestones

Table 3: Protocol Milestones

Date	Milestone
Clinical Trial Protocol	October 17,2003
Amendment #1	February 13, 2004
First patient enrolled	April 6, 2004
Amendment #2	August 16, 2004
Last patient completed	March 2, 2006
Clinical study report completed	September 21, 2007
NDA 21462 (b) (4) submission	September 17, 2010

Protocol Amendments

Amendment 1- February 13, 2004 (no subjects were yet enrolled)

- Minor editorial changes
- Changes to informed consent to clarify lack of experience with pemetrexed in pediatric population

Amendment 2-August 16, 2004

- Added criteria for removal from protocol
- Added pharmacogenetic sample as required testing
- Changes to informed consent to reflect above changes

Study Objectives

Primary Objectives:

- To estimate the maximum tolerated dose (MTD) of pemetrexed administered as a 10-minute intravenous (iv) infusion every 3 weeks to children with refractory solid tumors
- To determine the dose-limiting toxicities (DLTs) of pemetrexed given on this schedule
- To characterize the pharmacokinetic (PK) behavior of pemetrexed in children with refractory cancer.

Secondary Objectives:

- To preliminarily define the antitumor activity of pemetrexed within the confines of a Phase 1 study
- To examine the relationship, within the confines of a Phase 1 study, between the presence of the (b) (4) and toxicity of patients being treated with pemetrexed, and between the presence of a (b) (4) toxicity of patients being treated with pemetrexed

- To examine the relationship, within the confines of a Phase 1 study, between the response data and tumoral TS, dihydrofolate reductase (DHFR), glycinamide ribonucleotide formyltransferase (GARFT), reduced folate carrier (RFC), folylpolyglutamate synthetase (FPGS), and gammaglutamyl hydrolase (GGH) expression levels as well as methylthioadenosine phosphorylase (MTAP) deletion status
- To examine the correlation between homocysteine (Hcy) and methylmalonic acid (MMA) levels at study entry with toxicity in patients treated with pemetrexed.

Study Design

This was an open-label, dose escalation study with a standard 3+3 design. Patients received a pemetrexed as a 10-minuted intravenous infusion on day 1 of a 21-day cycle with co-administration of a multivitamin and vitamin B12.

Figure 1: Study Schema

	Course 1						Course 2	
Week		1		2	3		1	
Day	-1	1	2	8	15	21	(22)	23
Pemetrexed [a]		P					P	
Multivitamin [b]	MVI →							
Dexamethasone [c]	DD	DD	DD			DD	DD	DD
Cyanocobalamine [d] **(Vitamin B_{12})**		B_{12}						

Note: Each cycle was to be 21 days long, consisting of 1 day of pemetrexed and 20 days of follow-up. A cycle could be repeated every 21 days if the patient had at least stable disease and has recovered from the prior cycle of therapy. Day 1 of the subsequent cycle immediately follows Day 21 of the preceding cycle.
Abbreviations: B_{12} = cyanocobalamine or Vitamin B_{12}; DD = dexamethasone; MVI = multivitamin; P = pemetrexed.
[a] Pemetrexed given as iv over 10 minutes. In patients receiving trimethoprim/sulfa for pneumocystis prophylaxis, trimethoprim/sulfa must be held for 2 days pre- and post-pemetrexed treatment.
[b] Multivitamin (MVI) taken orally, daily. Patients were required to take MVI for at least 5 of the 7 days preceding the first dose of pemetrexed and continue MVI supplementation for at least 21 days following their last dose of pemetrexed.
[c] Dexamethasone was given orally, twice a day for 3 days, beginning 1 day before pemetrexed until 1 day after pemetrexed therapy.
[d] Cyanocobalamine (vitamin B_{12}) administered as 500 μg intramuscular (im) for children below the age of 12 years and 1000 μg im for children and adolescents 12 years of age and older, prior to the first dose of pemetrexed and following every 3 cycles (every 9 weeks). This may be on the same day as the pemetrexed infusion.

Eligibility Criteria

Inclusion criteria:

- Age: patients were >12 months and ≤21 years of age at the time of study entry.
- Diagnosis:
    - Histologic verification: patients had histologic verification of a solid tumor at original diagnosis (excluding intrinsic brain stem tumors).
    - Disease status: patient's current disease state was one for which there was no known curative therapy or therapy that was known to prolong survival with acceptable quality of life.
- Performance level: Karnofsky ≥50% for patients >10 years of age and Lansky ≥50 for patients ≤10 years of age. Neurologic deficits in patients with central nervous system (CNS) tumors were relatively stable for a minimum of 1 week prior to study entry. Patients who were unable to walk because of paralysis, but who were up in a wheelchair, were considered ambulatory for the purpose of assessing the performance score.
- Life expectancy was ≥8 weeks.
- Prior therapy: patients were fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy (XRT) prior to entering this study.
    - Myelosuppressive chemotherapy: must not have been received within 3 weeks of entry into this study (4 weeks if prior nitrosourea).
    - Biologic (antineoplastic agent): at least 7 days since the completion of therapy with a biologic agent
    - Radiotherapy (XRT): ≥2 wks must have elapsed for local palliative XRT (small port); ≥6 months must have elapsed if prior craniospinal XRT or if ≥50% radiation of pelvis; ≥6 wks must have elapsed if other substantial bone marrow radiation.
    - Stem cell transplant (SCT): no evidence of active graft versus host disease. For allogeneic SCT, ≥6 months must have elapsed.
    - There were no study-specific limitations on prior therapy.
- Concomitant medications:
    - Growth factor(s): none received within 1 week of entry into this study.
    - Steroids: patients with central nervous system (CNS) tumors who were receiving dexamethasone must have been on a stable or decreasing dose for at least 1 week prior to study entry.
    - Study specific: patients refrained from taking nonsteroidal agents (such as ibuprofen and aspirin) while on protocol therapy.
- Organ function requirements:
    - Adequate bone marrow function defined for patients with solid tumors (including status post-SCT) as peripheral absolute neutrophil count (ANC) ≥1000/μL; platelet count ≥100,000/μL (transfusion independent); hemoglobin ≥8.0 g/dL (may receive red blood cell [RBC] transfusions)
    - Adequate renal function defined as creatinine clearance or radioisotope glomerular filtration rate (GFR) ≥70mL/min/m2 OR a maximum serum creatinine (mg/dL) based on the following age (years) groupings: for

patients ≤5 years of age (0.8 mg/dL), for patients 5 to ≤10 years of age (1.0 mg/dL), for patients 10 to ≤15 years of age (1.2 mg/dL), and for patients >15 years of age (1.5 mg/dL)
- Adequate liver function defined as total bilirubin ≤1.5 × upper limit of normal (ULN) for age, and serum glutamic pyruvic transaminase (SGPT [ALT]) ≤2.5 × ULN for age and albumin ≥2 g/dL
- Adequate pulmonary function defined as no evidence of dyspnea at rest, no exercise intolerance, and a pulse oximetry >94% if there was clinical indication for determination
- Central nervous system (CNS) function defined as patients with seizure disorder were enrolled if on anticonvulsants and well controlled; CNS toxicity <Grade 2.

Exclusion Criteria:

- Patients who were pregnant or breastfeeding were not eligible for this study as there is yet no available information regarding human fetal or teratogenic toxicities. Pregnancy tests were obtained in girls who were postmenarchal. Males or females of reproductive potential may not have participated unless they agreed to use an effective contraceptive method.
- Concomitant medications:
  - Growth factor(s): growth factors that support platelet or white cell number or function must not have been administered within the past 7 days.
  - Steroids: patients with CNS tumors who were not a stable or decreasing dose of dexamethasone for the past 7 days.
  - Investigational drugs: patients who were currently receiving another investigational drug.
  - Anticancer agents: patients who were currently receiving other anticancer agents.
- Patients who had an uncontrolled infection.
- Patients with pleural effusions or ascites.
- Patients who had previously received pemetrexed.

Discontinuation/Withdrawal from Study

Criteria for Removal from Protocol Therapy:

a) Progressive disease (PD)
b) Toxicity requiring removal from protocol therapy
c) Patient who received concurrent cancer therapy
d) Refusal of further protocol therapy by patient/parent/guardian
e) Completion of 17 cycles of therapy
f) Physician determines it is in the patient's best interest
g) Patient found to be noncompliant with vitamin supplementation.

Patient Evaluations

Plasma samples obtained during this study were analyzed at the (b) (4) in

(b) (4). The samples were analyzed for pemetrexed using a modification of a previously described liquid chromatography tandem mass spectrometry (LC/MS/MS) method (Chaudhary et al. 1999). For patients who participated in the PK portion of the study, blood samples were collected during Cycle 1. Samples were obtained prior to drug infusion, at the end of infusion, and 15 minutes, 30 minutes, 60 minutes, 2 hours, 4 hours, 6 to 8 hours, and 24 hours following infusion. Patients with measurable disease were evaluated using RECIST. The schedule for these evaluations is detailed in Table 2 below.

Figure 2: Patient Evaluation Schedule

STUDIES TO BE OBTAINED	Pre-Study	Course 1	Subsequent Courses
History	X	X	X
Physical Exam (Ht, Wt, BSA, VS)	X	Weekly	X
Performance Status	X	X	X
CBC, differential, platelets	X	Twice Weekly (every 3 to 4 days)*	Weekly^^
Pharmacokinetics*		X	
Urinalysis	X	-	-
Electrolytes including Ca++, PO_4, Mg++	X	Weekly	X
Creatinine, SGPT, bilirubin	X	Weekly	X
Total protein/albumin	X	-	X
Tumor Disease Evaluation	X	End of course	Every other course[@]
Pregnancy Test**	X		
Folic acid level	X	X	X
Homocysteine level	X	X	X
Patient diary of vitamin intake		X	X

* See Section 8.2 for timing of PK studies.
** Patients of childbearing potential require a negative pregnancy test prior to starting treatment.
* If patients have grade 4 neutropenia then CBCs should be checked at least every other day until recovery to grade 3.
^^ If patients develop grade 4 neutropenia then CBCs should be checked every 3 to 4 days until recovery to grade 3
@ Tumor Disease Evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR.

5.3.2 Protocol JMHW

Study Title
A Phase II Study of Pemetrexed in Children with Recurrent Malignancies

Protocol Milestones

Table 4: Protocol Milestones

Date	Milestone
Clinical Trial Protocol	February 12, 2007
First patient enrolled	September 25, 2007
Amendment #1	March 31, 2008
Amendment #2	July 14, 2008
Amendment #3	August 2, 2010
Last patient completed	February 3, 2010
Clinical study report completed	July 28, 2010
NDA 21462 (b) (4) submission	September 17, 2010

Protocol Amendments

Amendment #1-March 31, 2008
- Institutional pathology report submission added
- Guidelines regarding prior XRT added
- Maximum pemetrexed dose added
- Guidelines for administration of subsequent cycles amended
- Administration guidelines updated
- Pancreatitis added as potential toxicity
- Adverse event reporting guidelines updated
- Informed consent updated to reflect above changes

Amendment #-July 14, 2008
- Patient eligibility changes
- Dose modification changes
- Laryngeal edema and esophagitis added as potential toxicities
- Informed consent updated to reflect above changes

Amendment #3-August 2, 2010
- Editorial/administrative changes only

Study Objectives

Primary Objectives:
- To estimate the response rate to pemetrexed administered intravenously every 21 days in children with relapsed or refractory osteosarcoma, Ewing sarcoma/peripheral PNET, rhabdomyosarcoma, neuroblastoma, ependymoma, medulloblastoma/supratentorial PNET or non-brainstem high grade glioma.
- To further define and describe the toxicities of pemetrexed.

Secondary Objectives:

- To examine the relationship between the presence of the (b) (4) and toxicity of patients being treated with pemetrexed.
- To examine the relationship between the presence of a (b) (4) and toxicity of patients being treated with pemetrexed.
- To examine the relationship between response and tumor expression of the enzymes TS, DHFR, GARFT, RFC, FPGS and GGH as well as MTAP deletion status.

Study Design

Table 5: Study Schema

	Pre Cycle 1	Cycle 1					Cycle 2	
Week	**-1**	**1**		**2**	**3**		**1**	
Day(s)	**-7 to -1**	**0**	**1**	**2**	**8**	**15**	**21/0**	**(22)/1**	**(23)/2**
Pemetrexed			P^					P	
Dexamethasone		DD#	DD	DD			DD	DD	DD
Vitamin B12*			X						
Multivitamin	MVI@	----------						----------	→

^P - Pemetrexed (IV over 10 min)
#DD - Dexamethasone (by mouth two times per day for three days, beginning the day prior to pemetrexed)
*B12 - Vitamin B12 (given by intramuscular injection before the first dose of pemetrexed and then every 3 cycles)
@MVI - Patients must begin taking MVI for at least 5 of the 7 days preceding the first dose of pemetrexed and must continue MVI supplementation for at least 21 days following their last dose of pemetrexed.

Eligibility Criteria

Inclusion Criteria:

- Patients must be less than 22 years of age when originally diagnosed with the malignancy to be treated on this protocol.
- Patients with any of the following tumors (no other histology is eligible):
  - Osteosarcoma
  - Ewing sarcoma / peripheral PNET
  - Rhabdomyosarcoma
  - Neuroblastoma
  - Ependymoma
  - Medulloblastoma / Supratentorial PNET
  - Non-brainstem high grade glioma
- Patients must have had histologic verification of the malignancy at original diagnosis.
- Patients must have measurable disease; patients with neuroblastoma who do not have measurable disease but have MIBG+ evaluable disease are eligible.
- Patient's current disease state must be one for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life.

- Patients must have an ECOG performance status of 0, 1 or 2 (Appendix I). Use Karnofsky for patients > 16 years of age and Lansky for patients ≤ 16 years of age.
- Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.
    - Myelosuppressive chemotherapy: Must not have received within 3 weeks of entry onto this study (4 weeks if prior nitrosourea).
    - Biologic (anti-neoplastic agent): At least 7 days since the completion of therapy with a biologic agent. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur.
    - XRT: ≥ 2 wks for local palliative XRT (small port); ≥ 6 months must have elapsed if prior craniospinal XRT or if ≥ 50% radiation of pelvis; ≥ 6 wks must have elapsed if other substantial BM radiation.
    - Stem Cell Transplant (SCT): No evidence of active graft vs. host disease. For allogeneic SCT, ≥ 6 months must have elapsed.
- Concomitant Medications Restrictions
    - Growth factor(s): Must not have received within 1 week prior to study entry (14 days if Neulasta®).
    - Steroids: Patients with CNS tumors who are receiving dexamethasone or other corticosteroid must be on a stable or decreasing dose for at least 2 weeks prior to study entry.
    - TMP/Sulfa, aspirin, NSAIDs and other drugs excreted via the renal tubules must be held or avoided for at least two days pre and post pemetrexed.
- Adequate Bone Marrow Function defined as:
    - Patients without bone marrow involvement must have:
        - Peripheral absolute neutrophil count (ANC) ≥ 1000/μL
        - Platelet count ≥ 100,000/μL (transfusion independent, defined as not receiving platelet transfusions within a 7 day period prior to enrollment.)
        - Hemoglobin ≥ 8.0 gm/dL (may receive RBC transfusions).
    - Patients with known bone marrow metastatic disease will be eligible for study but not evaluable for hematologic toxicity. These patients must be known **not** to be refractory to red cell or platelet transfusions.

- Adequate Renal Function defined as:
    - Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m2 OR A serum creatinine within normal limits based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this table were derived from the Schwartz formula for estimating GFR[72] utilizing child length and stature data published by the CDC.

- Adequate Liver Function defined as:
    - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
    - SGPT (ALT) ≤ 110 U/L. For the purpose of this study, the ULN for SGPT is 45 U/L.
    - Serum albumin ≥ 2 g/dL
- All patients and/or their parents or legal guardians must sign a written informed consent.
- All institutional, FDA, and NCI requirements for human studies must be met.

Exclusion criteria

- Patients who are pregnant or breast-feeding are not eligible for this study as there is yet no available information regarding human fetal or teratogenic toxicities. Negative pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method.
- Concomitant Medications
    - Growth factor(s): Growth factors that support platelet or white cell number or function must not have been administered within the past 7 days prior to enrollment (14 days if Neulasta®).
    - Steroids: Patients with CNS tumors who have not been on a stable or decreasing dose of dexamethasone or other corticosteroid for 7 days prior to enrollment on this study.
    - Investigational Drugs: Patients who are currently receiving another investigational drug.

  - Anti-cancer Agents: Patients who are currently receiving other anticancer agents.
  - TMP/Sulfa, aspirin, NSAIDs and other drugs excreted via then renal tubules must be held or avoided for at least two days before and after pemetrexed.
- Patients who have an uncontrolled infection.
- Patients with pleural effusions or ascites.
- Patients who have previously received pemetrexed.
- Patients who have had an allergic reaction to Mannitol.

Discontinuation/Withdrawal from Study

Criteria for Removal from Protocol Therapy

- Progressive disease.
- Toxicity requiring removal from protocol therapy.
- Patients who receive concurrent cancer or investigational therapy.
- Refusal of further protocol therapy by patient/parent/guardian.
- Completion of 17 cycles of therapy.
- Physician determines it is in patient's best interest.
- Repeated eligibility studies (if required) are outside the parameters required for eligibility.

Patient Evaluations

The schedule for patient evaluations is detailed in Figure 3 below.

Figure 3: Patient Evaluations

STUDIES TO BE OBTAINED	Baseline	Cycle 1[a]	Subsequent Cycles[a]	Off Protocol / Off Therapy[b]
History	X	X	X	X
Physical Exam (Ht, Wt, BSA, VS)	X	Weekly	X	X
Performance Status	X	X	X	X
CBC, differential, platelets	X	Weekly[c]	Weekly[c]	X
Urinalysis	X	-	-	-
Electrolytes including Ca++, PO_4, Mg++	X	Weekly	X	X
Creatinine, SGPT, bilirubin	X	Weekly	X	X
Creatinine clearance or GFR (if serum creatinine abnormal)	X[d]		X[e]	X[e]
Total protein/albumin	X	-	X	X
Tumor Disease Evaluation[f]	X	End of cycle	Every 2nd cycle[g]	X
Pregnancy test[h]	X			
Pharmacogenetic and correlative studies[i]	X			

[a] When an "X" is used for a required observation in this column, it means obtain before beginning the cycle.

[b] Every effort should be made to obtain these studies.

[c] Obtain twice weekly if ANC < 500/μL or platelets < 50,000/μL.

[d] 24 hours Creatinine clearance or radionuclide GFR must be obtained ***IF*** serum Creatinine not within normal limits for age/sex OR rapidly changing due to underlying disease condition.

[e] If Creatinine abnormal or significantly changed from baseline.

[f] The same imaging modality should be used throughout the study. Bone marrow and/or CSF studies should be obtained as clinically indicated, e.g., in patients with a prior history of a positive study and/or clinical symptoms suggestive of disease.

[g] Starting with cycle 1 (e.g., cycles 3, 5, 7, etc.). In addition, Tumor Disease Evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR, and then every 2nd cycle thereafter.

[h] Female patients of childbearing potential require a negative pregnancy test prior to starting treatment.

[i] Optional studies, not required for study participation. Additional consent required. See Sections 7.2 and 7.3 for details of tests.

6 Evaluation of the Applicant's Fulfillment of the PWR Requirement

Table 6 lists each item as requested in the PWR and the clinical study reports/datasets submitted by the applicant to fulfill these items. There were no deficiencies identified in which the Applicant did not completely meet the requirements set forth in the PWR. Therefore, this reviewer found that the Applicant has fulfilled the requirements set forth in the PWR and that Pediatric Exclusivity should be granted.

Table 6: Applicant's Fulfillment of PWR Requirement (Applicant's Table)

Overview of Pediatric Written Request Amendments and Clinical Study Reports	
Pediatric Written Request (WR) History: • October 5, 2001 – Pediatric Written Request • July 9, 2001 – Amendment #1 • July 3, 2002 – Amendment #2 • May 7, 2004 – Amendment #3 • April 16, 2007 – Amendment #4 • July 2, 2010 – Amendment #5 The template is filled out using the section order of Written Request (WR) Amendment #5. Two clinical study reports were submitted in response to this WR: H3E-US-JMFC, *Clinical Study Report: A Phase 1 Study of Pemetrexed (LY231514, Alimta) in Children and Adolescents with* *Recurrent Solid Tumors* H3E-MC-JMHW, *A Phase II Study of Pemetrexed in Children with Recurrent Malignancies* *Italics are used in this document to differentiate Lilly summaries that are not direct citations from the clinical study reports.*	
Written Request Items	**Information Submitted/ Applicant's response**
Types of studies/ Study Design: Phase 1: A dose finding study, including pharmacokinetics, with doses determined for all appropriate age groups. The number of patients entered should be sufficient to achieve Phase 1 objectives, which may be in the range of 18-25.	**Types of studies:** Phase 1 Source: Study JMFC, Section 5.3 Study Design, pg 21. • Study H3E-US-JMFC was a Phase 1 multicenter, open-label, dose-escalation and pharmacokinetic study evaluating pemetrexed in pediatric and adolescents patients with refractory solid tumors. Dose escalations occurred in a standard 3+3 design (described in Section 5.3.2.2). Patients were allowed to remain on study until any of the reasons described in Section 5.3.1.3 occurred, including 17 cycles or until disease progression. Figure JMFC.5.1 illustrates the study design. Source: Study JMFC Synopsis, pgs 2-3. • Patients were studied in cohorts of 3 to 6 patients at each dose level. The starting dose was 400 mg/m^2, with subsequent dose escalations occurring in increments of

	30%. A total of 33 patients were enrolled with 32 patients completing the study including 21 males and 11 females. Source: Study JMFC, Section 5.3.2.1, pg 25. • Lilly contracted with the Children's Oncology Group (COG) to provide Study Operations Management for the Phase 1 study of pemetrexed in children.
Phase 2: Enrollment of at least 10 pediatric patients in each of the following disease strata: osteosarcoma, Ewing sarcoma/peripheral PNET, and neuroblastoma. At least nine patients should be enrolled in a rhabdomyosarcoma stratum. The study should be performed at facilities that have the experience, support, and the expertise to care for children with cancer.	Phase 2 Source: Study JMHW Clinical Study Report Title Pg, pg. 1. • Study H3E-MC-JMHW was a Phase 2, multicenter, open-label study of pemetrexed every 21 days in children and adolescents with recurrent solid tumors. Target tumor types are osteosarcoma, Ewing sarcoma/peripheral PNET, rhabdomyosarcoma, neuroblastoma, ependymoma, medullablastome/supratentorial PNET, and nonbrainstem high-grade glioma. Source: Study JMHW, Section 9.1 Overall Study Design and Plan: Description, pg 16. • Table JMHW.9.1 presents the study design for enrollment and decision criteria within each tumor type. This study had a 2-stage design with an initial enrollment of 10 patients with each tumor type. If at least 1 partial or complete response was observed within a tumor type, an additional 10 patients with that tumor type could have been enrolled. All patients were to receive pemetrexed on Day 1 of each 21 Day cycle. Table JMHW.9.2 presents the study drug dosing schedule. Patients could remain on therapy up to a maximum of 17 cycles. Source: Study JMHW, Section 10.1 Disposition of Patients, pg 26. • Of the 75 patients that entered the study, 72 were enrolled and received at least 1 dose of study drug. Table JMHW.10.1 shows the number of patients entered and enrolled within each tumor stratum by

	country of origin. Study was only conducted in the USA and Canada. It was anticipated that 10 patients would be enrolled in each tumor stratum, including 10 each in neuroblastoma (measurable disease) and neuroblastoma (MIBG+ evaluable). A total of 11 patients were enrolled in the 2 neuroblastoma strata, and after assessing the data on these 11 patients, both of the neuroblastoma strata were closed. Subsequently, based on a Data Safety Monitoring Board recommendation, the rhabdomyosarcoma stratum was closed after 9 patients had been enrolled in this group. Both of these decisions reflect the difficulty in enrolling patients with relatively rare pediatric solid tumors to Phase 2 trials and were acceptable to the regulatory agency consulted. Source: Study JMHW, Section 6 Investigators and Administrative Structure, pg 11. • Lilly contracted with the Children's Oncology Group (COG) to provide Study Operations Management for the Phase 2 study of pemetrexed in children.
Written Request Items	**Information Submitted/ Applicant's response**
Indication(s) to be studied: Phase 1: Refractory solid tumors Phase 2: Refractory or relapsed pediatric patients with osteosarcoma, Ewing sarcoma/peripheral PNET, rhabdomysarcoma and neuroblastoma.	**Indication(s) studied:** Phase 1 Source: Study JMFC, Section 5.2 Study Objectives, pg 20. There were 3 primary objectives to the study: • To estimate the MTD of pemetrexed administered as a 10-minute intravenous (iv) infusion every 3 weeks to children with refractory solid tumors • To determine the DLT of pemetrexed given on the schedule • To characterize the pharmacokinetic (PK) behavior of pemetrexed in children with refractory cancer. Source: Study JMFC, Section 5.3 Study Design, pg 21. This was a multicenter, open-label, dose-escalation study evaluating pemetrexed in pediatric and adolescent patients with recurrent solid tumors. Phase 2 Source: Study JMHW, Section 10.1 Disposition of Patients, pg 26.

	Of the 75 patients that entered the study, 72 were enrolled and received at least 1 dose of study drug. Table JMHW.10.1 shows the number of patients entered and enrolled within each tumor stratum by country of origin. Study was only conducted in the USA and Canada. It was anticipated that 10 patients would be enrolled in each tumor stratum, including 10 each in neuroblastoma (measurable disease) and neuroblastoma (MIBG+ evaluable). A total of 11 patients were enrolled in the 2 neuroblastoma strata, and after assessing the data on these 11 patients, both of the neuroblastoma strata were closed. Subsequently, based on a Data Safety Monitoring Board recommendation, the rhabdomyosarcoma stratum was closed after 9 patients had been enrolled in this group. Both of these decisions reflect the difficulty in enrolling patients with relatively rare pediatric solid tumors to Phase 2 trials and were acceptable to the regulatory agency consulted.
Written Request Items	**Information Submitted/ Applicant's response**
Age group and population in which stud(ies) will be performed: Infants> 1 month of age to adolescents	**Age group and population in which studies were performed:** Phase 1 Source: Study JMFC, Section 5.3.1.1 Inclusion Criteria #1, pg 22. Age: patients were >12 months and ≤21 years of age at the time of study entry. Source: Study JMFC, Section 6.1 Demographics, pg 34. A total of 33 patients with refractory solid tumors, 21 male and 12 female, between the ages of 1 year and 21 years participated in this study. *The median age was 12.0 yrs (range 1.0-21.0)* Phase 2 Source: Study JMHW, Section 11.2 Demographic and Other Baseline Characteristics, Table JMHW.11.1., pg 32. *Narrative summary of Table JMHW 11.1:* *A total of 72 patients were treated. The median age of all treated patients was 11.5 yrs (range 3.1-23.5 yrs). There were 8 disease stratum for these 72 treated patients: Osteosarcoma, N=10, median age=13.9 yrs (range 8.0-21.5 yrs); Ewing Sarcoma/Peripheral PNET, N=11, 19.2*

	yrs (range 12.3-22.5 yrs); Rhadbomyosarcoma, N=9, 8.2 yrs (range 3.1-16.7 yrs); Neuroblastoma (measureable disease), N=5, 4.9 yrs (range 3.9-11.4 yrs); Neuroblastoma (MIGB + evaluable), N=6, 8.4 yrs (range 4.5-18.2 yrs); Ependymoma, N=10, 7.5 yrs (range 3.4-17.8 yrs); Medulloblastoma/Supratentorial PNET, N=11, 9.9 yrs (range 3.7-23.5 yrs); Non-Brainstem High-Grade Glioma, N=10, 12.3 yrs (range 4.5-19.2 yrs).
Written Request Items	**Information Submitted/ Applicant's response**
Study endpoints: <u>Phase 1:</u> The Phase 1 study should have maximum tolerated dose (MTD) (or biologically effective dose = BED) as a primary endpoint with measurements of blood (and CSF if appropriate) concentrations, and clearance as secondary endpoints. A traditional or sparse sampling technique may be used to estimate the PK parameters and develop pharmacokinetic-pharmacodynamic relationship.	**Study endpoints:** <u>Phase 1:</u> <u>Source: Study JMFC, Section 5.2 Study Objectives, pg 20.</u> There were 3 primary objectives to the study: • To estimate the MTD of pemetrexed administered as a 10-minute intravenous (iv) infusion every 3 weeks to children with refractory solid tumors • To determine the DLT of pemetrexed given on the schedule • To characterize the pharmacokinetic (PK) behavior of pemetrexed in children with refractory cancer. Additionally, there are 4 secondary objectives to the study: • To preliminarily define the antitumor activity of pemetrexed within the confines of a Phase 1 study. To examine the relationship, within the confines of a Phase 1 study, between the presence of the (b) (4) and toxicity of patients being treated with pemetrexed. To examine the relationship, within the confines of a Phase 1 study, between the presence of a (b) (4) and toxicity of patients being treated with pemetrexed (pharmacogenomic objective) • To examine the relationship, within the confines of a Phase 1 study, between the response data and tumoral TS, DHFR, GARFT, reduced folate carrier (RFC), folylpolyglutamate synthetase (FPGS), and gamma-glutamyl hydrolase (GGH) expression levels, as well as methylthioadenosine phosphorylase (MTAP)deletion

	status (pharmacogenomic objective) • To examine the correlation between Hcy and MMA levels at study entry with toxicity in patients treated with pemetrexed. Source: Study JMFC, Section 5.5.2 Pharmacokinetic Analyses, pgs 28-29 For patients who participated in the PK portion of the study, blood samples were collected during Cycle 1. Samples were obtained prior to drug infusion, at the end of infusion, and 15 minutes, 30 minutes, 60 minutes, 2 hours, 4 hours, 6 to 8 hours, and 24 hours following infusion. Plasma concentrations of pemetrexed were determined at each time point using a modification of a previously described LC/MS/MS method (Chaudhary et al. 1999). Appendix 11.3 provides a summary of the method used. A noncompartmental PK analysis was performed in WinNonlin® Enterprise Version 5.0.1 (Pharsight Corporation; Mountain View, CA). The PK data and analysis results were summarized and plotted using S-PLUS 6.2 and S-PLUS 2000. Source: Study JMFC Synopsis, Results, pg 3 The MTD of pemetrexed was 1910 mg/m^2 when administered as a 10-minute iv infusion every 3 weeks to children with refractory solid tumors. Source: Study JMFC, Section 7.1, pg 51 Figure JMFC.7.6 shows the relationship between renal function and pemetrexed clearance. It is seen from this figure that the range of creatinine clearance is similar between pediatric patients and adults. The clearance in pediatric patients appear to be in the low range of the clearances in adults, but likely not significantly different from the values seen in adults. The relationship between clearance of pemetrexed and dose is shown in Figure JMFC.7.7. As can be seen from this figure, the clearance appears to remain constant across the dose range studied and hence shows that pemetrexed PK is linear in this dose range. There does not appear to be any obvious non-linearity in pemetrexed disposition with
Phase 2: The Phase 2 study should have a disease-specific surrogate or clinically relevant endpoint.	

	increasing dose. Phase 2 Source: Study JMHW, Section 9.5.3 Primary Efficacy Variable(s), pg 22. Tumor response rate was the primary endpoint of this study. Any patient who was enrolled and received at least 1 dose of pemetrexed was considered for response provided: • the patient demonstrates progressive disease or death while on protocol therapy; or • the patient is observed on protocol therapy for at least 1 cycle and the tumor is not removed surgically prior to the time complete or partial response is confirmed, or • the patient demonstrates a complete or partial response as confirmed by protocol criteria Patients who demonstrate a complete or partial response confirmed by central review will be considered to have experienced a response for the application of the rule given in Section 10.2 of the protocol (see appendix). The evaluation period for determination of the best response will be 6 treatment cycles. All other patients will be considered nonresponders. All patients considered to have a response (complete response [CR] or partial response [PR]) must have imaging studies reviewed centrally at the COG. Centers will be notified by the COG about requests for scans of patients with stable disease.
Written Request Items	**Information Submitted/ Applicant's response**
Drug information: • **Dosage form:** Age appropriate formulation • **Route of administration:** Intravenous • **Regimen:** As determined by Phase 1 study	**Drug information:** Phase 1 Source: Study JMFC, Section 5.3.2 Patient Accrual and Dose Escalation, pg 25. The use of pemetrexed in children and adolescents with various solid tumors has not been evaluated. Pemetrexed has been evaluated in adult patients with various solid tumors, with pemetrexed 500 mg/m2 as the MTD. To determine the MTD for children and adolescents, patients were treated for at least 1 cycle; and the starting dose was pemetrexed 400 mg/m2 (approximately 80% of the original adult MTD), with subsequent dose escalations occurring in increments of 30%. As with adults, all children and adolescent patients were to take daily oral sources of folic

	acid and an intramuscular (IM) injection of vitamin B12 every 9 weeks (Figure JMFC.5.1) while on study. Source: Study JMFC, Section 5.4.2 Study Drug Administration, pg 28. Pemetrexed was administered as a 10-minute IV infusion on Day 1 of a 21-day cycle. Treatment consisted of 1 cycle; however, additional cycles were given every 21 days if the patient did not have PD and had recovered from the prior cycle, with ANC of ≥1000/μL, platelet count ≥75,000/μL, and other drug-related toxicities ≤Grade 1 or to baseline values. With each treatment cycle, dexamethasone 0.1 mg/kg/dose was given orally twice daily for 3 days beginning 1 day prior to pemetrexed. All patients were required to take a daily oral multivitamin (MVI) supplement containing 400 μg of folic acid, and 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. For reporting purposes, body surface area was derived at each cycle by taking the square root of height multiplied by weight and divided by 3600. Actual dose received (mg/m2) was calculated as the total dose of pemetrexed (mg) divided by this quantity (m2). Phase 2 Source: Study JMHW, Section 9.4.1 Treatments Administered, pg 18. Pemetrexed 1910 mg/m2 (or 60 mg/kg if patient <12 months old) was to be administered via central or peripheral line as a 10-minute IV infusion once every 21 days. Dexamethasone (Decadron®) 0.1 mg/kg/dose (maximum dose = 4 mg/dose) was to be given orally twice a day for three days, beginning the morning before the pemetrexed infusion. Ondansetron or another 5-HT3 receptor antagonist could have been administered 30 minutes prior to pemetrexed according to institutional guidelines.

	Patients were to begin taking a daily oral multivitamin supplement (MVI) containing at least 0.4 mg (400 micrograms) folic acid (100% of the adult recommended allowance) for at least 5 of the 7 days preceding the first dose of pemetrexed and were to continue MVI supplementation for at least 21 days following their last dose. Patients were to be given an intramuscular (IM) injection of cyanocobalamin (Vitamin B12) prior to the first dose of pemetrexed and every subsequent 3 cycles (every 9 weeks). The dose was to be 0.5 mg (500 micrograms) IM for children below the age of 12 years and 1 mg (1000 micrograms) IM for children and adolescents 12 years of age and older.
Written Request Items	**Information Submitted/ Applicant's response**
Drug specific safety concerns: Myelosuppression, hearing loss, nephrotoxicity	**Drug specific safety concerns evaluated:** <u>Phase 1</u> <u>Source: Study JMFC, Section 8.4.1, pg 62.</u> During the course of the study, there were no clinically significant alterations in laboratory values. Individual patient laboratory listings are provided in Appendix 11.2.4.1 for hematological values and Appendix 11.2.4.2 for chemistry values. *Hearing loss was not reported during Study JMFC as a treatment emergent adverse event (TEAE).* <u>Source: Study JMFC Synopsis, Conclusions, pg 4.</u> Overall, pemetrexed was well tolerated in children. The MTD of pemetrexed 1910 mg/m2 in this study was significantly higher than the recommended dose of 500 mg/m2 used for adult patients. The toxicity profile of pemetrexed in children with refractory solid tumors was similar to that which has been reported in adults. The most common toxicities in this Phase 1 study were hematologic. Consistent with adult Phase 1 studies, the most common DLT was neutropenia. Dermatitis and GI toxicity, which were also seen in adults, were dose limiting in 1 patient treated at the pemetrexed 2480-mg/m2 dose level. The dose-limiting electrolyte disturbances (hypophosphatemia, hyponatremia, hypokalemia) in 1 patient treated at the pemetrexed 2480-mg/m2 dose level have not been identified as significant problems in adults

	Phase 2 Source: Study JMHW, Section 12.2.2. All Grade Toxicities, pg 47. Table JMHW.12.5: Summary of CTCAE Grades 1 through 4: • Under the heading, "AUDITORY/EAR Hearing: patients with/without baseline audiogram and enrolled in a monitoring program" lists 1 patient with a Grade 3 toxicity. • An additional patient with a Grade 2 toxicity was listed under the next row entry, "AUDITORU/EAR Hearing: patients without baseline audiogram and not enrolled in a monitoring program". • Under the heading, "RENAL/GENITOURINARY Renal failure" lists one patient with a Grade 3 toxicity. Source: Study JMHW, Section 12.2.3 Grade 3 and 4 Toxicities, pg 55. Table JMHW.12.6 summarizes Grade 3 and 4 toxicities as graded by CTCAE. The most commonly reported Grade 3 or 4 toxicity was neutrophils/granulocytes (30.6%). Other commonly reported Grade 3 or 4 toxicities were hemoglobin (18.1%), leukocytes (16.7%), platelets (16.7%), ALT/SGPT (15.3%) and lymphopenia (12.5%). Table JMHW.14.2 summarizes Grade 3 and 4 toxicities as graded by CTCAE that are possibly related to study drug. The most commonly reported Grade 3 or 4 toxicity possibly related to study drug was neutrophils/granulocytes (30.6%). Other commonly reported Grade 3 or 4 toxicities possibly related to study drug were hemoglobin (16.7%), leukocytes (16.7%), platelets (15.3%), ALT/SGPT (15.3%), and lymphopenia (9.7%). Source: Study JMHW Synopsis, Conclusions, pgs 3-4. In the pediatric population, the most common toxicities seen regardless of causality, including all grade toxicities and Grade 3-4 toxicities, were hematological. The most common all grade nonhematological toxicities were liver function abnormalities, fatigue, and nausea. The most common Grade 3-4 nonhematologic toxicity regardless of causality was the elevation of ALT/SGPT. The most

	frequent adverse event requiring expedited reporting was infection with normal ANC or Grade 1 ANC. The frequency of hematological and transaminase elevation was higher than seen in adult studies, which may at least in part be due the higher dose of pemetrexed used in this study. There were no deaths that were considered possibly related to study treatment; however, 3 deaths within 30 days of last dose of study drug did occur and were attributed to progressive disease. Pemetrexed was not efficacious in the pediatric tumors studied, and no safety concerns were identified; no unexpected toxicities were identified. and no deaths occurred related to study treatment.
Written Request Items	**Information Submitted/ Applicant's response**
Statistical information, including power of study and statistical assessments: Statistics appropriate to the phase of the study.	**Statistical information, including power of study and statistical assessments:** <u>Phase 1</u> <u>Source: Study JMFC, Section 5.5.4 Statistical Methods, pg 29.</u> The sample size for this dose-escalation study was empirically based, dependent on the safety profile of pemetrexed in this patient population. A maximum of 36 patients were expected to be enrolled. There was a single full-analysis set (FAS) as the population for all efficacy and safety analyses for this study. The FAS consisted of all patients who had enrolled in the study. Efficacy, demographic and baseline, study drug exposure, and safety information were descriptively summarized and listed. Ninety-five percent confidence intervals were computed. No inferential statistical tests were performed. The primary analysis consisted of the summary of DLTs, as reported by the Study Chair. Secondary efficacy analyses included summary of best overall tumor response, and summary of serum folate and Hcy [homocysteine] levels. Treatment summaries included cycles completed and dose adjustments. All results were calculated using SAS® software version

8.2 (SAS 2001).

Phase 2
Source: Study JMHW, Section 9.7 Statistical Methods and Determination of Sample Size, pg 23.

9.7. Statistical Methods and Determination of Sample Size

Review of patient accrual onto recent Phase 2 solid tumor studies indicated the following entry rates for the various tumors under study could have been expected:

Disease Group/Strata	**Patients/Year**
Osteosarcoma	24
Ewing Sarcoma/peripheral PNET	24
Rhabdomyosarcoma	12
Neuroblastoma (measurable disease)	18
Neuroblastoma (MIBG+ evaluable disease)	18
Non-brainstem high grade glioma	36
Ependymoma	17
Medulloblastoma/Supratentorial PNET	36

Abbreviations: MIBG+ = metaiodobenzylguanidine positive; PNET = primitive neuroectodermal tumors.

With these entry rates, the probability of accruing 10 patients to complete the initial stage of evaluation in all 8 categories within 12 months was 71%. The corresponding probability for enrolling 20 patients in all eight above named disease categories in 36 months exceeded 99%. If activity was detected in any category, further trials in subcategories of category may have been conducted at the discretion of the Developmental Therapeutics Steering and study committees. A maximum of 160 patients was anticipated.

Response rates were calculated as the percent of patients whose best response was a CR or PR, and the confidence intervals were be constructed according to the method of Chang and O'Brien (Chang, et al. 1987; Chang and O'Brien 1987). Toxicity tables were constructed to summarize the observed incidence by severity and type of

	toxicity. ***9.7.1. Statistical and Analytical Plans*** The protocol for this study was approved on 12 February 2007. The analyses presented in this report are based on data contained in the reporting database, an archived production database used for analysis purposes, which contains data collected on the CRFs. The reporting database was validated and transferred for analysis on 08 June 2010. **9.7.1.1. General Considerations** All confidence intervals for parameters to be estimated were constructed using a two sided, 5% significance level. Additional exploratory analyses of the data were conducted as deemed appropriate. **9.7.1.2. Multiple Comparisons/Multiplicity** No multiplicity adjustments were planned for any of the analyses. **9.7.1.3. Efficacy Analyses** Response rates were calculated as the percent of patients whose best response is a CR or PR, and the confidence intervals will be constructed according to the method of Chang and O'Brien (Chang, et al. 1987; Chang and O'Brien 1987).
Written Request Items	**Information Submitted/ Applicant's response**
Labeling that may result from the study(ies): Appropriate sections of the label may be changed to incorporate the findings of the studies.	**Labeling that may result from the study(ies):** <u>Source: Proposed label submitted to NDA 21-462 on October 27, 2010, sequence number 0072:</u> **8.4 Pediatric Use** The effectiveness of ALIMTA in pediatric patients has not been established. ALIMTA was administered as an intravenous infusion over 10 minutes on Day 1 of a 21 day cycle in patients with recurrent solid tumors in a Phase 1 study (32 patients) and a Phase 2 study (72 patients). All patients received pretreatment with vitamin B_{12} and folic acid supplementation and dexamethasone. The dose escalation in the Phase 1 study determined the maximum tolerated dose was 1910 mg/m^2 and this dose (or 60 mg/kg for patients <12 months old) was evaluated in the Phase 2

	study of patients with relapsed or refractory osteosarcoma, Ewing sarcoma/peripheral PNET, rhabdomyosarcoma, neuroblastoma, ependymoma, medulloblastoma/supratentorial PNET, or non-brainstem high grade glioma. The mean plasma clearance and half-life of ALIMTA in 22 patients in the Phase 1 study were similar to those reported in adults *[see Pharmacokinetics (12.3)]*. The most common toxicities reported were hematological (leukopenia, neutropenia/granulocytopenia, anemia, thrombocytopenia, and lymphopenia), liver function abnormalities (increased ALT/AST), fatigue, and nausea. No meaningful clinical activity in pediatric patients was observed in the Phase 2 trial. **12.3 Pharmacokinetics**
Written Request Items	**Information Submitted/ Applicant's response**
Format of reports to be submitted: Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation.	**Format of reports to be submitted:** Full study reports were provided in the original supplemental NDA submitted on September 17, 2010, sequence number (b) (4) for: H3E-US-JMFC, Clinical Study Report: A Phase 1 Study of Pemetrexed (LY231514, Alimta) in Children and Adolescents with Recurrent Solid Tumors H3E-MC-JMHW, A Phase II Study of Pemetrexed in Children with Recurrent Malignancies
Written Request Items	**Information Submitted/ Applicant's response**

Timeframe for submitting reports of the studies:	**Timeframe for submitting reports of the studies:**
Reports of the studies that meet the terms of the Written Request dated October 5, 2001, and re-issued July 3, 2002, as amended by this letter, must be submitted to the Agency as part of a new drug application or supplement to an approved new drug application on or before October 15, 2010, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.	The requested Phase 1 and Phase 2 studies were completed sequentially and submitted with proposed labeling in a supplemental new drug application on September 17, 2010, sequence number (b) (4)

7 Review of Efficacy

Efficacy Summary

Overall, the data submitted in this supplement did not demonstrate any treatment benefits with pemetrexed for pediatric patients with a variety of different solid tumor types. In the Phase 2 trial, no patients experienced either a complete response or a partial response. Additionally, although it is was not the primary endpoint of the Phase 1 trial, there were no responses seen in 32 patients in the Phase 1 dose-finding trial.

7.1 Indication

The applicant is not seeking a pediatric indication for pemetrexed.

7.1.1 Methods

Clinical review is based primarily on the CSR for the JMHW trial, case report forms and primary data sets for efficacy and toxicity submitted by the applicant.

7.1.2 Demographics

The applicant's summary of baseline and demographic characteristics in the ITT population are depicted in Table 7. Forty males and 32 females were enrolled and treated. Of these subjects, 48 were Caucasian/white, 14 were black, two were Asian, two were American Indian or Alaska Native, and six were other or unknown. Median age was 11 years.

Table 7: Patient demographics (applicant's table)

Parameter		Osteo-sarcoma (N=10)	Ewing Sarcoma/ Peripheral PNET (N=11)	Rhabdo-myosarcoma (N=9)	Neuro-blastoma (measurable disease) (N=5)	Neuro-blastoma (MIBG + evaluable) (N=6)	Ependymoma (N=10)	Medulloblastoma / Supratentorial PNET (N=11)	Non-Brainstem High-Grade Glioma (N=10)	Total (N=72)
Gender [n (%)]										
	Number of Patients	10	11	9	5	6	10	11	10	72
	Male	6 (60%)	3 (27.27%)	3 (33.33%)	4 (80%)	5 (83.33%)	7 (70%)	7 (63.64%)	5 (50%)	40 (55.56%)
	Female	4 (40%)	8 (72.73%)	6 (66.67%)	1 (20%)	1 (16.67%)	3 (30%)	4 (36.36%)	5 (50%)	32 (44.44%)
Age (Years)										
	Number of Patients	10	11	9	5	6	10	11	10	72
	Mean	14.94	18.24	8.74	6.23	9.62	8.42	12.00	12.75	11.96
	SD	4.28	3.35	4.96	2.98	5.38	4.59	7.13	5.15	5.97
	Median	13.93	19.18	8.22	4.87	8.41	7.45	9.88	12.30	11.52
	Minimum	7.98	12.33	3.05	3.92	4.51	3.41	3.68	4.53	3.05
	Maximum	21.46	22.46	16.73	11.35	18.16	17.84	23.46	19.21	23.46
Weight (Kg)										
	Number of Patients	10	11	9	5	6	10	11	10	72
	Mean	56.42	67.14	32.38	21.16	30.85	43.39	38.29	44.72	44.27
	SD	24.12	32.39	15.94	6.15	18.60	33.19	24.58	20.86	27.11
	Median	59.40	57.50	31.00	21.30	26.65	29.00	29.30	38.30	36.25
	Minimum	20.10	28.80	9.40	12.70	15.10	13.30	10.90	16.80	9.40
	Maximum	89.70	119.40	55.60	30.00	63.00	107.50	89.90	73.40	119.40
BSA (m^2)										
	Number of Patients	10	11	9	5	6	10	11	10	72
	Mean	1.56	1.72	1.04	0.81	1.04	1.10	1.18	1.34	1.27
	SD	0.44	0.49	0.37	0.17	0.42	0.50	0.52	0.43	0.50
	Median	1.63	1.63	1.07	0.80	0.97	0.93	1.01	1.23	1.20
	Minimum	0.82	1.05	0.48	0.59	0.66	0.59	0.52	0.69	0.48
	Maximum	2.12	2.47	1.55	1.06	1.72	2.06	2.15	1.91	2.47
Race [n (%)]										
	Number of Patients	10	11	9	5	6	10	11	10	72
	American Indian or Alaska Native	0 (0%)	0 (0%)	2 (22.22%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (2.78%)
	Asian	0 (0%)	1 (9.09%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	2 (2.78%)
	Black or African American	4 (40%)	0 (0%)	0 (0%)	2 (40%)	1 (16.67%)	1 (10%)	3 (27.27%)	3 (30%)	14 (19.44%)
	White	4 (40%)	8 (72.73%)	7 (77.78%)	2 (40%)	4 (66.67%)	9 (90%)	8 (72.73%)	6 (60%)	48 (66.67%)
	Other	1 (10%)	1 (9.09%)	0 (0%)	1 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (4.17%)
	Unknown	1 (10%)	1 (9.09%)	0 (0%)	0 (0%)	1 (16.67%)	0 (0%)	0 (0%)	0 (0%)	3 (4.17%)

Abbreviations: kg = kilograms; m = meters; MIBG+ = metaiodobenzylguanidine positive; N = total treated patients in each column; n = number of patients in each category; ; PNET = primitive neuroectodermal tumors; SD = standard deviation.

7.1.3 Subject Disposition

Patient disposition is shown in Table 8. The vast majority of patients (n=60) discontinued due to progressive disease. Three patient discontinued secondary to the

physician's determination that it was in the patient's best interest; four patients had a protocol violation; three patients had toxicity requiring their removal from the protocol; and one patient refused further treatment.

Table 8: Patient Disposition

Reasons	Stratum																Total (N=72)	
	Osteo-sarcoma (N=10)		Ewing Sarcoma/ Peripheral PNET (N=11)		Rhabdo-myosarcoma (N=9)		Neuroblastoma (measurable disease) (N=5)		Neuroblastoma (MIBG + evaluable) (N=6)		Ependymoma (N=10)		Medulloblastoma / Supratentorial PNET (N=11)		Non-Brainstem High-Grade Glioma (N=10)			
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Physician determines it is in the patient's best interest	0	0	2	18.18	1	11.11	0	0	0	0	0	0	0	0	0	0	3	4.17
Refusal of further protocol therapy by patient/parent/ guardian	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	10.00	1	1.39
Progressive disease	10	100.00	7	63.64	7	77.78	5	100.00	5	83.33	10	100.00	7	63.64	9	90.00	60	83.33
Toxicity requiring removal from study	0	0	1	9.09	0	0	0	0	0	0	0	0	2	18.18	0	0	3	4.17
Death	0	0	0	0	0	0	0	0	0	0	0	0	1	9.09	0	0	1	1.39
Protocol violation	0	0	1	9.09	1	11.11	0	0	1	16.67	0	0	1	9.09	0	0	4	5.56

Abbreviations: MIBG+ = metaiodobenzylguanidine positive; N = total treated patients; n = number of patients in each category; PNET = primitive neuroectodermal tumors; N = total treated patients in each column; n = number of patients with discontinuation.

7.1.4 Analysis of Primary Endpoint(s)

There were no CRs or PRs observed in this trial. Table 9 summarizes best overall response to therapy.

Table 9: Summary of Best Overall Tumor Response

Overall Response	Osteo-sarcoma (N=10)	Ewing Sarcoma/ Peripheral PNET (N=11)	Rhabdo-myosarcoma (N=9)	Neuroblastoma (measurable disease) (N=5)	Neuroblastoma (MIBG + evaluable) (N=6)	Ependymoma (N=10)	Medulloblastoma / Supratentorial PNET (N=11)	Non-Brainstem High-Grade Glioma (N=10)	Total (N=72)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Complete Response	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Partial Response	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Stable Disease	1 (10%)	1(9.1%)	0 (0%)	0 (0%)	1 (17%)	1 (10%)	1(9.1%)	0 (0%)	5 (6.9%)
95% CI	0.3%-45%	0.2%-41%	0%-34%	0%-52%	0.4%-64%	0.3%-45%	0.2%-41%	0%-31%	2.3%-15%
Progressive Disease	9 (90%)	6 (55%)	8 (89%)	5 (100%)	4 (67%)	9 (90%)	7 (64%)	9 (90%)	57 (79%)
95% CI	55%-99.7%	23%-83%	52%-99.7%	48%-100%	22%-96%	55%-99.7%	31%-89%	55%-99.7%	68%-88%
Patients not evaluable	0 (0%)	1 (9.1%)	1 (11%)	0 (0%)	1 (17%)	0 (0%)	1 (9.1%)	0 (0%)	4 (5.6%)
Non-responders[a]	0 (0%)	3 (27%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (18%)	1 (10%)	6 (8.3%)
Number of Responders (CR+PR)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Number of Clinical Benefit (CR+PR+SD)	1 (10%)	1(9.09%)	0 (0%)	0 (0%)	1 (17%)	1 (10%)	1(9.09%)	0 (0%)	5 (6.9%)
95% CI[b]	0.3%-45%	0.2%-41%	0%-34%	0%-52%	0.4%-64%	0.3%-45%	0.2%-41%	0%-31%	2.3%-15%

Abbreviations: CI=confidence interval; CR=complete response; N=total treated patients in each column; n = number of patients in each category; MIBG+ = metaiodobenzylguanidine positive; PNET = primitive neuroectodermal tumors; PR=partial response; RECIST = Response Evaluation Criteria in Solid Tumor; SD=stable disease.

[a] Patients without sufficient information to assess for RECIST response: considered non-responders for statistical analyses.

[b] Exact conditional marginal confidence interval.

7.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoint examining the relationship between response and tumor expression of specific proteins could not performed as there were no responses.

7.1.6 Other Endpoints

The secondary objectives were included as optional pharmacogenetic and correlative studies done on this protocol. Outcomes of this research may be reported in the future by the Children's Oncology Group in the peer-reviewed literature, according to the applicant.

7.1.7 Subpopulations

No subpopulations were studied.

7.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

7.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

8 Review of Safety

Safety Summary

The overall safety profile of pemetrexed in pediatric patients was found to be similar to that of the adult population.

8.1 Methods

8.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety data from 72 patients on trial JMHW were used in the safety evaluation.

8.1.2 Categorization of Adverse Events

The type and grade of the event were determined by the investigator according to the National Cancer Institute (NCI) Common Terminology Criteria (Version 3.0).

8.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable.

8.2 Adequacy of Safety Assessments

8.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Drug exposure for patients by tumor type is summarized in Table 10 below. The median number of cycles was 1 cycle (range 1-13 cycles). There were no dose delays or omissions. One patient received one cycle of therapy at a reduced dose, while a second patient received two cycles of therapy at a reduced dose.

Table 10: Summary of Drug Exposure

Parameter	Osteo-sarcoma (N=10)	Ewing Sarcoma/ Peripheral PNET (N=11)	Rhabdo-myosarcoma (N=9)	Neuroblastoma (measurable disease) (N=5)	Neuroblastoma (MIBG + evaluable) (N=6)	Ependymoma (N=10)	Medullo-blastoma / Supratentorial PNET (N=11)	Non-Brainstem High-Grade Glioma (N=10)	Total (N=72)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients completed >= 1 cycle	10 (100%)	11 (100%)	9 (100%)	5 (100%)	6 (100%)	10 (100%)	11 (100%)	10 (100%)	72 (100%)
Patients completed >= 2 cycles	2 (20%)	3 (27.27%)	2 (22.22%)	0 (0%)	1 (16.67%)	2 (20%)	4 (36.36%)	4 (40%)	18 (25%)
Patients completed >= 3 cycles	1 (10%)	2 (18.18%)	2 (22.22%)	0 (0%)	1 (16.67%)	2 (20%)	2 (18.18%)	3 (30%)	13 (18.06)
Patients completed >= 4 cycles	1 (10%)	1 (9.09%)	0 (0%)	0 (0%)	1 (16.67%)	1 (10%)	1 (9.09%)	0 (0%)	5 (6.94%)
Patients completed >= 5 cycles	1 (10%)	1 (9.09%)	0 (0%)	0 (0%)	1 (16.67%)	1 (10%)	0 (0%)	0 (0%)	4 (5.56%)
Patients completed >= 6 cycles	0 (0%)	1 (9.09%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.39%)
Patients completed >= 7 cycles	0 (0%)	1 (9.09%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.39%)
Patients completed >= 8 cycles	0 (0%)	1 (9.09%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.39%)
Patients completed >= 9 cycles	0 (0%)	1 (9.09%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.39%)
Patients completed >= 10 cycles	0 (0%)	1 (9.09%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.39%)
Patients completed >= 11 cycles	0 (0%)	1 (9.09%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.39%)
Patients completed >= 12 cycles	0 (0%)	1 (9.09%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.39%)
Patients completed >= 13 cycles	0 (0%)	1 (9.09%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.39%)
Cycles Received									
Patients that received >=1 cycle	10	11	9	5	6	10	11	10	72
Mean	1.50	2.36	1.44	1.00	1.67	1.60	1.64	1.70	1.67
SD	1.27	3.59	0.88	0.00	1.63	1.35	1.03	0.95	1.70
Median	1	1	1	1	1	1	1	1	1
Minimum	1	1	1	1	1	1	1	1	1
Maximum	5	13	3	1	5	5	4	3	13
Total number of cycles received	15	26	13	5	10	16	18	17	120

8.2.2 Explorations for Dose Response

All patients received the same dose in this trial; therefore, there was not enough information to explore dose response.

8.2.3 Special Animal and/or In Vitro Testing

Not applicable.

8.2.4 Routine Clinical Testing

Not applicable.

8.3 Major Safety Results

8.3.1 Deaths

There were 3 deaths within 30 days after the last dose of study drug due to progressive disease. These were not considered possibly related to study treatment. There were no deaths at any time considered to be possibly related to study treatment.

8.3.2 Nonfatal Serious Adverse Events

SAEs were observed in 72.2% of the patients in trial JMHW. The most commonly reported SAEs were hematologic in nature, including neutropenia (30.6%), anemia (18.1%), thrombocytopenia (16.7%) and lymphopenia (12.5%). The most commonly reported non-hematologic SAE was increased ALT/SGPT (15.3%). See Table below for a summary of the SAEs in trial JMHW.

Table 11: Summary of Grade 3 and 4 Adverse Events

	Grade					
	3		4		3 or 4	
	Number	Percent	Number	Percent	Number	Percent
Toxicity Type						
Any Type	34	47.2	18	25.0	52	72.2
ALLERGY/IMMUNOLOGY Allergic reaction/hypersensitivity (including drug fever)	2	2.8			2	2.8
AUDITORY/EAR Hearing: patients with/without baseline audiogram and enrolled in a monitoring program	1	1.4			1	1.4
BLOOD/BONE MARROW Hemoglobin	12	16.7	1	1.4	13	18.1
BLOOD/BONE MARROW Leukocytes (total WBC)	6	8.3	6	8.3	12	16.7
BLOOD/BONE MARROW Lymphopenia	9	12.5			9	12.5
BLOOD/BONE MARROW Neutrophils/granulocytes (ANC/AGC)	10	13.9	12	16.7	22	30.6
BLOOD/BONE MARROW Platelets	6	8.3	6	8.3	12	16.7
CARDIAC GENERAL Hypotension			1	1.4	1	1.4
CONSTITUTIONAL SYMPTOMS Fatigue (asthenia, lethargy, malaise)	2	2.8			2	2.8
CONSTITUTIONAL SYMPTOMS Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	3	4.2			3	4.2
DERMATOLOGY/SKIN Pruritus/itching	1	1.4			1	1.4
DERMATOLOGY/SKIN Rash/desquamation	1	1.4			1	1.4
DERMATOLOGY/SKIN Rash: erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	1	1.4			1	1.4
GASTROINTESTINAL Anorexia	1	1.4			1	1.4
GASTROINTESTINAL Dehydration	1	1.4	1	1.4	2	2.8
GASTROINTESTINAL Nausea	3	4.2			3	4.2
GASTROINTESTINAL Vomiting	3	4.2			3	4.2

	Grade					
	3		4		3 or 4	
	Number	Percent	Number	Percent	Number	Percent
HEMORRHAGE/BLEEDING Hemorrhage, CNS			1	1.4	1	1.4
HEMORRHAGE/BLEEDING Hemorrhage, GI Rectum	1	1.4			1	1.4
HEMORRHAGE/BLEEDING Hemorrhage, GU Urinary NOS	1	1.4			1	1.4
INFECTION Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection)(ANC <1.0 x 10e9/L, fever >=38.5 d	4	5.6			4	5.6
INFECTION Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) Lung (pneumonia)	1	1.4	1	1.4	2	2.8
INFECTION Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) Upper airway NOS	1	1.4			1	1.4
INFECTION Infection with normal ANC or Grade 1 or 2 neutrophils Abdomen NOS	1	1.4			1	1.4
INFECTION Infection with normal ANC or Grade 1 or 2 neutrophils Catheter-related	1	1.4			1	1.4
INFECTION Infection with normal ANC or Grade 1 or 2 neutrophils Lung (pneumonia)	2	2.8			2	2.8
INFECTION Infection with normal ANC or Grade 1 or 2 neutrophils Meninges (meningitis)	1	1.4			1	1.4
INFECTION Infection with normal ANC or Grade 1 or 2 neutrophils Pharynx	1	1.4			1	1.4
INFECTION Infection with normal ANC or Grade 1 or 2 neutrophils Wound	1	1.4			1	1.4
LYMPHATICS Edema: limb	1	1.4			1	1.4
METABOLIC/LABORATORY Alkaline phosphatase	1	1.4			1	1.4
METABOLIC/LABORATORY ALT, SGPT (serum glutamic pyruvic transaminase)	11	15.3			11	15.3

	Grade					
	3		4		3 or 4	
	Number	Percent	Number	Percent	Number	Percent
METABOLIC/LABORATORY AST, SGOT(serum glutamic oxaloacetic transaminase)	5	6.9			5	6.9
METABOLIC/LABORATORY Calcium, serum-high (hypercalcemia)	1	1.4			1	1.4
METABOLIC/LABORATORY GGT (gamma-Glutamyl transpeptidase)	1	1.4			1	1.4
METABOLIC/LABORATORY Phosphate, serum-low (hypophosphatemia)	1	1.4	1	1.4	2	2.8
METABOLIC/LABORATORY Potassium, serum-low (hypokalemia)	3	4.2	1	1.4	4	5.6
METABOLIC/LABORATORY Sodium, serum-low (hyponatremia)	1	1.4			1	1.4
MUSCULOSKELETAL/SOFT TISSUE Osteonecrosis (avascular necrosis)	1	1.4			1	1.4
NEUROLOGY Hydrocephalus	1	1.4	1	1.4	2	2.8
NEUROLOGY Mood alteration Depression			1	1.4	1	1.4
NEUROLOGY Neuropathy: cranial CN IX Motor-pharynx; Sensory-ear, pharynx, tongue	1	1.4			1	1.4
NEUROLOGY Neuropathy: cranial CN X Motor-palate; pharynx, larynx	1	1.4			1	1.4
NEUROLOGY Neuropathy: cranial CN XII Motor-tongue	1	1.4			1	1.4
NEUROLOGY Seizure	2	2.8			2	2.8
NEUROLOGY Syncope (fainting)	1	1.4			1	1.4
PAIN Pain Abdomen NOS	2	2.8			2	2.8
PAIN Pain Extremity-limb	2	2.8	1	1.4	3	4.2
PAIN Pain Head/headache	3	4.2			3	4.2
PAIN Pain Muscle	1	1.4			1	1.4
PAIN Pain Tumor pain	1	1.4	1	1.4	2	2.8
PAIN Pain - Other (Specify, __)	1	1.4			1	1.4

	Grade					
	3		4		3 or 4	
	Number	Percent	Number	Percent	Number	Percent
PULMONARY/UPPER RESPIRATORY Cough	1	1.4			1	1.4
PULMONARY/UPPER RESPIRATORY Dyspnea (shortness of breath)			2	2.8	2	2.8
PULMONARY/UPPER RESPIRATORY Hypoxia	1	1.4			1	1.4
RENAL/GENITOURINARY Renal failure	1	1.4			1	1.4
VASCULAR Thrombosis/thrombus/embolism	1	1.4			1	1.4

8.3.3 Dropouts and/or Discontinuations

Three patients had toxicity that required removal from the protocol. The first patient had hematologic toxicity in the first cycle consisting of neutropenia, anemia and thrombocytopenia that was of sufficient severity and duration to require removal from

the protocol. The second patient was removed from the protocol after the second cycle, during which a Grade 3 infection was reported. The parent/guardian requested removal due to this toxicity. The third patient was removed after one cycle of therapy for prolonged Grade 4 neutropenia.

8.4 Supportive Safety Results

8.4.1 Common Adverse Events

The most commonly reported all grade toxicities were leukocytes (48.5%), neutrophils/granulocytes (47.3%), hemoglobin (45.9%), platelets (40.3%), and lymphopenia (27.8%). Other frequently reported all grade toxicities were alanine aminotransferase/serum glutamic-pyruvic transaminase (ALT/SGPT) (47.2%), and aspartate aminotransferase/serum glutamicoxaloacetic transaminase (AST/SGOT (40.2%), fatigue (32.0%), and nausea (23.7%).

8.4.2 Laboratory Findings

See above.

8.4.3 Vital Signs

Vital sign data was not submitted with this application.

8.4.4 Electrocardiograms (ECGs)

Electrocardiograms were not regularly performed as part of this trial.

8.4.5 Special Safety Studies/Clinical Trials

No special safety studies were performed as part of this study.

8.4.6 Immunogenicity

Not applicable.

8.5 Other Safety Explorations

8.5.1 Dose Dependency for Adverse Events

One dose of pemetrexed was used in JMHW and thus dose dependency for adverse events cannot be evaluated.

8.5.2 Time Dependency for Adverse Events

Not applicable.

8.5.3 Drug-Demographic Interactions

Not applicable.

8.5.4 Drug-Disease Interactions

Not applicable.

8.5.5 Drug-Drug Interactions

Not applicable.

8.6 Additional Safety Evaluations

8.6.1 Human Carcinogenicity

Not applicable.

8.6.2 Human Reproduction and Pregnancy Data

Not applicable.

8.6.3 Pediatrics and Assessment of Effects on Growth

Assessment of effects on growth was not performed.

8.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

8.7 Additional Submissions / Safety Issues

There was no 120-day safety update for this supplement as there was no additional safety data collected after the original submission.

9 Postmarket Experience

Not applicable. Pemetrexed has not been marketed for any pediatric indication.

10 Appendices

10.1 Labeling Recommendations

The following will be inserted into the label in Section 8.4, titled Pediatric Use:

"Efficacy of ALIMTA in pediatric patients has not been demonstrated. ALIMTA was administered as an intravenous infusion over 10 minutes on Day 1 of a 21 day cycle to pediatric patients with recurrent solid tumors in a Phase 1 study (32 patients) and a Phase 2 study (72 patients). All patients received pretreatment with vitamin B_{12} and folic acid supplementation and dexamethasone. The dose escalation in the Phase 1 study determined the maximum tolerated dose was 1910 mg/m^2 and this dose (or 60 mg/kg for patients <12 months old) was evaluated in the Phase 2 study of patients with relapsed or refractory osteosarcoma, Ewing sarcoma/peripheral PNET, rhabdomyosarcoma, neuroblastoma, ependymoma, medulloblastoma/supratentorial PNET, or non-brainstem high grade glioma. No responses were observed among the 72 patients in this Phase 2 trial. The most common toxicities reported were hematological (leukopenia, neutropenia/granulocytopenia, anemia, thrombocytopenia, and lymphopenia), liver function abnormalities (increased ALT/AST), fatigue, and nausea.

The single dose pharmacokinetics of ALIMTA administered in doses ranging from 400 to 2480 mg/m^2 were evaluated in the Phase 1 trial in 22 patients (13 males and 9 females) aged 4 to 18 years (average age 12 years). Pemetrexed exposure (AUC and C_{max}) appeared to increase proportionally with dose. The average pemetrexed clearance (2.30 L/h/m^2) and half-life (2.3 hours) in pediatric patients were comparable to values reported in adults."

10.2 Advisory Committee Meeting

Not applicable.

10.3 Pediatric Exclusivity Board Meeting

This reviewer presented the review findings for pediatric exclusivity determination to the Pediatric Exclusivity Board (PEB) on 12-03-2010. The Pediatric Exclusivity Board granted pediatric exclusivity for pemetrexed, effective December 3, 2010.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

AMY E MCKEE
03/04/2011

JOHN R JOHNSON
03/04/2011