CLINICAL REVIEW

Application Type	Commercial-Supplement
Application Number(s)	NDA 22088-s014
Priority or Standard	Standard
Submit Date(s)	12/2/2011
Received Date(s)	12/2/2011
PDUFA Goal Date	6/2/2012
Division / Office	CDER/OHOP/DOP1
Reviewer Name(s)	Paul G. Kluetz, M.D.
Review Completion Date	5/3/2012
Established Name	Temsirolimus
(Proposed) Trade Name	Torisel
Therapeutic Class	mTOR inhibitor
Applicant	Wyeth Pharmaceuticals, a Pfizer Company
Formulation(s)	Intravenous
Dosing Regimen	Weekly (dose finding study)
Indication(s)	None. This is a Request for Pediatric Exclusivity Determination
Intended Population(s)	None

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

No pediatric indication is being sought in this submission. Following review of the application, it is my assessment that the applicant has fairly responded to all of the elements of the pediatric written request (PWR). I recommend that pediatric exclusivity be granted for Torisel and that clinical trial information from the submitted pediatric study is included in the Torisel label.

1.2 Risk Benefit Assessment

The adverse event profile of Torisel appears to be similar in the pediatric and adult populations. A review of the safety data was performed and no significant novel safety signal was appreciated that was unique to the pediatric population. Frequencies of adverse events at the 75mg/m^2 dose level will be included in the product label under section 8.4.

Review of the efficacy data reveals that Torisel had limited activity in the pediatric population treated in the phase I/II clinical trial. (b) (4)

1.3 Recommendations for Risk Evaluation and Mitigation Strategies (REM)

No new safety signals were identified that would warrant a REMS.

1.4 Recommendations for Postmarket Requirements and Commitments

No post-marketing requirements or commitments are generated from this review.

2.0 Introduction and Regulatory Background

Wyeth Pharmaceuticals, Inc., a Pfizer Company, submitted a request for Pediatric Exclusivity Determination on December 2, 2011. The initial pediatric written request was issued on January 12, 2001 and had been subsequently revised with the most recent amendment dated 2/25/2011. Details regarding the amendments to the pediatric written request and significant protocol amendments can be found in section 2.5 Summary of Presubmission Regulatory Activity Related to Submission.

Following preliminary review of the submitted study report for trial 3066K-1, "A Phase 1/2 Safety and Exploratory Pharmacodynamic Study of Intravenous Temsirolimus in Pediatric Subjects with Relapsed/Refractory Solid Tumors", pediatric exclusivity was granted on February 28, 2012.

2.1 Product Information

Established Name: Temsirolimus
Proprietary Name: Torisel®
Applicant: Wyeth Pharmaceuticals, Inc., A subsidiary of Pfizer, Inc.
Pharmacological Class: Small molecule kinase inhibitor of mTOR

Torisel® (temsirolimus) is an inhibitor of the mammalian target of rapamycin (mTOR) and gained approved for the treatment of adults with advanced renal cell carcinoma in May of 2007. The approved dose for this indication is 25 mg infused intravenously over a 30-60 minute period once per week.

Proposed Indication for Current Submission: The applicant is not seeking an indication for pediatric patients based on this submission.

Proposed Dosage and Administration: There is no proposed dose or route of administration in pediatric patients. Information regarding the clinically tolerable dose taken into the phase 2 clinical trial (75mg/m^2) will be included in the product label section 8.4, Pediatric Use.

2.2 Tables of Currently Available Treatments for Proposed Indications

The applicant is not pursuing a pediatric indication based on the submitted data.

2.3 Availability of Proposed Active Ingredient in the United States

Temsirolimus is available as a white to off-white powder with a molecular formula of $C_{56}H_{87}NO_{16}$ and a molecular weight of 1030.30. It is non-hygroscopic. Temsirolimus is practically insoluble in water and soluble in alcohol. It has no ionizable functional groups, and its solubility is independent of pH.

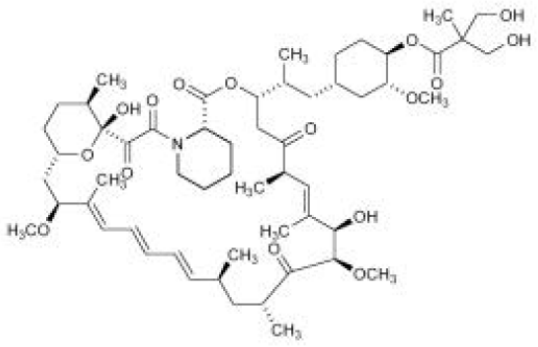

Figure 1: Structure of Temsirolimus

TORISEL (temsirolimus) injection, 25 mg/mL, is a clear, colorless to light yellow, non-aqueous, ethanolic, sterile solution. TORISEL (temsirolimus) injection requires two

dilutions prior to intravenous infusion. TORISEL (temsirolimus) injection should be diluted only with the supplied DILUENT for TORISEL®.

2.4 Important Safety Issues With Consideration to Related Drugs

On October 29, 2010, Afinitor® (everolimus), an oral mTOR inhibitor, was granted accelerated approval for adults and children ≥3 years of age with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TSC) who require intervention but are not candidates for curative surgical resection.[1] The starting dose of Afinitor® was based on body surface area and the dose was adjusted throughout treatment based on serum trough concentrations. In the small single arm study, 28 patients ages 3-34 (median 11 years old) were treated with Afinitor® . The most common adverse events (>30%) included stomatitis, upper respiratory tract infection, sinusitis, otitis media and pyrexia. Grade 3 adverse reactions included convulsions, infections and single cases of stomatitis, aspiration, cyclic neutropenia, sleep apnea syndrome, vomiting, dizziness, WBC decreased and neutrophil count decreased.[2]

In addition, both everolimus and sirolimus, an oral mTOR inhibitor, have been studied in pediatric transplant patients as an immunosuppressant. [3]

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Torisel is approved for the treatment of adults with advanced renal cell carcinoma. A brief regulatory history regarding the pediatric development plan is presented in Table 1 below.

Table 1: Important time points in Pediatric Development Program

12-Jan-2001	Original Pediatric Written Request (PWR)
30-Sep-2004	Resubmitted PWR with substantial changes
15-Jun-2006	Protocol Amendment #3 Submitted *
28-Sep-2007	PWR Amendment #1: Extends timeframe for submission of study reports.
29-Sep-2010	PWR Amendment #2: Extends timeframe for submission of study reports.
25-Feb-2011	PWR Amendment #3: Extends timeframe for submission of study reports.

* Protocol Amendment #3 made several changes affecting the pediatric written request. Details of this amendment including correspondence between the FDA and the applicant during this time can be found in section 6.2 Evaluation of the Applicant's Fulfillment of the Pediatric Written Request Requirement.

The September 30, 2004 amendment to the PWR made the following substantial changes:

[1] FDA label for everolimus available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022334s017lbl.pdf
[2] Krueger et al., Everolimus for Subependymal Giant-Cell Astrocytomas in Tuberous Sclerosis, *NEJM* 2010; 363: 1801-11.
[3] Kasap B. Sirolimus in Pediatric Renal Transplantation, Pediatr Transplant. 2011 Nov; 15(7): 673-85.

- Part 2 patients will be treated at the MTD determined by the Part 1 dose escalation.
- Defined objective response (CR+PR) as primary anti-tumor activity measure and primary endpoint of Part 2.
- Freedom from progression (CR+PR+MR+SD) at 3 months can be used as a secondary efficacy endpoint.
- Simon 2 stage design utilized for Part 2.
- PK parameters will be estimated for all subjects.

Subsequent PWR amendments simply extended the timeframe for submission of study reports.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission contains the debarment certification signed 11/4/2011. The submission contains datasets and other information sufficient for the pediatric exclusivity determination and labeling review. The overall quality and integrity of the submission is adequate.

3.2 Compliance with Good Clinical Practices

The study report section 2.2 notes that "This study was conducted in accordance with the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) and the ethical principles that have their origins in the Declaration of Helsinki. All investigators have provided written commitments to comply with GCP standards and the protocol."

In addition, the applicant notes that either an institutional review board or an independent ethics committee reviewed the protocol, protocol amendments, investigator brochure and informed consent documents for this clinical study.

The applicant noted 9 protocol violations (Table 2) and determined that they did not affect the safety of the subjects or impact on the conclusions of their study. The clinical reviewer agrees with this assessment:

Table 2: Protocol Violations Reported by Applicant

Subject Number	Deviation
Part 1	
139-002-000022	The subject received dexamethasone less than 2 weeks prior to first dose of test article.
139-002-000023	Baseline performance status not obtained (inclusion criterion 7)
139-002-000025	The subject received dexamethasone less than 2 weeks prior to first dose of test article.
Part 2	
139-203-000498	Eligibility source documents not able to be verified by the site monitor
139-003-000233	Surgery for treatment purposes on study (subject underwent partial left lung resection).
139-200-000447	Subject had ineligible absolute neutrophil count (inclusion criterion 8)
139-205-000518	Incorrect diluting of temsirolimus by pharmacist.
139-009-000327	Echocardiogram and chest X-ray performed before obtaining subject's informed consent form.
139-207-000558	Response evaluation criteria in solid tumors not followed and patient on study despite PD per RECIST.

Abbreviations: PD = progressive disease; RECIST = Response Evaluation Criteria In Solid Tumors.
Source: Applicant csr76631 full body: verified by FDA reviewer.

3.3 Financial Disclosures

The submission contains a 19 page document (section 1.3.4 Financial Disclosure) discussing financial disclosures. A total of 157 of 158 investigators are certified as having no Financial Arrangement per 21 CFR 54.2. One investigator did have equity in the sponsor to disclose, but there were no significant payments of other sorts to disclose. This investigator disclosed shares in Wyeth valued at $78,358.24. (b) (6)

The submitted financial disclosure document also provided information regarding steps taken to minimize bias. There does not appear to be any significant financial conflicts of interest that would materially bias the outcome of the study.

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

Temsirolimus is an inhibitor of mTOR (mammalian target of rapamycin). Temsirolimus binds to an intracellular protein (FKBP-12), and the protein-drug complex inhibits the activity of mTOR. Inhibition of mTOR activity resulted in a G1 growth arrest in treated tumor cells. When mTOR was inhibited, its ability to phosphorylate p70S6k and S6 ribosomal protein, which are downstream of mTOR in the PI3 kinase/AKT pathway was blocked. In in-vitro studies using renal cell carcinoma cell lines, temsirolimus inhibited the activity of mTOR and resulted in reduced levels of the hypoxia-inducible factors HIF-1 and HIF-2 alpha, and the vascular endothelial growth factor.[4]

4.4.2 Pharmacodynamics

Please see the clinical pharmacology review for details. Briefly, the PD measurements by Western blot assays were highly variable among the 3 biomarkers examined in the phase 1 portion of the study. Given the limited data and high variability, no dose-exposure-response analysis was performed.

4.4.3 Pharmacokinetics

Please see the complete clinical pharmacology review for details. Briefly, it is the clinical pharmacology reviewer's determination that the dose-dependent PK of temsirolimus and sirolimus in pediatric subjects is consistent with that observed in adults. In addition, the mean exposure to temsirolimus and sirolimus in pediatric patients at the 75-mg/m^2 dose, given as a 60-minute IV infusion, is approximately 6-fold and 2-fold higher, respectively, than the mean exposure in adult patients when a 25-mg dose is administered as an intravenous infusion.

Table 3: PK Parameters of Temsirolimus in Pediatric versus Adult Patients (from FDA clinical pharmacology review)

Age (y)	Dose	n	Mean ± SD, CV%	
			AUC(ng*h/mL)	Cmax (ng/mL)
0-18	75-mg/m^2	25[a]	8025±5993, 75%[c]	1327±669, 50%[d]
Adult	25-mg[b]	11	1349±232, 17%	443±109, 25%

[a] Excludes two patients with unexplained high concentrations (subject ID 204 and 231)
[b] 25-mg flat dose is 14.4 mg/m^2 for BSA of 1.73 m^2
[c] Geometric mean (cv%) of AUC: 6364 (68%)
[d] Geometric mean (cv%) of Cmax: 1107(72%)

[4] FDA label for Temsirolimus, http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022088s002s004s005s007s010s012lbl.pdf

5 Sources of Clinical Data

The clinical data for this submission consists of data from protocol 3066k1-139-US, a two part clinical trial of temsirolimus given as 60-minute IV infusions once weekly in 3 week cycles to pediatric subjects with advanced solid tumors.

5.1 Tables of Studies/Clinical Trials

Table 4: Table of Studies

Study	Primary Objective	Treatment Plan	Number of patients	Diagnosis
3066K1-139-US: A Phase 1/2, safety and exploratory pharmacodynamic study	Determine the MTD or BED and to obtain Preliminary antitumor activity of temsirolimus in pediatric patients with refractory solid tumors	Part 1: Temsirolimus given once weekly IV at 10mg/m^2, 25mg/m^2, 75mg/m^2 and 150mg/m^2. Part 2: Temsirolimus given once weekly IV at 75mg/m^2	Part 1: 19 Part 2: 52	Part 1: Pediatric Refractory solid tumors Part 2: Pediatric Refractory: Neuroblastoma High Grade Glioma Rhabdomyosarcoma

5.2 Review Strategy

The primary focus of this review was to determine whether the clinical trial conduct and results from protocol 3066k1-139-US have fulfilled the pediatric written request initially issued January 12, 2001 and subsequently amended September 30, 2004, September 28, 2007, September 29, 2010 and February 25, 2011. Care was also taken to ensure that the proposed labeling for the pediatric section was supported by data presented in this submission.

To this end, submitted study reports were reviewed and the primary datasets were analyzed in order to verify the data presented in the reports. Proposed labeling was carefully reviewed for clarity and accuracy.

5.3 Discussion of Individual Studies/Clinical Trials

Study Title:
Protocol 3066k1-139-US: A phase 1/2 safety and exploratory pharmacodynamic study of intravenous temsirolimus (CCI-779) in pediatric subjects with relapsed/refractory solid tumors

Study Objectives:
Part 1:
Primary:

- Evaluate the safety of IV temsirolimus given once weekly to children with solid tumors with disease that is recurrent or refractory to standard therapy or for whom standard therapy is not available.

Secondary:

- Identify MTD or a biologically effective dose of IV temsirolimus administered once weekly

- Obtain preliminary information on the anti-tumor activity of IV temsirolimus
- Determine single and multiple-dose PK of temsirolimus in children given weekly IV treatment
- Determine effects of IV temsirolimus on changes in mTOR signaling pathway in PBMCs

Part 2:

Primary:

- Preliminary anti-tumor activity of IV temsirolimus in children with relapsed/refractory neuroblastoma, high-grade glioma, and rhabdomyosarcoma.

Secondary:

- Verify safety of selected dose
- Evaluate percentage of subjects exhibiting freedom from progression at 3 months
- Determine multiple-dose PK of temsirolimus in children with once weekly IV treatment

Design:

3066k1-139-US was an open-label, single arm, two-part clinical trial:

Part 1: Ascending dose of temsirolimus IV weekly in 21 day cycles given to pediatric patients with advanced solid tumors

Part 2: Simon two-stage design intended to assess preliminary antitumor activity of temsirolimus in three groups of children with refractory or relapsed neuroblastoma, rhabdomyosarcoma, or high-grade glioma.

- Primary endpoint Response Rate defined as complete response (CR) or partial response (PR) by RECIST criteria.
- At least 12 evaluable patients per group.
- All subjects who receive 1 cycle (3 weekly doses) of temsirolimus are considered evaluable for clinical activity.
- If there were fewer than 2 evaluable subjects with an objective response at 12 weeks, enrollment in the group will be stopped.
- If 2 or more evaluable subjects have an objective response, an additional 13 patients could be enrolled for a total of 25 possible patients per cohort.

Eligibility Criteria:

Part 1 Only:

1. Histologic diagnosis of advanced cancer (solid tumor or CNS) with disease that is recurrent or refractory to standard therapy or for whom standard therapy is not available.
2. Evaluable disease.

Part 2 Only:

1. Subjects with a diagnosis of refractory or relapsed:
    - Neuroblastoma

- High grade gliomas: glioblastoma multiforme, anaplastic astrocytoma, and other high-grade gliomas
- Rhabdomyosarcoma

Histologic confirmation is required at time of initial diagnosis and not at time of relapse. Histologic confirmation is not required for brain stem gliomas.

2. Measurable disease (for subjects with neuroblastoma, evaluable disease as determined by a positive metaiodobenzylguanidine (MIBG) scan will also be permitted)

Parts 1 and 2:

1. At least 3 months since prior autologous or allogenic BMT or SCT at the time of study entry.
2. Prior radiotherapy:
   At least 2 weeks since prior local radiation therapy at the time of study entry.
   At least 3 months since prior craniospinal radiotherapy at the time of study entry.
   At least 3 months since prior radiotherapy to: whole abdomen or pelvis, whole lungs, >25% of bone marrow reserve; or total body irradiation at the time of study entry.
3. At least 3 weeks since prior chemotherapy (6 weeks since nitrosoureas) at the time of study entry.
4. At least 3 weeks since prior immunotherapy at the time of study entry.
5. At least 3 weeks since any other prior investigational therapy at the time of study entry. Investigational therapy is defined as treatment that is not approved for any indication.
6. Age: 1-21 years or up to pediatric age limit as defined by local regulations at the time of study entry.
7. Lansky performance status 60%-100% for subjects aged 1 to 10 or Karnofsky performance status 60%-100% for subjects aged 11 to 21 or up to pediatric age limit as defined by local regulations
8. Absolute Neutrophil Count (ANC) >1000/mm^3, platelet count >75,000/mm^3 (≥50,000/mm^3 for subjects with bone marrow involvement. Platelet count must not be transfusion dependent.), and hemoglobin ≥ 8 g/dL (transfusion of packed red blood cells is permitted if subject is known to have bone marrow involvement).
9. Adequate renal function based on either of the following criteria:
   Creatinine clearance ≥ lower limit for age OR
   Serum creatinine concentration ≤2x normal for age.
10. Adequate hepatic function: Bilirubin ≤1.5 x institutional upper limit of normal (ULN), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) ≤3 x institutional ULN.
11. Life expectancy of at least 2 months.
12. Subjects of childbearing potential or with partners of childbearing potential were to be willing to use a reliable method of birth control during entire course of study and for 12 weeks after study completion.
13. Signed and dated, IEC- or IRB-approved ICF (and documented assent for subjects of appropriate age, as required by each institution or local regulation) before any screening procedures not considered standard-of-care are performed.

Exclusion Criteria:

1. Subjects known to be human immunodeficiency virus positive.
2. Active infection or serious intercurrent illness.
3. Subjects with known hepatitis C or known active hepatitis B.
4. History of or known pulmonary hypertension or pneumonitis.
5. Any other major illness, which, in the investigator's judgment, would substantially increase the risk associated with the subject's participation in this study.
6. Concomitant therapy with any other investigational therapy.
7. Subjects receiving enzyme-inducing anticonvulsants.
8. Major surgery within 6 weeks prior to study entry. (Central line and shunt placement were not considered major surgery.)
9. Pregnant or lactating women.
10. Known hypersensitivity to temsirolimus or any of the components or other medical reasons for not being able to receive adequate premedication (e.g., antihistamine such as diphenhydramine).
11. Unwillingness or inability to comply with procedures required in this protocol.

Discontinuation/Withdrawal from Study:

A subject may be withdrawn from the treatment phase of the study at any time if the subject and/or the investigator feel that it is not in the best interest to continue participating in the study. In addition, a subject may be discontinued if:

- The subject has an AE or SAE that is considered possibly, probably, or definitely related to the study drug administration.
- The subject requires therapy with concomitant medications not permitted in this protocol.
- The subject receives any investigational drug other than the study medication.
- The subject is not compliant with study procedures.
- The subject has progressive disease as determined by investigator (investigator should follow definitions provided in sections 23.4.1 and 23.4.2).
- Subject request.
- Discontinuation of study by sponsor.

Patient Evaluations:

Figure 2: Patient Evaluations (Part 2 from applicant CSR-76631)

Study Procedures	Screening/ Baseline[a]	Cycles[b] 1, 3, 5, and 7			Cycles[b] 2, 4, 6, and 8				End of Treatment Visit
	Day −14 to −1	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 16-21	Within approx. 30 days of last dose
Informed consent[aa]	X								
Inclusion/exclusion criteria	X								
Medical/medication history[w]	X								
Cardiac and Pulmonary history	X								
Complete physical exam	X								X
Modified physical exam		X[c,g,n]			X[c,u]				
Vital signs[d]	X	X[e]	X	X	X[u]	X	X		X
Weight/Height[f]	X	X[e, g]			X[e]				
Karnofsky/Lansky status[h]	X	X[e]			X[e]				X
Disease Evaluation[i]	X							X[j,v]	X[i]
Chest X – ray: A/P and lateral[k]	X								X
ECG[x]	X	X							X
Echo or MUGA	X								X
Pulmonary function test, if age appropriate[z]	X								
O2 saturation (pulse oximetry)	X								
Test article administration[l]		X	X	X	X	X	X		
Adverse events	**** To be collected throughout the study****								
Concomitant medications	**** To be collected throughout the study****								
LABORATORY EXAMS									
Serum β-HCG[m]	X[n]								X
CBC with differential	X[n]	X[n,g]	X[n]	X[n]	X[n,u]	X[n]	X[n]		X
Chemistry panel/electrolytes[n]	X[n]	X[n,g]			X[n,u]				X
Coagulation profile[p]	X[n]	X[n, g]	Performed on Day 1 of every cycle only if clinically indicated						X

Study Procedures	Screening/ Baseline[a]	Cycles[b] 1, 3, 5, and 7			Cycles[b] 2, 4, 6, and 8				End of Treatment Visit
	Day −14 to −1	Day 1	Day 8	Day 15	Day 1	Day 8	Day 15	Day 16-21	Within approx. 30 days of last dose
Liver function test[q]	X[n]	X[n, g]			X[n, u]				X
Glycosylated hemoglobin (Hemoglobin A1c)[y]	X	X (approximately every 3 months)							X
Urine catecholamines[r]	X[n]							X[v]	X
Urinalysis[s]	X[n]	X[n,g]							X
Pharmacodynamics – bone marrow	See PD/PK flowchart for details of sampling times								
Pharmacokinetics	See PD/PK flowchart for details of sampling times								
WR number[t]	1	2/3	5	6	7	11	12	13	98

a. Screening/baseline evaluations must be done within 2 weeks prior to the first dose of temsirolimus, unless otherwise indicated.
b. Cycles are defined as 3 weekly doses of temsirolimus.
c. Obtain prior to temsirolimus administration.
d. Vital signs will be assessed prior to temsirolimus administration and before the subject leaves the hospital. Vital signs include respiration rate, blood pressure, pulse, and temperature.
e. For Cycle 1 Day 1 only vital signs will be assessed prior to infusion, 15 minutes, 30 minutes, 1 hour, and 2 hours after the start of infusion.
f. Height will be measured at screening and approximately every 12 weeks only.
g. Cycle 1 Day 1 test does not need to be done if the baseline/screening test is done within 72 hours of first dose.
h. Lansky performance status 60%-100% for subjects ages 1 to 10 years or Karnofsky performance status 60%100% for subjects aged 11 to 21 years or up to pediatric age limit as defined by local regulations.
i. Disease evaluation will be conducted as appropriate for disease and may be performed within 4 weeks prior to the first dose of temsirolimus. Evaluation may include any of the following CT, MRI, technetium-99m-bone scan, metaiodobenzylguanidine (MIBG) scintigraphy, bone marrow aspirations/biopsies, PET scans, clinical exam of lymph nodes (palpable nodes), AP/lateral chest x-rays, vanillymandelic acid (VMA) and homovanillic acid (HVA), ferritin, serum LDH, neuron-specific enolase and tumor markers. End of treatment disease assessment is not required if previous assessment within 6 weeks (12 weeks for those subjects on treatment longer than 6 months).
j. Evaluation of tumor status will be performed approximately every 6 weeks for the first 6 months of treatment. If after 6 months a subject is still experiencing clinical benefit, tumor status will be performed approximately every 12 weeks. For subjects with Neuroblastoma who are being followed by MIBG, scans should be made available for submission to an independent reader as determined by Wyeth.
k. Chest X-ray will be done within 2 weeks prior to the first dose of temsirolimus, but is not required if subject has had a thoracic CT scan within 4 weeks prior to the first dose of temsirolimus.
l. Temsirolimus will be administered once weekly. The first dose must be given within 2 business days of randomization.
m. Serum β-Human chorionic gonadotropin. For all female subjects of childbearing potential obtain serum β-HCG at baseline/screening visit and at final visit and whenever clinically indicated.
n. Tests must be done within 72 hours prior to temsirolimus administration.
o. Chemistry panel includes albumin, blood urea nitrogen (BUN), calcium, chloride, carbon dioxide (CO_2), creatinine,

Figure 3: Pharmacokinetic / Pharmacodynamic Evaluation (From Applicant CSR-76631)

Cycle (Approximately 21 Days)	Screening/ Baseline	1						2								End of Treatment Visit
Day of Cycle	-14 to –1	1				2	8	1				2	4	5	8	16-21	
Time (hours)		0	1[a]	2	6[g]	24[b]	168[c]	0	1[a]	2	6[g]	24[b]	72	96	168[c]		
Whole blood for Pharmacokinetics[d]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Whole blood for Pharmacodynamic Assays - PBMCs[e]	X		X	X	X	X	X	X	X			X	X	X	X	X	X
Bone Marrow Pharmacodynamic Assays	X[f]															X[f]	X[f]
WR number[h]	1	2	3			4	5	7				8	9	10	11	13	98

a. This sample must be collected immediately before the end of infusion. If the rate of the infusion is slowed to more than 60 minutes this sample should be collected prior to the end of the infusion.
b. Must be collected within –4/+12 hours.
c. Must be collected within ± 24 hours, but prior to subsequent dose.
d. 2 mL collected in an EDTA-treated tube.
e. 5 mL collected in a CPT tube. PBMCs will be isolated from whole blood for analysis of phosphorylation levels of mTOR pathway proteins, including p70s6 kinase. Other proteins that may be examined include S6K, 4 EBP1, eIF4E and AKT.
f. If available at the time of disease evaluation, bone marrow samples will be collected for pharmacodynamic analysis.
g. This sample should be collected approximately 6 hours after the start of infusion.
h. For sponsor use only.

There was one significant protocol amendment (amendment #3) which made changes that affected the pediatric written request. Please see section 6.2 for details.

6 Review of Efficacy

Efficacy Summary
Overall, the activity of temsirolimus in pediatric patients was not felt to be sufficient to warrant further study. In phase 1, one patient achieved a complete response out of 18 evaluable patients for an ORR of 5.6%. In phase 2, one patient with neuroblastoma achieved a partial response out of 52 evaluable patients for an ORR of 1.9%. In all three disease cohorts (Rhabdomyosarcoma, High Grade Glioma and Neuroblastoma); of the 12 or more evaluable patients who received at least 3 treatments at the 75mg/m^2 dose level in the phase 2 portion of the trial, no cohort achieved the prespecified Simon-2-stage cutoff for efficacy (≥ 2 responses). Thus, no disease cohort in phase 2 was expanded into the 2nd stage.

The data provided in this application do not provide sufficient efficacy to support approval of Temsirolimus at 75mg/m^2 infused once weekly in the pediatric indications studied. No new indication is being sought.

6.1 Indication

(b) (4) the applicant is not seeking a pediatric indication for Torisel.

6.1.1 Methods

The clinical review is based on the submitted clinical study report (CSR) for trial 3066k1-139-US, case report forms, listings and primary efficacy and toxicity datasets submitted by the applicant.

6.1.2 Demographics

Baseline characteristics of patients in the study are presented in Table 5 and Table 6 below. Patient characteristics revealed a reasonable representation of age ranges, sex and race. The majority of patients received 2 or more prior chemotherapy regimens, although 6/17 high grade glioma patients had received only 1 prior line of chemotherapy.

Table 5: Patient Demographics and Baseline Characteristics

	Phase 1	Phase 2		
	N = 19	Rhabdomyosarcoma N = 16	Glioma N = 17	Neuroblastoma N = 19
Age				
0-< 2 years	0	1	1	0
2-11	10	8	7	16
12-18	5	5	6	3
19-21	4	2	3	0
Sex				
Female	8	5	6	6
Male	11	11	11	13
Race				
White/Hispanic	13/2	10/0	12/2	12/1
Black	3	3	3	4
Other	1	3	0	1
Missing	0	0	0	1
Performance Status-Lansky or Karnofsky				
100-80	15	13	15	18
≤ 70	3	2	2	1
Missing	1	1	0	0
Prior Surgery	18	16	8	19
Prior Radiation Therapy	13	15	15	15
Number of Prior Chemotherapy Regimens				
1	2	3	6	2
2	3	3	6	1
≥ 3	14	10	5	16

Table 6: Patient Age by Study Arm

			Patient Age			
ARM	**Dose**	**#Patients**	**0-5**	**6-12**	**13-17**	**18-21**
E	75mg/m^2	52	16	20	9	7
D	150mg/m^2	7	2	2	2	1
C	75mg/m^2	3	1	1	0	1
B	25mg/m^2	5	1	1	1	2
A	10mg/m^2	4	0	2	1	1
Total		**71**	**20**	**26**	**13**	**12**

Arm A,B,C,D from Phase 1, Arm E from Phase 2.

6.1.3 Subject Disposition

The subject disposition is presented in Table 7 below. In the Phase 1 portion of the study, 2 out of 19 patients discontinued due to an AE. The 150mg/m^2 dose level accrued 7 patients and recorded 1 protocol-defined DLT of grade 3 anorexia. The MTD was not reached by protocol definition. The applicant did not investigate an intermediate dose between 75mg/m^2 and 150mg/m^2.

Table 7: Part 1 Patient Disposition

	Temsirolimus Dose			
	10 mg/m^2	25 mg/m^2	75 mg/m^2	150 mg/m^2
Treated	4	5	3	7
Completed	1	1	0	1
Discontinued	3	4	3	6
Progressive Disease	3	4	1	3
Adverse Event	0	0	1	1
Patient Decision	0	0	1	2[1]

[1]1 pt discontinued due to surgery, 1 pt discontinued due to radiation therapy

The reviewer acknowledges that the MTD was not attained by strict DLT criteria noted in the protocol. However, one patient in the 150mg/m^2 cohort did have grade 4 thrombocytopenia lasting 6 days (DLT criteria necessitated 7 days of grade 4 neutropenia). Additionally, the 150mg/m^2 appeared to have several significant GI and hematologic AEs suggesting poor tolerability (Table 20).

In the phase 2 portion of the study (Table 8), the majority of patients were taken off study due to disease progression or death. Only two patients were taken off study for adverse events. One patient (patient 203) with neuroblastoma was discontinued from study treatment due to Grade 4 pneumonitis thought possibly related to study drug. A second patient (patient 324) with high grade glioma had a pulmonary embolism leading to respiratory distress. The applicant determined this was not related to study drug however we believe this attribution is unclear and the discontinuation is more appropriately captured as due to treatment emergent AE. One other discrepancy with the applicant's analysis was the case of a patient (799) who had somnolence followed by uncal herniation and was thought to be discontinued due to an AE by the applicant. This patient was moved to disease progression in our analysis.

Table 8: Phase 2 Patient Disposition

	Rhabdomyosarcoma	Glioma	Neuroblastoma
Treated	16	17	19
Ongoing	0	0	2
Completed	0	1	0
Discontinued	16	16	17
Progressive Disease/Death	14/1	12[1]/2	16[1]/0
Adverse Event	0	1	1
Patient/Investigator Decision	0	1	0
Other	1	0	0

[1]Includes progressive disease, symptomatic deterioration, and clinical disease progression

6.1.4 Analysis of Primary Endpoint(s)

The efficacy evaluable (EE) population included all randomized subjects who received at least 3 treatments with temsirolimus. A total of eleven patients (one patient in phase 1 and 10 patients in phase 2) were not evaluable for efficacy based on the EE criteria. Table 9: Primary Endpoint Analysis, details the response outcome for the EE population in phase 1 and 2.

In Part 2, the primary endpoint was objective response rate (CR+PR) within 12 weeks. The pre-specified Simon two-stage design stated that in each of the three disease cohorts, at least 2 of the 12 patients from each disease cohort in stage 1 must have achieved an objective response for an additional 13 patients to be accrued in stage 2. Analysis reveals that 12 or more patients were enrolled to each of the 3 arms, however, there were no cohorts with 2 or more responses and the study had no expansion into the second stage. There was only 1 partial response in a neuroblastoma patient which had a duration of 6.9 months at time of data cutoff. While ORR was not the primary objective of phase 1, there was one patient with neuroblastoma who achieved a complete response by MIBG scan lasting 7.1 months. No other objective responses were seen in Part 1.

Table 9: Primary Endpoint Analysis

	Phase 1	Phase 2		
	N = 18	Rhabdomyosarcoma N = 12	Glioma N = 15	Neuroblastoma N = 15
Complete Response	1	0	0	0
Partial Response	0	0	0	1
Stable Disease	8	4	7	7
Progressive Disease	8	8	6	7
Unknown	1	0	2	0

6.1.5 Analysis of Secondary Endpoints(s)

Not applicable.

6.1.6 Other Endpoints

Not applicable.

6.1.7 Subpopulations

Not applicable.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

None.

6.2 Evaluation of the Applicant's Fulfillment of the Pediatric Written Request Requirement.

The applicant supplied a completed pediatric exclusivity determination template with this submission. The completed template with reviewer comments is presented in section 6.2.2 Pediatric Exclusivity Determination Template.

6.2.1 Pediatric Written Request Amendment History:

Table 10 below documents the pediatric written request amendment history. The initial pediatric written request (WR) for Torisel was issued on 1/12/2001. In 2004 a new protocol was drafted and the WR was reissued on 9/30/2004 which forms the backbone of the most current version of the written request. The WR was subsequently amended 9/28/2007, 9/29/2010 and 2/25/2011. All three of these amendments simply extend the timeframe for submission of study reports and note that all other terms of the WR as amended 9/30/2004 remain the same.

Table 10: Pediatric Written Request (PWR) Amendment History

PWR Version	Date	Change
Initial Pediatric WR:	January 12, 2001	Initial
PWR Amendment #1:	September 30, 2004	- Defined objective response (CR+PR) as primary anti-tumor activity measure. Freedom from progression (CR+PR+MR+SD) at 3 months can be used as a secondary efficacy endpoint. - PK parameters will be estimated for all subjects
PWR Amendment #2:	September 28, 2007	- Timeframe for submitting reports changed from 10/1/2007 to 9/30/2010.
PWR Amendment #3:	September 29, 2010	- Timeframe for submitting reports changed from 9/30/2010 to 2/25/2011.
PWR Amendment #4:	February 25, 2011	- Timeframe for submitting reports changed from 2/25/2011 to 5/31/2012.

6.2.2 Pediatric Exclusivity Determination Template

The pediatric exclusivity determination template (Table 11) was completed and submitted to supplement 014 by the applicant and provides information arranged to follow the exact order of the Written Request, as amended on September 30, 2004. The table was verified by the clinical reviewer. It is the reviewer's determination that the applicant has fulfilled the requirements set forth in the pediatric written request. Where there was not exact concordance with the pediatric written request dated 9/30/2004, the applicant provides adequate explanation regarding the discrepancy.

Table 11: Pediatric exclusivity determination template (Provided by Applicant)

Pediatric Written Request Items from September 30, 2004	Information Submitted/ Sponsor's response
	Type of studies: Study Report CSR 76631 A Phase I/II Safety and Exploratory Pharmacodynamic Study of Intravenous Temsirolimus in Pediatric Subjects with Relapsed/Refractory Solid Tumors were conducted (page 1). The study consisted of two parts and included evaluation of pharmacodynamic information (Section 5.0, 5.1 and 5.2, page 14 - 16). **The evaluation of exploratory pharmacogenomic information was removed per Protocol Amendment #3 (protocol no 3066K1-139-US, dated May 8, 2006), as explained in CSR section 6.1.1. Amendment 3 was submitted to the IND on June 15, 2006. A copy of the amendment is included in Module 1.9.3.** **The FDA informed the sponsor upon their request that an amendment to the IND is sufficient in this case and it would not require a re-issued Written Request (**correspondence from FDA on Aug 4, 2006**).** The pharmacokinetic analyses included single and multiple-dose pharmacokinetics of temsirolimus in this population (Section 7.3.1., sections 11.1.1 and 11.1.2).
-	**Part 1:** Part 1 was conducted as an ascending-dose study in subjects ages 1-21 years with advanced solid tumors (section 6.1). In part 1, at least 3 to 6 subjects were to be enrolled at each dose level. Dose escalation to the next level occurred based on safety evaluation for at least 3 weeks after the first dose of temsirolimus for all subjects at a particular dose level. A minimum of 6 subjects were to be treated with the maximum tolerated dose of temsirolimus. (Section 7.4). A total of 19 subjects were enrolled in Part 1. Subjects received 10 mg/m^2 (4 subjects), 25 mg/m^2 (5 subjects), 75 mg/m^2 (3 subjects) and 150 mg/m^2 (7 subjects). Dose escalation was halted at 150 mg/m^2 based on 2 subjects reporting DLTs; 1 subject with grade 3 anorexia and 1 subject with grade 4 thrombocytopenia lasting less than 7 days. **Although this was not the protocol specified definition of MTD, the 150 mg/m^2 dose was not considered by the investigators and Pfizer to be well tolerated, so the 75 mg/m^2 dose was selected as the dose for evaluation in Part 2 (Section 8.1, and Section 10.2.2.1). This change to the protocol**

	was submitted to the IND via Amendment 3 to the protocol 3066K1-139-US on June 15, 2006. **The FDA informed the sponsor upon their request that an amendment to the IND is sufficient in this case and it would not require a re-issued Written Request (**correspondence from FDA on Aug 4, 2006**).** **Part 2:** The primary objective of part 2 of the study was to obtain preliminary information on the antitumor activity of IV temsirolimus in children with relapsed/refractory neuroblastoma, rhabdomyosarcoma and high-grade gliomas (section 6.1). It was expected that 25 subjects would be enrolled in each of 3 cohorts for the indications of neuroblastoma, rhabdomyosarcoma, and high-grade gliomas. (Section 7.4). The study design for Part 2 was based on a Simon Two-Stage Design. (Section 7.4). For each group, the sample size for the first stage was at least 12 evaluable patients and the sample size for the second stage was at least 13 evaluable patients. (Section 7.4). Fifty-two (52) subjects were enrolled in the first stage of part 2: 17 had glioma, 19 had neuroblastoma, and 16 had rhabdomyosarcoma. However, enrollment in part 2 was halted because of insufficient antitumor activity in all 3 indications. None of the cohorts met the criterion for advancing to the second stage of the Simon 2-stage design, which was that at least 2 out of 12 evaluable subjects in a cohort have an objective response within the first 12 weeks of treatment. (Section 8.1). Overall, the objective response rate within the first 12 weeks of treatment was 2.38% (95% CI (%), 0.06-12.57), with 1 patient with neuroblastoma experiencing a confirmed Partial Response and no objective responses observed in patients with high-grade glioma or rhabdomyosarcoma (Section 9.4, Table 9-5). Within the first 12 weeks, Stable Disease was the best tumor response for 18 (43%) patients: 7 (47%) with high-grade grade glioma (5 with diffuse pontine glioma and 2 with glioblastoma multiforme), 7 (47%) with neuroblastoma, and 4 (33%) with rhabdomyosarcoma (Section 9.4, Table 9-3). At week 12, disease control (i.e., PR + SD) was observed in 7 (47%) patients with high-grade glioma, 6 (40%) with neuroblastoma, and 1 (8%) with rhabdomyosarcoma (Section 9.4, Table 9-6). The PFS rate at 12 weeks (i.e., the Kaplan-Meier estimate at 12 weeks was 40% (95% CI, 16.5-62.8) for patients

with high-grade glioma, 45% (95% CI, 19.4-67.8) for those with neuroblastoma, and 8% (95% CI, 0.5-31.1) for those with glioblastoma [sic][*] (Section 9.4, Table 9-7).

Despite prolonged disease stabilization, none of the cohorts met the criterion for advancing to the second stage of the Simon 2-stage design (i.e., ≥2 of 12 evaluable patients in a cohort have an objective response within the first 12 weeks). Therefore, enrollment was halted for all 3 tumor types.

In part 1, dose escalation was halted at 150 mg/m^2 based on 2 subjects reporting DLTs; 1 subject with grade 3 anorexia and 1 subject with grade 4 thrombocytopenia lasting less than 7 days. Although this was not the protocol specified definition of MTD, the 150 mg/m^2 dose was not considered by the investigators and Pfizer to be well tolerated, so the 75 mg/m^2 dose was selected as the dose for evaluation in Part 2 (Section 8.1, and Section 10.2.2.1).
This change to the protocol was submitted to the IND via Amendment 3 to the protocol 3066K1-139-US on June 15, 2006. The FDA informed the sponsor upon their request that an amendment to the IND is sufficient in this case and it would not require a re-issued Written Request (correspondence from FDA on Aug 4, 2006).

All participating sites were selected based on a thorough qualification process, which included the selection of investigators and site staff who were skilled and experienced in pediatric oncology clinical trials with an ability to comply with all of the requirements of the study. In part 1, 3 sites within the United States participated; St. Jude's Children's Hospital, Children's Hospital Philadelphia and Indiana University Riley Hospital for Children. In part 2, site selection was expanded to include Children's Memorial Hospital Chicago, University of California San Francisco, Texas Children's Cancer Center, Dana Farber Cancer Institute, Seattle Children's Hospital, Memorial Sloan Kettering, Morgan Stanley's Children's Hospital of New York Presbyterian, Washington University Medial Center, Children's' Hospital of Alabama and Children's' Hospital of Greenville Hospital, Institut Gustave Roussy (France), Institut Curie (France), Klinika Hematologii and Onkologii Dzieciecej (Poland), Klinika Onkologii (Poland), Federal Center for Pediatric Hematology(Russia), N.N. Blokhin Russian Center Research Center (Russia), and the 31st Hospital of St. Petersburg (Russia).

[*] Pediatric exclusivity determination template is reproduced here as received by the applicant. Applicant typo noted, glioblastoma should read "rhabdomyosarcoma".

-	**Indication(s) to be studied (i.e., objective of each study):** In part 1, subjects with a diagnosis of advanced cancer (Section 6.3.1) were enrolled. In part 2, subjects with neuroblastoma, high grade glioma or glioblastoma [sic][*] (Section 6.3.1) were enrolled in separate cohorts.

[*] Pediatric exclusivity determination template is reproduced here as received by the applicant. Applicant typo noted, glioblastoma should read "rhabdomyosarcoma".

	Age group in which study(ies) will be performed: In both parts 1 and 2, pediatric subjects aged 1 year to 21 years (Section 6.3.1). In part 1, the population consisted of 11 male and 8 female subjects, aged 4 to 21 years, with a median age of 11 years. In part 2, the population consisted of 35 male and 17 female subjects, aged 1 to 21 years, with a median age of 8 years (Table 8.4). Of the subjects in Part 1, 12 (63%) were between the ages of 4 and 15, 2 (11%) were between the ages of 16 and 17 and 5 (26%) were between the ages of 18 and 21. Of the subjects in Part 2, 42 (81%) were between the ages of 1 and 15, 3 (6%) were between ages 16 and 17 and 7 (14%) were between the ages of 18 and 21 (Section 8.2, Table 8-4).
	Study endpoints: **Phase 1** The primary objective of the study part 1 was to evaluate the safety of IV temsirolimus given once weekly to children with solid tumors with disease that was recurrent or refractory to standard therapy or for whom standard therapy was not available. (Section 5.1.) The secondary objectives of part 1 of the study were as follows: To identify the maximum tolerated dose (MTD) or a biologically effective dose of IV temsirolimus when administered once weekly. (Section 5.1). The MTD

	determined in Part 1 was 75 mg/m^2 (Section 8.1, Section 10.2.2.1). To obtain preliminary information on the antitumor activity of IV temsirolimus. (Section 5.1.) To determine the single- and multiple-dose pharmacokinetics (PK) of temsirolimus in children with once-weekly IV treatment. (Section 5.1.)
Phase 2 Objectives include: Collection of preliminary information on the anti-tumor activity of IV temsirolimus in children with neuroblastoma, high-grade gliomas, and rhabdomyosarcoma. Anti-tumor activity will be assessed by determining the percentage of subjects exhibiting objective response (CR + PR). Freedom from progression (disease stabilization defined as CR+PR+MR+SD) at 3 months may be used as a secondary endpoint. Verification of the safety of the selected dose. Determination of the single- and multiple-dose pharmacokinetics of temsirolimus in children with once-weekly IV treatment	**Phase 2** The primary objective of part 2 of the study was to obtain preliminary information on the antitumor activity of IV temsirolimus in children with relapsed/refractory neuroblastoma, high-grade gliomas, and rhabdomyosarcoma. Antitumor activity was assessed by determining the percentage of subjects exhibiting objective response (complete and partial responses) within 12 weeks. (Section 5.2) The secondary objectives of part 2 of the study included the following: To evaluate the percentage of subjects exhibiting freedom from progression (i.e., disease stabilization) at 3 months. (Section 5.2) To verify the safety of the selected dose. (Section 5.2) To determine the multiple-dose PK of temsirolimus in children with once-weekly IV treatment. (section 5.2 , section 11.1.2) **Drug information** Dosage Form: Solution, 125 mg 5 mL vials (Section 6.4.2). Route of administration: Temsirolimus was to be administered weekly over approximately 60 minutes as an IV infusion. (Section 6.4.1) Regimen: Once weekly intravenous infusion until disease progression as long as temsirolimus is tolerated. In both parts, subjects were considered to have completed the study if they received 6 months of temsirolimus. After 6 months of treatment, at the discretion of the investigator and sponsor, subjects who had not progressed and who were tolerating treatment could remain on temsirolimus as long as there was a continued evidence of clinical benefit (Section 6.1). In part 1, 2 subjects remained on treatment

	longer than 6 months without PD (1 neuroblastoma and 1 posterior fossa ependymoma) and in part 2, nine (9) subjects remained on treatment longer than 6 months without PD (3 glioma, 5 neuroblastoma and 1 rhabdomyosarcoma). (Supportive Tables 15.16 and 15.17).
	Drug specific safety concerns: The observed serious adverse events (SAE) in this study are described in section 10.3.2, pages 55-56 of the clinical study report. In part 1 of the study, 9 (47%) subjects experienced at least 1 SAE (Supportive Table 15.22). SAEs experienced by more than 1 subject included pain (3 subjects, 16%), fever, sarcoma, and vomiting (2 subjects, 11% each). The only temsirolimus related SAE reported in part 1 was vomiting, which occurred at the 150 mg/m^2 dose level. (Table 10-11). Grade 3 and 4 AEs were reported for 9 (47%) subjects in Part 1, with the most frequent reported events occurring at the 75 mg/m^2 (2 subjects, 67%) and the 150 mg/m^2 (4 subjects, 57%) dose levels. Grade 3 and 4 AEs reported include anorexia (1 subject, 5%), neutropenia (5 subjects, 26%), leukopenia (3 subjects, 16%), anemia (2 subjects, 11%), thrombocytopenia (2 subjects, 11%), prolonged activated partial thromboplastin time (1 subject, 5%) and increased SGPT (1 subject, 5%) (Section 10.2.2.3., Table 10-7). AEs leading to dose delay in Part 1 include allergic reaction (2 subjects, 11%), infection (1 subject, 5%), thrombocytopenia (1 subject, 5%) and neuropathy (1 subject, 5%) (Section 10.3.4.1, Table 10-13, page 57) and AEs leading to dose reduction include thrombocytopenia (1 subject, 5%) (Section 10.3.4.2). For safety related discontinuations in part 1, one (1) subject receiving 75 mg/m^2 temsirolimus was discontinued due to grade 4 infection (reported as serious) and grade 3 hypotension (reported as serious) associated with grade 2 pain, and 1 subject receiving 150 mg/m2 temsirolimus was discontinued due to grade 3 thrombocytopenia. None of these events were considered related to temsirolimus (Section 10.3.3).

	In the dose escalation phase of Part 1, there were no DLTs reported at the first 3 dose levels (10mg/m^2, 25 mg/m^2 and 75mg/m^2). At the 150 mg/m^2 dose, 2 subjects reported DLTs (1 grade 3 anorexia and 1 grade 4 thrombocytopenia lasting less than 7 days) and the MTD was determined to be 75 mg/m^2 (Section 10.2.2.1). In part 2, 25 (48%) of subjects experienced at least 1 SAE (Supportive Table 15.23). Eight (8, 15%) subjects experienced at least 1 temsirolimus related SAE. Temsirolimus related SAEs reported in part 2 include abscess (1 subject, 2%), fever (2 subjects, 4%), infection (1 subject, 2%), sepsis (1 subject, 2%), abnormal ECG finding (1 subject, 2%), abnormal cardiovascular physical examination finding (1 subject, 2%), hypotension (1 subject, 2%), stomatitis (1 subject, 2%), increased cough (1 subject, 2%), pneumonia (1 subject, 2%) and pneumonitis (1 subject, 2%) (Table 10-12). Grade 3 and 4 AEs were reported for 23 (44%) in part 2, which included abscess (1 subject, 2%), asthenia (1 subject, 2%), fever (1 subject, 2 %), infection (2 subjects, 4%), hypotension (1 subject, 2%), anorexia (1 subject, 2%), mucositis (1 subject, 2%), stomatitis (1 subject, 2%), anemia (4 subjects, 8%), leukopenia (1 subject, 2%), lymphopenia (1 subject, 2%), neutropenia (3 subjects, 6%), thrombocytopenia (9 subjects, 17%), acidosis (1 subject, 2%), hyperlipemia (2 subjects, 4%), hypophosphatemia (2 subjects, 4%), lipase increased (1 subject, 2%), SGOT increased (2 subjects, 4%), SGPT increased (2 subjects, 4%), neuropathy (1 subject, 2%), dyspnea (2 subjects, 4%), hypoxia (2 subjects, 4%), pneumonia (1 subject, 2%) and pneumonitis (1 subject, 2%) (Section 10.2.2.3. Table 10-8). For safety related discontinuations in part 2, one (1) subject was withdrawn due to grade 4 pneumonitis, which was considered at least possibly related to temsirolimus and 1 subject was withdrawn due to grade 4 somnolence and depressed level of consciousness, which was not considered related to temsirolimus (Section 10.3.3). * AEs leading to dose delay in part 2 include abscess (1 subject, 2%), asthenia (1 subject, 2%), fever (3 subjects, 6%), vasodilation (1 subject, 2%), stomatitis (1 subject, 2%), ADH inappropriate (1 subject, 2%), leukopenia (1 subject, 2%), neutropenia (3 subjects, 6%), thrombocytopenia (18 subject, 35%), hyperglycemia (1 subject, 2%), hyperlipemia (2 subjects, 4%), hyponatremia (1 subject, 2%), hypophosphatemia (2 subjects, 4%), SGOT increased (3 subjects, 6%), SGPT increased (4 subjects, 8%), thirst (1 subject, 2%),

* See section 7.3.3 Dropouts and/or Discontinuations

	bronchitis (1 subject, 2%), upper respiratory infection (1 subject, 2%), acne (1 subject, 2%), polyuria (1 subject, 2%) (Section 10.3.4.1, Table 10-14). AEs leading to dose reduction in part 2 include asthenia (1 subject, 2%), fever (1 subject, 2%), infection (1 subject, 2%), stomatitis (1 subject, 2%), leukopenia (1 subject, 2%), thrombocytopenia (3 subjects, 6%), hyperlipemia (1 subject, 2%), hypophosphatemia (1 subject, 2%), SGOT increased (1 subject, 2%), SGPT increased (3 subjects, 6%), arthralgia (1 subject, 2%), neuropathy (1 subject, 2%), vertigo (1 subject, 2%), upper respiratory infection (1 subject, 2%) (Section 10.3.4.2, Table 10-16).
	Statistical information, including power of study and statistical assessments: The statistical methods are described in section 7.0. No efficacy analyses were performed in part 1. Only best overall response will be provided in this clinical study report for part 1. In part 2, the study design for each tumor group was based on the Simon 2-stage design. This is an optimal design that minimizes expected sample size when the true response probability is ≤ p0, where p0 represents an uninterestingly low response rate. This design minimizes subject exposure to an ineffective drug. The intent-to-treat (ITT) population includes all subjects who were enrolled into the study. All subjects who received at least 3 doses (i.e., 1 cycle) of temsirolimus were considered evaluable for clinical activity (efficacy evaluable [EE] population). For each subject group, the sample size for the first stage was 12 evaluable subjects, and the sample size for the second stage was 13 evaluable subjects. This design is based on the response probability of an ineffective drug of 0.08, the response probability of an effective drug of 0.30, probability of accepting an ineffective drug = 0.10, and the probability of rejecting an effective drug = 0.10. In this design, for each tumor type, if after the first stage there were fewer than 2 evaluable subjects with an objective response (CR+PR) within 12 weeks, then temsirolimus was to be considered an ineffective drug for that tumor type and enrollment in the group was to be stopped. Otherwise, the trial was to be continued until 25 evaluable subjects were enrolled. Normally, when using the Simon 2-stage design as defined above, temsirolimus would be considered for further development in phase 2 and 3 trials only if ≥ 4 evaluable subjects had an objective response within 12 weeks. (Section 7.1).

	Safety data are summarized for all subjects who receive at least one dose of study medication. These data (adverse events, laboratory data and vital signs) are summarized for all subjects. (Section 10.2. – 10.6)
	Pharmacokinetic parameters including clearance (CL), volume of distribution (Vd), area under the concentration-time curve (AUC), and half-life ($t_{1/2}$) are estimated, as appropriate and as dictated by available data for all subjects in part 1 (Section 11.1.1) and in part 2 (Section 11.1.2).
	Labeling that may result from the study(ies): The findings from this study are included in the section 8.4 of the Package Insert. (Module 1.14.1 Draft Labeling).
	Format of reports submitted: The full study report CSR-76631 not previously submitted to the Agency including full analysis, assessment, and interpretation of the data were submitted. The report included information on the representation of pediatric patients of the following ethnic and racial minorities:. The Case Report Form (CRF) for study included the following variables as designation for race: White, Black, Asian, Hispanic, Other. These designations were based on standard CRF forms available to capture data pertaining to race. Subjects who were designated as something other than White, Black, Asian or Hispanic, were categorized in the "Other" category (i.e., American

	Indian, Native Hawaiian or other Pacific blander). For ethnicity, the variables included were: 1) Hispanic or Latino; or 2) Non Hispanic and non-Latino

Clinical Reviewer Comments:

There are discrepancies between the most recent pediatric written request and the submitted clinical study report. Protocol amendment #3 was submitted to the Agency on June 15, 2006 as Serial Number 715 to IND 55,830. It is this amendment which makes changes to the protocol that lead to discrepancies between the submitted study report and the pediatric written request. In the cover letter for the submission, the sponsor notes, "The purpose of this submission is to inform the Agency of changes to the protocol...and to highlight protocol changes that affect the previously issued Written Request." They discuss the fact that the 75 mg/m^2 dose would be used in the phase 2 portion, not the MTD of 150 mg/m^2, given investigator concern over tolerability of the 150 mg/m^2 dose. The submission included a suggested amended pediatric written request. Following this submission, an email correspondence occurred between the sponsor and the FDA on 8/4/2006. The sponsor inquired regarding the necessity of amending the pediatric written request. The FDA replied that "...an amendment is sufficient in this case. It would not require a re-issued WR."

Based on the correspondence between the FDA and the sponsor as well as information requests received during the pediatric exclusivity review, it is determined that any significant discrepancies were in large part due to the change in protocol that occurred with amendment #3. This change, and the request to amend the pediatric WR, was captured in an email correspondence with the FDA and the recommendation by the agency at that time was that no change in the written request would be required. Given the above, and following review of the submitted study report, it is the clinical reviewer's opinion that the sponsor fairly responded to the pediatric written request.

7 Review of Safety

Safety Summary
The interpretation of the safety data for temsirolimus in pediatric patients is limited by the single arm trial design. Overall, the reported adverse events for temsirolimus appear to be similar in pediatric patients and adult patients. In the phase I portion of the trial, the tolerable dose was determined to be 75mg/m^2 given intravenously once per week. The most frequent adverse events (> 30%) experienced by patients receiving the 75mg/m^2 dose included thrombocytopenia, infection (any), asthenia, fever, pain, leukopenia, rash, anemia, hyperlipidemia, increased cough,

and stomatitis. All of these adverse events are reported in the Torisel label in adults at frequencies of 20% or greater.

7.1 Methods

The study report and primary datasets were evaluated during this safety review.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical data for this submission consists of data from protocol 3066k1-139-US, a single two part clinical trial of temsirolimus given as 60-minute IV infusions once weekly in 3 week cycles to pediatric subjects with advanced solid tumors.

7.1.2 Categorization of Adverse Events

The Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) terminology was used to categorize the reported AEs. The severity of AEs was graded according to the National Cancer Institute Common Toxicity Criteria (NCI CTC), version 3.0.

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

Not Applicable in this submission of a single study.

7.2 Adequacy of Safety Assessments

In general, the determination of the reliability of coding adverse events into COSTART preferred terms is limited secondary to the lack of verbatim term in the AE dataset [adverse.xpt]. Of 3,250 adverse events in the dataset [adverse.xpt], there were 2,184 events that were coded to a preferred term different from the adverse event description (AEX not equal to AEPTX). Analysis of these events revealed a few systematic coding choices that were thought to be either inappropriate or too general:

Table 12: Adverse Event Coding Review

AEX (Adverse Event)→	AEPTX (COSTART PT)	# (% of total)
Hypertriglyceridemia[1]	Hypercholesterolemia	135 (4.2%)
Bicarbonate Low	Lab Test Abnormal	26 (0.8%)
Pyodermia	Infection	10 (0.3%)
Neuropathy-motor	Neuropathy	8 (<0.3%)
Cranial nerve AEs	Neuropathy	6 (<0.3%)
Pain GI (esophagus)	Abdominal Pain	5 (<0.3%)
Pain-oral cavity	Pain	5 (<0.3%)
Pyramidal Tract Dysfunction	Neuropathy	3 (<0.3%)
Increasing R leg Weakness	Asthenia	3 (<0.3%)

[1] Includes multiple AEX terms for high triglycerides

It is this reviewer's determination that the above coding choices by the applicant do not materially affect the pediatric exclusivity determination or proposed labeling changes.

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

Table 13 reveals the median exposure in days and dose delay and reduction in both phase 1 and 2 of the clinical trial.

Table 13: Exposure to Temsirolimus at the 75mg/m2 weekly dose

	Phase 1 N = 3	Phase 2 N = 52
Median Exposure (range)	35 d (22-132)	37 d (1-834)
Dose Delay[1]	0	24 (46%)
Dose Reduction	0	22 (42%)

[1] Dosing >9 days apart

In addition, the FDA clinical pharmacology review notes that for the 75mg/m^2 IV once weekly cohort, the mean exposure (AUC) to temsirolimus and active metabolite sirolimus was approximately 6-fold and 2-fold higher respectively than the exposure in adult patients receiving the 25-mg intravenous dose (Table 3). Given these findings, it is my determination that the exposure to temsirolimus was sufficient to determine safety and preliminary activity in this clinical protocol.

7.2.2 Explorations for Dose Response

There were two documented responses. One complete response occurred at 10mg/m^2 and one partial response at 75mg/m^2. There is insufficient data to explore dose response.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Not applicable.

7.3 Major Safety Results

7.3.1 Deaths

The applicant notes in the clinical study report that there were 8 deaths within 30 days of last dose in part 1 and part 2 of the study respectively. The applicant listed all deaths as due to disease progression:

Table 14: Summary of Deaths Part 1 and Part 2 (from applicant CSR)

	TEMSR 10 mg/m² (n = 4)	TEMSR 25 mg/m² (n = 5)	TEMSR 75 mg/m² (n = 3)	TEMSR 150 mg/m² (n = 7)	Total (n = 19)
No. Subjects who Died[a]					
Yes	3 (75)	1 (20)	0	0	4 (21)
No	1 (25)	4 (80)	3 (100)	7 (100)	15 (79)
No. Subjects who Died Within 30 Days of Last Dose					
Yes	2 (50)	0	0	0	2 (11)
No	2 (50)	5 (100)	3 (100)	7 (100)	17 (89)
Reason for Death					
Disease Progression	3 (75)	1 (20)	0	0	4 (21)

	High-Grade Glioma (n = 17)	Neuroblastoma (n = 19)	Rhabdomyosarcoma (n = 16)
No. Subjects who Died[a]			
Yes	5 (29)	2 (11)	4 (25)
No	12 (71)	17 (89)	12 (75)
No. Subjects who Died Within 30 Days of Last Dose			
Yes	3 (18)	0	3 (19)
No	14 (82)	19 (100)	13 (81)
Reason for Death			
Disease Progression	5 (29)	2 (11)	4 (25)

The FDA analysis of deaths noted that of the eight patients who died within 30 days of study drug, six of these patients were listed as death due to disease progression. For the other two, the cause of death for patient 41 on (b) (6) is listed as shock. The cause of death for patient 324 on (b) (6) was listed as respiratory distress. An information request was sent to the sponsor asking for clarification of these events. Following review of this information, it is concluded that 7 patients died of disease progression. Patient 324 (high grade glioma patient receiving 75mg/m^2 in Part 2) sustained a large pulmonary embolus on cycle 14 week 3 leading to death on (b) (6). As pulmonary embolism could be at least possibly considered drug-related, the reviewer considers that this death was due to adverse event pulmonary embolism rather than disease progression.

7.3.2 Serious Adverse Events

Patients experiencing any severe adverse events were reviewed regardless of relationship to drug (Table 15). Nearly 50% of patients experienced at least one SAE. The most frequently reported SAE was fever (11%) followed by pain (7.3%).

Table 15: SAEs in patients receiving 75mg/m^2

	Patients Receiving 75mg/m^2	n=55	
		All Grade	%
Patients with any SAE		27	49.1%

BODY AS A WHOLE			
	ABDOMINAL PAIN	2	3.6%
	ABSCESS	1	1.8%
	ASTHENIA	1	1.8%
	CARCINOMA	1	1.8%
	FEVER	6	10.9%
	HEADACHE	1	1.8%
	INFECTION	2	3.6%
	NEOPLASM	2	3.6%
	PAIN	4	7.3%
	SARCOMA	1	1.8%
	SEPSIS	1	1.8%
CARDIOVASCULAR SYSTEM			
	CARDIOVASCULAR PHYSICAL FINDING	1	1.8%
	CEREBRAL HEMORRHAGE	1	1.8%
	DEEP VEIN THROMBOSIS	2	3.6%
	ELECTROCARDIOGRAM ABNORMAL	1	1.8%
	HEART ARREST	1	1.8%
	HYPOTENSION	2	3.6%
	PULMONARY EMBOLUS	1	1.8%
	THROMBOSIS	1	1.8%
DIGESTIVE SYSTEM			
	COLITIS	1	1.8%
	INCREASED SALIVATION	2	3.6%
	NAUSEA	1	1.8%
	STOMATITIS	2	3.6%
	VOMITING	2	3.6%
ENDOCRINE SYSTEM			
	ADH INAPPROPRIATE	1	1.8%
HEMIC AND LYMPHATIC SYSTEM			
	ANEMIA	1	
	THROMBOCYTOPENIA	1	1.8%
METABOLIC AND NUTRITIONAL			
	DEHYDRATION	2	3.6%
	HYPERGLYCEMIA	1	
	HYPONATREMIA	1	1.8%
	HYPOPHOSPHATEMIA	1	1.8%
	PERIPHERAL EDEMA	1	1.8%
NERVOUS SYSTEM			
	BRAIN STEM DISORDER	1	1.8%
	CNS DEPRESSION	1	1.8%
	CNS NEOPLASIA	1	1.8%
	CONVULSION	1	1.8%
	GRAND MAL CONVULSION	1	1.8%
	INCOORDINATION	1	1.8%
RESPIRATORY SYSTEM			

	COUGH INCREASED	1	1.8%
	DYSPNEA	1	1.8%
	HEMOTHORAX	1	1.8%
	HYPOXIA	2	3.6%
	PNEUMONIA	2	3.6%
	PNEUMONITIS	2	3.6%
	RESPIRATORY DISTRESS SYNDROME	2	3.6%
SKIN AND APPENDAGES			
	ACNE	1	1.8%
	RASH	1	1.8%
UROGENITAL SYSTEM			
	HEMATURIA	1	1.8%
	URINARY RETENTION	1	1.8%

7.3.3 Dropouts and/or Discontinuations

See section 6.1.3, Table 7 and Table 8. The majority of patients in phase 2 of the trial discontinued therapy due to disease progression.

In the Phase 1 portion of the study, 2 patients discontinued due to an adverse event. Patient 5 discontinued due to grade 4 colitis and grade 3 hypotension with a normal ANC and patient 48 discontinued due to grade 3 thrombocytopenia. In the Phase 2 portion of the study, 2 patients were reported to have discontinued due to an adverse event. Patient 203 discontinued due to grade 4 pneumonitis which resolved with steroids and discontinuation of study drug. Patient 799 was reported to discontinue due to grade 4 somnolence. This patient had an underlying glioma and shortly after discontinuation died due to uncal herniation (progressive disease rather than AE).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Evaluation of adverse events is limited by this single arm clinical trial. In general, the adverse event profile for temsirolimus in pediatric patients was similar to that seen in adults (Table 16). The most common adverse events (> 30%) in those pediatric patients receiving 75mg/m^2 regardless of attribution included thrombocytopenia, infection (any), asthenia, fever, pain, leukopenia, rash, anemia, hyperlipidemia, increased cough, and stomatitis.

Table 16: Adverse Events reported in over 10% of subjects receiving 75mg/m2

Grade 1-4 Adverse Events in > 10% of Patients Receiving Temsirolimus 75 mg/m^2				
	Regardless of Relationship		Related[1]	
	Grade 1-4 N = 55	Grade 3-4 N = 55	Grade 1-4 N = 55	Grade 3-4 N = 55
Any	55 (100%)	41 (75%)	51 (93%)	25 (45%)

General Disorders				
Infection-Any[2]	31 (56%)	8 (15%)	17 (31%)	4 (7%)
Asthenia/Fatigue	20 (36%)	4 (7%)	15 (27%)	1 (2%)
Fever	19 (35%)	2 (4%)	11 (20%)	1 (2%)
Pain	19 (35%)	4 (7%)	6 (11%)	0
Anorexia	16 (29%)	3 (5%)	9 (16%)	1 (2%)
Headache	13 (24%)	1 (2%)	3 (5%)	0
Back Pain	9 (16%)	2 (4%)	1 (2%)	0
Cellulitis[3]	7 (13%)	0	1 (2%)	0
Oral Candidiasis	7 (13%)	0	5 (9%)	0
Cardiovascular Disorders				
Hypertension	6 (11%)	0	5 (9%)	0
Gastrointestinal Disorders				
Stomatitis[4]	17 (31%)	3 (5%)	13 (24%)	2 (4%)
Abdominal Pain	14 (25%)	1 (2%)	5 (9%)	0
Nausea	12 (22%)	1 (2%)	7 (13%)	0
Vomiting	11 (20%)	1 (2%)	3 (5%)	0
Diarrhea	9 (16%)	0	1 (2%)	0
Constipation	7 (13%)	0	3 (5%)	0
Blood and Lymphatic Disorders				
Thrombocytopenia	32 (58%)	10 (18%)	31 (56%)	9 (16%)
Leukopenia	18 (33%)	3 (5%)	17 (31%)	2 (4%)
Anemia	17 (31%)	5 (9%)	16 (29%)	4 (7%)
Neutropenia	12 (22%)	6 (11%)	11 (20%)	5 (9%)
Metabolic and Nutritional Disorders				
Hyperlipidemia	17 (31%)	2 (4%)	17 (31%)	2 (4%)
ALT Increased	16 (29%)	6 (11%)	13 (24%)	5 (9%)
AST Increased	16 (29%)	5 (9%)	11 (20%)	4 (7%)
Hypercholesterolemia	15 (27%)	0	15 (27%)	0
Hyperglycemia	14 (25%)	2 (4%)	9 (16%)	0
Hypokalemia	12 (22%)	2 (4%)	7 (13%)	0
Hypophosphatemia	11 (20%)	7 (13%)	10 (18%)	7
Hypoalbuminemia	9 (16%)	0	5 (9%)	0
Hyponatremia	7 (13%)	3 (5%)	1 (2%)	0
Hypermagnesemia	6 (11%)	0	3 (5%)	0
Increased Alkaline Phosphatase	6 (11%)	0	1 (2%)	0
Musculo-Skeletal Disorders				
Arthralgia	13 (24%)	5 (9%)	5 (9%)	0
Nervous System Disorders				
Anxiety/Agitation	8 (15%)	0	0	0
Respiratory Disorders				
Increased Cough	17 (31%)	1 (2%)	5 (9%)	0
Upper Respiratory Infection	13 (24%)	2 (4%)	3 (5%)	0
Dyspnea	8 (15%)	4 (7%)	2 (4%)	2 (4%)
Rhinitis	8 (15%)	0	2 (4%)	0
Pharyngitis	7 (13%)	1 (2%)	2 (4%)	0
Hypoxia	6 (11%)	4 (7%)	2 (4%)	2 (4%)
Skin Disorders				
Rash[5]	18 (33%)	1 (2%)	10 (18%)	0
Dry Skin	8 (15%)	0	2 (4%)	0
Pruritus	6 (11%)	0	5 (9%)	0
Special Senses				
Ear Pain or Infection	7 (13%)	0	1 (2%)	0

[1]Includes definitely, probably and possibly related

[2]Includes abscess, cellulitis, colitis, cystitis, ear disorder (if infectious), gastroenteritis, herpes simplex, infection, lung infiltration, oral candidiasis, otitis externa and media (if infectious), periodontitis, pneumonia, rhinitis, sepsis, sinusitis, URI, and UTI
[3]Includes infection over port site, infection subcutaneous port site, nail infection, pyoderma, staph skin infection
[4]Includes aphthous stomatitis, cheilitis, mucositis, and stomatitis
[5]Includes acne, exfoliative dermatitis, pruritic rash, rash, follicular rash
[6]Includes ear drainage, febrile otitis, otitis, ear pain, perforated ear drum
Source: [adverse.xpt]

7.4.2 Laboratory Findings

As with the reported adverse events, the interpretation of the laboratory dataset is limited by the lack of a comparator arm. Where there were no reference laboratory values, a reasonable cutoff value was used for all grade abnormalities. CTCAE version 4.0 guidelines were used for grading unless otherwise indicated. FDA analysis of the laboratory dataset labtest.xpt can be found in Table 17. Abnormalities in phosphorus, glucose, alanine aminotransferase (ALT), hematologic labs and lipid profile were seen frequently in the pediatric trial. These abnormalities are also noted as common adverse reactions in the current Torisel label. The incidence of grade 3 or higher thrombocytopenia does appear to be higher in this study when compared to the adult label (22% vs 1%), however the meaning of this finding is unclear given the small number of patients, unique population and single arm nature of this study. Two patients had triglyceride levels of over 1,000 (patient 232 and 327). Patient 232 had a baseline triglyceride value of 576 that increased to a high of 1,945 on visit 17 and down to 848 on visit 21. Patient 327 had a baseline triglyceride value of 112 which increased during treatment to a high of 1,097 on visit 21. A search of the AE dataset revealed no reports of pancreatitis or elevated amylase or lipase associated with either of these patients.

Table 17: Laboratory Findings for Patients Receiving the 75mg/m2 Dose

Dose Cohort	75mg/m^2 n=55	
	Any Grade	Grade 3-4
	N (%)	N (%)
Basic Metabolic Profile		
Low Potassium	20 (36)	0
Low Phosphorus	24 (44)	5 (9)
High Creatinine	5 (9)	0
High Blood Glucose [1]	29 (53)	2 (4)
Liver Panel		
High ALT	31 (56)	5 (9)
High total Bilirubin	3 (6)	0
Hematologic Profile		
Low Hematocrit [2]	43 (78)	3 (6)
Low Platelet	42 (76)	12 (22)
Low ANC [3]	16 (29)	8 (15)
Lipid Profile		
High Triglycerides	30 (55)	9 (16)
High Cholesterol [4]	29 (53)	4 (7)

Grading by CTCAE 4.0 with exceptions below:
[1] Any Grade considered Glucose > 105 mg/dL, Grade 3-4 considered Glucose > 250 mg/dL
[2] Any Grade considered HCT < LLN, Grade 3-4 considered HCT < 24%
[3] Any Grade Low ANC considered <1500, Grade 3-4 considered <1000
[4] Any Grade High Cholesterol considered > 200mg/dL, Grade 3-4 considered > 400mg/dL

7.4.3 Vital Signs

Applicant tables for clinically significant vital sign abnormalities were reviewed (Table 18 and Table 19 below). The majority of clinically significant vital sign abnormalities appeared to be due to tachypnea.

The cutoff used by the applicant for clinically significant hypertension (>200/>110 mm/Hg) is not appropriate for young children. Review of the vital signs dataset reveals that:

- For patients < 12 years of age (N=43), only 2 had systolic blood pressures over 140. One 4 year old (patient 368 receiving 75mg/m2) had a systolic blood pressure of 164 and one 8 year old (patient 310 receiving 75mg/m2) had a systolic BP of 158.
- For patients ≥ 12 years of age (N=30), only 2 patients had systolic blood pressure greater than 160. Patient 324 (18 year old, SBP 161), patient 323 (21 years old, SBP 175).
- Diastolic blood pressures above 95 occurred in 5 patients all age 14 or higher.

Table 18: Part 1 Clinically Important VS abnormalities (From Applicant CSR)

Parameter, n(%)	TEMSR 10 mg/m² n= 4	TEMSR 25 mg/m² n= 5	TEMSR 75 mg/m² n= 3	TEMSR 150 mg/m² n= 7	Total n= 19
Any abnormality (overall incidence)	4 (100)	5 (100)	3 (100)	7 (100)	19 (100)
Temperature (>39°C)	1 (25)	2 (40)	1 (33)	3 (43)	7 (37)
Respiratory rate (>20 bpm)	4 (100)	5 (100)	3 (100)	7 (100)	19 (100)
Systolic/diastolic blood pressure (>200/110 mm Hg)	0	0	0	0	0

Table 19: Part 2 Clinically Important VS Abnormalities (From Applicant CSR)

Parameter, n(%)	High-Grade Glioma n= 17	Neuroblastoma n= 19	Rhabdomyosarcoma n= 16
Any abnormality (overall incidence)	16 (94)	18 (95)	14 (88)
Temperature (>39°C)	0	0	0
Respiratory rate (>20 bpm)	16 (94)	18 (95)	14 (88)
Systolic/diastolic blood pressure (>200/110 mm Hg)	1 (6)	0	0

7.4.4 Electrocardiograms (ECGs)

The applicant states that no patients had clinically significant ECG abnormalities as defined by QTc increase of > 60 ms or absolute on-study QTc > 450 ms.

Review of the ECG dataset (ecgtest.xpt) revealed only 16 patients with ECG data. Of the 15 patients with QT information, none had a QTc > 450 ms.

There appears to be a large amount of missing data in the ECG dataset. This missing data does not materially affect the outcome of the review as the applicant is not requesting a pediatric indication with this submission. The data was discussed with the clinical pharmacology reviewer who concurs with this determination.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were performed.

7.4.6 Immunogenicity

No applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Part 1 of the clinical trial evaluated ascending doses of Temsirolimus at levels of 10mg/m^2, 25mg/m^2, 75mg/m^2 and 150mg/m^2. While the MTD was not reached as defined specifically in

the protocol, the 150mg/m^2 dose did have one patient with grade 3 anorexia meeting the definition of DLT and another patient with grade 4 thrombocytopenia lasting 6 days (7 days or greater required to meet DLT definition). The investigators and applicant felt that the 150mg/m^2 was less well tolerated and as such chose the 75mg/m^2 dose as the recommended phase 2 dose.

Analysis of the data (adverse.xpt) reveals several patients with grade 3 gastrointestinal and hematologic adverse events which likely also contributed to the decision to use 75mg/m^2 as the Part 2 dose. See Table 20 below. Additional data supporting the 150mg/m^2 being less tolerable includes all grade GI toxicity in 7/7 patients in the 150mg/m^2 cohort versus 40-75% in all other dose cohorts in the Phase I portion of the trial.

Table 20: Grade 3 Adverse Events Regardless of Attribution by Dose Cohort

		10mg/m^2		25mg/m^2		75mg/m^2		150mg/m^2	
		n=4		n=5		n=55		n=7	
PATIENTS WITH ANY GRADE 3 OR HIGHER AE		**3**	**75.0%**	**5**	**100.0%**	**43**	**78.2%**	**4**	**57.1%**
BODY AS A WHOLE		1	25.0%	1	20.0%	18	32.7%	2	28.6%
CARDIOVASCULAR SYSTEM		2	50.0%	0		6	10.9%	0	
DIGESTIVE SYSTEM		**0**		**0**		**10**	**18.2%**	**2**	**28.6%**
	ANOREXIA					3	5.5%	1	14.3%
	COLITIS					1	1.8%		
	INCREASED SALIVATION					2	3.6%		
	MUCOSITIS					1	1.8%		
	NAUSEA					1	1.8%	1	14.3%
	STOMATITIS					2	3.6%		
	VOMITING					1	1.8%	1	14.3%
ENDOCRINE SYSTEM		0		0		1	1.8%	0	
HEMIC AND LYMPHATIC SYSTEM		**2**	**50.0%**	**2**	**40.0%**	**17**	**30.9%**	**3**	**42.9%**
	ANEMIA	2	50.0%			5	9.1%	1	14.3%
	LEUKOPENIA			1	20.0%	3	5.5%	1	14.3%
	NEUTROPENIA			2	40.0%	6	10.9%	1	14.3%
	THROMBOCYTOPENIA	1	25.0%			11	20.0%	2	28.6%
METABOLIC AND NUTRITIONAL		1	25.0%	1	20.0%	19	34.5%	1	14.3%
MUSCULOSKELETAL SYSTEM		0		0		6	10.9%	0	
NERVOUS SYSTEM		0		1	20.0%	6	10.9%	1	14.3%
RESPIRATORY SYSTEM		0		2	40.0%	10	18.2%	0	
SKIN AND APPENDAGES	**ACNE**	0		0		1	1.8%	0	

SPECIAL SENSES	**CONJUNCTIVITIS**	0		0		1	1.8%	0	
UROGENITAL SYSTEM	**HEMATURIA**	0		0		1	1.8%	0	

7.5.2 Time Dependency for Adverse Events

The time dependency for adverse events analysis was not performed for this application.

7.5.3 Drug-Demographic Interactions

Not applicable.

7.5.4 Drug-Disease Interactions

Not applicable.

7.5.5 Drug-Drug Interactions

Not applicable.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Not applicable.

7.6.2 Human Reproduction and Pregnancy Data

Not applicable.

7.6.3 Pediatrics and Assessment of Effects on Growth

Assessment on effect on growth was not performed.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

7.7 Additional Submissions / Safety Issues

No 120-day safety update or additional information was received during the review of this submission.

8 Postmarket Experience

Not applicable. Torisel is not marketed for any pediatric indications.

9 Appendices

9.1 Labeling Recommendations

Revisions were made to the sponsor's proposed labeling. The following recommended labeling has been conveyed to the applicant and will be inserted into the label in Section 8.4, titled Pediatric Use:

8.4 Pediatric Use

Limited data are available on the use of temsirolimus in pediatric patients. The effectiveness of temsirolimus in pediatric patients with advanced recurrent/refractory solid tumors has not been established.

TORISEL was studied in 71 patients (59 patients ages 1 to 17 years and 12 patients ages 18 to 21 years) with relapsed/refractory solid tumors in a phase 1-2 safety and exploratory pharmacodynamic study.

In phase 1, 19 pediatric patients with advanced recurrent/refractory solid tumors received TORISEL at doses ranging from 10 mg/m^2 to 150 mg/m^2 as a 60-minute intravenous infusion once weekly in three-week cycles.

In phase 2, 52 pediatric patients with recurrent/relapsed neuroblastoma, rhabdomyosarcoma or high grade glioma received TORISEL at a weekly dose of 75 mg/m^2. One of 19 patients with neuroblastoma achieved a partial response. There were no objective responses in pediatric patients with recurrent/relapsed rhabdomyosarcoma or high grade glioma.

Adverse reactions associated with TORISEL were similar to those observed in adults. The most common adverse reactions (≥ 20%) in pediatric patients receiving the 75 mg/m^2 dose included thrombocytopenia, infections, asthenia/fatigue, fever, pain, leukopenia, rash, anemia, hyperlipidemia, increased cough, stomatitis, anorexia, increased plasma levels of alanine aminotransferase and aspartate aminotransferase, hypercholesterolemia, hyperglycemia, abdominal pain, headache, arthralgia, upper respiratory infection, nausea and vomiting, neutropenia, hypokalemia and hypophosphatemia.

Pharmacokinetics

In phase 1 of the above mentioned pediatric trial, the single dose and multiple dose total systemic exposure (AUC) of temsirolimus and sirolimus were less than dose-proportional over the dose range of 10 to 150 mg/m^2.

In the phase 2 portion, the multiple dose (Day 1, Cycle 2) pharmacokinetics of TORISEL 75 mg/m^2 were characterized in an additional 35 patients ages 28 days to 21 years (median age of 8 years). The geometric mean body surface adjusted clearance of temsirolimus and sirolimus was 9.45 L/h/m^2 and 9.26 L/h/m^2, respectively. The mean elimination half-life of

temsirolimus and sirolimus was 31 hours and 44 hours, respectively. The exposure (AUCss) to temsirolimus and sirolimus was approximately 6-fold and 2-fold higher, respectively than the exposure in adult patients receiving a 25 mg intravenous infusion.

9.2 Advisory Committee Meeting

An advisory committee meeting is not necessary for this submission.

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/s/

PAUL G KLUETZ
05/10/2012

VIRGINIA E MAHER
05/10/2012