CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-088

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-088 SUPPL # HFD # 150

Trade Name TORISEL

Generic Name Temsirolimus

Applicant Name Wyeth

Approval Date, If Known May 30, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Orphan drug - 7 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND #	YES ☐	! NO ☐
		! Explain:
Investigation #2		!
		!
IND #	YES ☐	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Carl Huntley
Title: Regulatory Project Manager
Date: May 3, 2007/finalized May 30, 2007

Name of Office/Division Director signing form: Robert Justice
Title: Division Director/DDOP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Robert Justice
5/30/2007 12:56:05 PM

4 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 1

7 Page(s) Withheld

✔ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 2

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Drug Oncology Products

Application Number: NDA 22-088

Name of Drug: TORISEL™ Kit (temsirolimus) injection, for intravenous infusion only

Applicant: Wyeth

Material Reviewed:

Submission Date(s): October 5, 2007

Receipt Date(s): October 5, 2007

Submission Date of Structure Product Labeling (SPL): November 17, 2006

Type of Labeling Reviewed: Word and SPL

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in your proposed labeling.

Highlights:

- Please maintain consistency between the highlights section (drug name, dosage form, route of administration) and section 3 of the FPI (Dosage Forms and Strengths).
- The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

  "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or rationale why pharmacologic class should be omitted from the Highlights.

- Regarding Contraindications, [redacted]). If the contraindication is not theoretical, then it must be reworded to explain the type and nature of the adverse reaction. The same applies to the Contraindications section in the FPI. [See 21 CFR 201.57(a)(9) and (c)(5)]
- Each statement under each heading must reference the section in the FPI. For example, the bullet concerning the recommended dose would have "(2)" after the statement.
- Under Warnings and Precautions, you list the subsection headings in the FPI. This information should be expanded.[See 21 CFR 201.57(a)(10)]
- The revision date is missing from Highlights and will be the month/year that the application is approved. [See 21 CFR 201.57(a)(15)] Also, delete "Revised Date" at the end of the FPI. The revision date at the end of Highlights replaces this information.

Full Prescribing Information (FPI): Contents:

- If there are no missing sections or subsections from the FPI, then there is no need to supply an asterisk referencing "Sections or subsections omitted from the Full Prescribing Information are not listed".
- Only include section and subsection headings. Delete all sub-sub headings from the Table of Contents (e.g., under 2.4 Dilution:, step1, 2)
- In the Table of Contents and FPI, avoid using caps on pronouns (or, of) in the heading titles. (e.g., section 2.4: Instructions for, not For).

Full Prescribing Information (FPI):

- The paragraphs in the full prescribing section should be indented under each section. Subsections should also be indented.

- The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, *[see Warnings and Precautions (5.1)]*, not [*see Hypersensitivity Reactions (5.1)*]. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Please fix all cross-references throughout the labeling. [See Implementation Guidance]
- Avoid using "trailing" zeros after whole numbers (e.g., see 2.4 Instructions for IV Administration). Please refer to the Institute for Safe Medication Practices website at http://www.ismp.org/Tools/abbreviationslist.pdf for a list of error-prone abbreviations, symbols, and dose designations.
- Delete unnecessary references. Include any references that are important to the prescriber. [21 CFR 201.5(c)(16)]

- Avoid using long lists of adverse reactions. See language below the table of adverse reactions. Please refer to the "Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biologcal Products – Content and Format," available at http://www.fda.gov/cder/guidance and revise the Adverse Reactions section accordingly.
- Under How Supplied/Storage and Handling, "U.S. Patent No. 5,362,718" appears out of place. Consider moving to end of labeling with manufacturer information.
- Regarding Patient Counseling Information, subsections 17.2 Increased Blood Glucose Levels and 17.7 Medications that can interfere with Torisel are written for the patient, not the prescriber. Please revise.
- At the end of the labeling, [redacted]. Also, do as this information already appears in Highlights.

Recommendations

Comments were conveyed in the 74-day letter.

Carl Huntley
REGULATORY PROJECT MANAGER

Supervisory Comment/Concurrence:

NAME OF CHIEF PROJECT MANAGER
Chief, Project Management Staff

Drafted: cwh/March 21, 2007
Revised/Initialed:
Finalized:
Filename: Document2
CSO LABELING REVIEW OF PLR FORMAT

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/s/

Carl Huntley
5/30/2007 10:03:31 AM
CSO

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF ONCOLOGY DRUG PRODUCTS

DIVISION OF DRUG ONCOLOGY PRODUCTS

5901-B Ammendale Road
Beltsville, Maryland 20705

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PHONE: (301) 796-1372 FAX: (301) 796-9845

TO: Patricia Johnson, Director I Worldwide Regulatory Affairs
Wyeth Pharmaceuticals

FAX: (617) 665-8039

FROM: Carl Huntley

DATE: May 25, 2007

Total number of pages, including cover sheet: 2

Re: NDA 22-088 Torisel®; Postmarketing study request.

COMMENTS: Regarding your New Drug Application 22-088 for TORISEL™ for advanced renal cell carcinoma, Post Marketing Commitments.

Please note that these are DRAFT recommendations for Post Marketing Commitments until our action letter is finalized. Please respond, however, so that we may incorporate the language into the letter (along with the completion dates of the commitments).

1. Submit the completed report for the thorough QT prolongation evaluation and datasets for study entitled "A single-dose, single-blind, placebo and moxifloxacin controlled 2-

period, randomized, crossover, 3rd-period sequential study of the effects of temsirolimus on cardiac repolarization in healthy subjects"

Protocol Submission: March 2006
Study Start: March 2006
Final Report Submission: September 2007

2. Submit the completed report and datasets for the hepatic impairment study (NCI study 6813 (3066K1-152-US))

Protocol Submission: November 2005
Study Start: January 2006
Final Report Submission: September 2008

Thanks

Regards,
-carl

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/s/

Carl Huntley
5/30/2007 09:50:51 AM
CSO

Huntley, Carl

From: Patricia M Johnson [pmjohnson@wyeth.com]
Sent: Thursday, May 24, 2007 5:24 PM
To: Huntley, Carl
Cc: Debra Segal; Patricia M Johnson
Subject: RE: Phase IV commitments
Attachments: emfinfo.txt

Hi Carl - got the info for you...see blue text below.

kind regards,
Patty

Patricia M. Johnson
Director I, GRA
Wyeth Pharmaceuticals
35 CambridgePark Drive
Cambridge MA 02140
e-mail: pmjohnson@wyeth.com
tel: (617) 665-8623
fax: (617) 665-8039

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>>> "Huntley, Carl" <Carl.Huntley@fda.hhs.gov> 5/24/2007 8:38:31 AM >>>

Hi Patty,
Here is what I have now. It doesn't have the language for CMC yet. I'll get an official fax to you soon but I thought you could start with getting the proposed starting date, end date, etc.

Thanks
-carl

pH. (301) 796-1372
FAX (301) 796-9845

Phase IV commitments

1. *Wyeth agrees to* submit the completed report for the thorough QT prolongation evaluation and datasets for study entitled "A single-dose, single-blind, placebo and moxifloxacin controlled 2- period, randomized, crossover, 3rd-period sequential study of the effects of temsirolimus on cardiac repolarization in healthy subjects"
   - **PROTOCOL SUBMISSION DATE** March 2006
   - **STUDY START** March 2006
   - **REPORT COMPLETE** September 2007

1. *Wyeth agrees to* submit the completed report and datasets for the hepatic impairment study (NCI study 6813 (3066K1-152-US)) *upon completion.*

- **PROTOCOL SUBMISSION DATE** (Not submitted under our IND...was NCI's - do we still put this in? We don't know the date it was submitted)
- **STUDY START** January 2006
- **REPORT COMPLETE** September 2008

"MMS <wyeth.com>" made the following
annotations on 05/24/2007 05:25:11 PM

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/s/

Carl Huntley
5/30/2007 11:39:54 AM
CSO

Bertha, Amy

From: Bertha, Amy
Sent: Wednesday, May 23, 2007 12:14 PM
To: 'Donald Esherick'
Subject: RE: Torisel Carton, NDA 22-088

Don-
Your proposal to move the word [redacted] is not acceptable. Due to our concern that the active and diluent vials might be separated prior to administration, the word "[redacted]

thank you, amy

Amy Bertha
Regulatory Health Project Manager
Office of New Drug Quality Assessment
OPS/ CDER/ FDA
tel: 301.796.1647
amy.bertha@fda.hhs.gov

From: Donald Esherick [mailto:ESHERID@wyeth.com]
Sent: Thursday, May 17, 2007 3:59 PM
To: Bertha, Amy
Cc: Byron A. Bravo; Patricia M Johnson
Subject: Torisel Carton

Amy,

I have been thinking about the carton labeling for a while. Since we are still in draft labeling discussions, Wyeth would like to propose a change in the placement of the word [redacted] on the carton . Our suggestion is to move the word .

TORISEL Kit (temsirolimus) injection

to

[redacted]

I know that this is last minute, but we are also still in negotiations on other parts of the carton text, so Wyeth would appreciate if the FDA team would consider this suggested change. I think this captures the idea that the [redacted] is the case with the first.

Thanks for your consideration of this suggestion.

- Don

"MMS <wyeth.com>" made the following
annotations on 05/17/2007 04:00:08 PM

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/s/

Amy Bertha
5/29/2007 03:50:04 PM
PROJECT MANAGER FOR QUALITY

Bertha, Amy

From: Bertha, Amy
Sent: Monday, April 30, 2007 4:50 PM
To: Donald Esherick (esherid@wyeth.com)
Subject: Torisel- NDA 22-088, c/c labeling- follow-up to 26.Apr2007 telecon

Don-
During the teleconference on 26.Apr2007, you did not agree to include the quantitative composition of all inactive ingredients on the carton label citing that the requested quantitative information is proprietary. We agreed to follow up after the telcon with our recommendation.

21CFR201.100 (5) (iii) states that, for parenteral drug products, the quantity or proportion of all inactive ingredients must be included on the label, with the exception of ingredients added to adjust the pH or to make the drug isotonic. The FDC Act 502 (e)(1)(A)(iii) states that the exemptions to this rule can be given if the inactive ingredients are proprietary in nature.

Since the qualitative compositions of the inactive ingredients are divulged on the label, the inactive ingredients cannot remain trade secret based on the guideline in USP <1091>. Specifically, an inactive ingredient is considered to be a trade secret only if its presence confers a significant competitive advantage upon its manufacturer and its identity cannot be ascertained by the use of modern analytical technology.

Therefore, please include the qualitative and quantitative compositions of all inactive ingredients for Torisel injection and the diluent on the carton label.

Any recommendations regarding the package insert will be communicated to you by the clinical division.

Thank you, amy

Amy Bertha
Regulatory Health Project Manager
Office of New Drug Quality Assessment
OPS/ CDER/ FDA
tel: 301.796.1647
amy.bertha@fda.hhs.gov

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/s/

Amy Bertha
5/29/2007 03:13:23 PM
PROJECT MANAGER FOR QUALITY

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 28, 2007

TO: Carl Huntley, R.Ph., MBA

FROM: CDER DCRP QT Interdisciplinary Review Team

SUBJECT: **NDA 22-088 QT IRT Consult**
Torisel (temisirolimus i.v.)

Please refer to your request for consultation from the CDER DCRP QT Interdisciplinary Review Team (QT IRT) dated January 18, 2007 for NDA 22-088, Torisel (temisirolimus i.v.).

To date, the QT IRT has not received the requested ECG, QT, and PK data. This information is necessary to complete the review of your consult. Furthermore, on her email dated April 27, 2007, Dr. Amna Ibrahim stated that this Study Report will be a post marketing commitment.

As a result, we are closing this consult request.

Please resubmit your consult to the QT IRT for review when the sponsor has submitted all ECG waveforms to FDA's ECG Warehouse and has submitted all SAS XPT datasets, including QT and PK results, to the Agency in CDISC SDTM format.

For future reference, please note that in order for the QT IRT to review a clinical report for a TQT study, the following items should be submitted at the same time as the consult request:

a. Copies of the study reports for any other clinical QT study of this product that has been performed
b. Electronic or hard copy of the study report
c. Electronic or hard copy of the clinical protocol
d. Electronic or hard copy of the Investigator's Brochure
e. Annotated CRF
f. A Define file which describes the contents of the electronic data sets
g. Electronic data sets as SAS transport files (in CDISC SDTM format – if possible) and all the SAS codes for the analyses

h. Narrative summaries and case report forms for any
    i. Deaths
    ii. Serious adverse events
    iii. Episodes of ventricular tachycardia or fibrillation
    iv. Episodes of syncope
    v. Episodes of seizure
    vi. Adverse events resulting in the subject discontinuing from the study

i. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)

j. A completed Highlights of Clinical Pharmacology Table

Table 1. Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen.	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	• Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	• Primary route; percent dose eliminated • Other routes
	Terminal t½	• Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and

Best Available Copy

		AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	

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For any additional information or questions you may have related to this consult, please contact us at CDERDCRPQT@fda.hhs.gov .

Thank you,

Devi Kozeli
Project Specialist &
Assistant to the Division Director
QT Interdisciplinary Review Team
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Office of New Drugs
Center of Drug Evaluation and Research
U.S. Food and Drug Administration

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/s/

Devi Kozeli
4/28/2007 12:10:48 PM
CSO

Norman Stockbridge
4/30/2007 06:40:16 AM
MEDICAL OFFICER

MEMORANDUM OF TELECON

DATE: April 26, 2007

APPLICATION NUMBER: NDA 22-088, Temsirolimus

BETWEEN:

Name: Byron Bravo, Manager, Global Regulatory Affairs CMC
Don Esherick, Director II, Global Regulatory Affairs CMC
Patricia Johnson, Director I, Global Regulatory Affairs
Susan Florian, Director, Pharmaceutical External Supply
Gary Peteritas, Strategic Product Leader
William A. Kentrup, VP, Pharma Quality Operations
Robert Oliver, VP, Oncology Business Unit
James Murphy, Director II, Global Regulatory Affairs

Representing: Wyeth

AND

Office of New Drug Quality Assessment
Chi-wan Chen, Deputy Director
Sarah Pope, Pharm. Assessment Lead, Division of Pre-Marketing Assessment III
David Lewis, Pharm. Assessment Lead, Division of Post-Marketing Evaluation
Amit Mitra, Chemist, Manufacturing Science Branch
Tamiji Nakanishi, Visiting Chemist from Japan Ministry of Health (observer)
Amy Bertha, Regulatory Health Project Manager

Representing: FDA

SUBJECT: Wyeth's amendment dated April 12, 2007. Response to IR letter dated March 28, 2007- carton and vial labeling

NDA 22-088 (temsirolimus) is for the treatment of patients with renal cell carcinoma [redacted] was submitted on October 5, 2006. The PDUFA user fee date is July 5, 2007 (extended from April 5, 2007). This NDA is part of the CMC pilot program. An IR letter was sent on December 19, 2007, a teleconference between FDA & Wyeth was held on February 9, 2007, and NDA amendments were submitted in response to the IR letter on January 19 and 26, 2007. A second IR letter dated March 28, 2007 (container/carton labeling) was sent to Wyeth and a teleconference was held April 5, 2007. FDA requested this teleconference to discuss Wyeth's responses to the IR letter dated April 12, 2007.

Meeting Discussion:

All comments referenced below are from the March 28, 2007 IR letter.

- Comment 1: FDA reiterated that the name "kit" be used as part of the name, as it appears on the carton label (Torisel Kit). The Drug Standards Manual defines Kit as "a packaged collection of related material" and there are other examples of products with the name "kit". Wyeth was in agreement with adding "kit" to the name pre-approval.
- Comment 3: FDA said that the "i" in "injection" of the "TORISEL (temsirolimus) injection" name should be lower case and consistently applied throughout the labeling. This change should be implemented pre-approval.
- [redacted]
- Comments 17, 18 and 19: FDA asked Wyeth to include the recommended statements on the label post-approval.
- Comment 30: FDA asked Wyeth to develop a flag vial (or propose an equivalent) post approval.
- Comment 34: Since 1.8 mL/vial is not the actual amount of solution in the diluent vial (the diluent vial has 2.2mL/vial), FDA asked Wyeth to eliminate the amount from the vial label to avoid confusion. This change should be implemented pre-approval. Wyeth agreed.

  FDA asked Wyeth to add the statement "for dilution of TORISEL (temsirolimus) injection" to the diluent vial post-approval.

  On the side panel of the carton label and PI the diluent amount should appear as "deliverable volume 1.8mL". This change should be done pre-approval. Wyeth agreed.
- Comments 38 & 40: FDA asked Wyeth to include the recommended statements on the label post-approval.
- FDA asked Wyeth to revise the composition statements on the carton. It was agreed that FDA would follow up with an email (the email is attached to these minutes) and provide Wyeth their recommendations in the PI comments with the understanding that how the composition is written in the PI should match the composition on the carton.

  Supporting background of which not all was communicated to Wyeth at the telecon: Under Torisel injection carton label should read "Each . [redacted] contains: temsirolimus (25 mg), *dl*-alpha-tocopherol (0.75 mg), propylene glycol (50[redacted]3 mg), and anhydrous citric acid (0.025 mg). It also contains [redacted] dehydrated alcohol [redacted] {Alcohol shall be stated in terms of percent volume of absolute alcohol at 60°F (21CFR 201.10). The sponsor may want to revise the value (%) according to the CFR reference above.}. Similarly, under diluent for Torisel the following statement should be incorporated. "Each [redacted] contains "polysorbate 80 [redacted] polyethylene glycol 400 [redacted] · It also contains 199 mg dehydrated alcohol [redacted]

- Wyeth will submit an amendment with the agreed upon pre-approval changes discussed at this teleconference. Additionally, FDA asked Wyeth to provide a clearly defined strategy, including timelines, for implementation and resolution of the post-approval issues (possible Phase IV commitments) in the amendment.

{See appended electronic signature page}

Amy Bertha
Regulatory Health Project Manager

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[1] 2.3.P.1 Section 1.0 (temsirolimus and diluent)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-088

Wyeth Pharmaceuticals, Inc.
Attention: Patricia Johnson
Associate Director Worldwide Regulatory Affairs
87 Cambridge Park Drive
Cambridge, MA 02140

Dear Ms. Johnson:

Please refer to your October 5, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TORISEL (temsirolimus) injection.

On March 7, 2007, we received your March 7, 2007 major amendment to this application. The receipt date is within 3 months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is July 5, 2007.

If you have any questions, please call Carl Huntley, Regulatory Project Manager, at 301 796-1372.

Sincerely,

{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Dotti Pease
4/5/2007 03:22:43 PM

MEMORANDUM OF TELECON

DATE: April 5, 2007

APPLICATION NUMBER: NDA 22-088, Temsirolimus

BETWEEN:

Name: Byron Bravo, Manager, Global Regulatory Affairs CMC
Don Esherick, Director II, Global Regulatory Affairs CMC
Patricia Johnson, Director I, Global Regulatory Affairs
Susan Florian, Director, Pharmaceutical External Supply

Representing: Wyeth

AND

Office of New Drug Quality Assessment
Chi-wan Chen, Deputy Director
Sarah Pope, Pharm. Assessment Lead, Division of Pre-Marketing Assessment III
David Lewis, Pharm. Assessment Lead, Division of Post-Marketing Evaluation
Amit Mitra, Chemist, Manufacturing Science Branch
Tamiji Nakanishi, Visiting Chemist from Japan Ministry of Health (observer)
Amy Bertha, Regulatory Health Project Manager

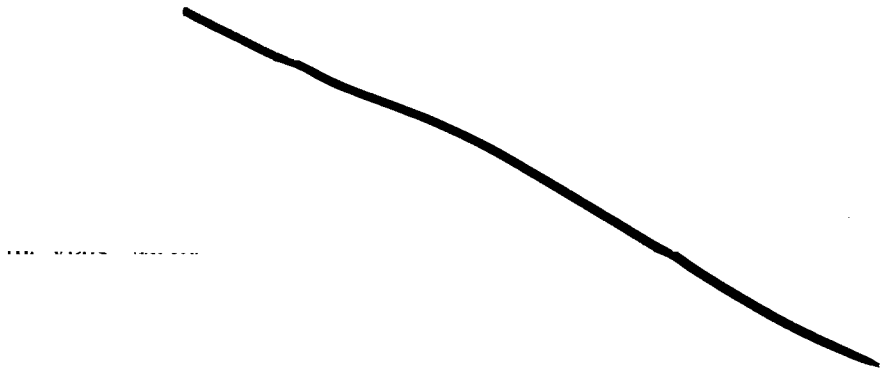
Representing: FDA

SUBJECT: IR letter dated March 28, 2007- carton and vial labeling

NDA 22-088 (temsirolimus) is for the treatment of patients with renal cell carcinoma [redacted] was submitted on October 5, 2006. The PDUFA user fee date is April 5, 2007. This NDA is part of the CMC pilot program. An IR letter was sent on December 19, 2007, a teleconference between FDA & Wyeth was held on February 9, 2007, and NDA amendments were submitted in response to the IR letter on January 19 and 26, 2007. A second IR letter dated March 28, 2007 was sent to Wyeth. Wyeth requested this teleconference to discuss items related to the March 28, 2007 IR letter, namely, 1) the carton design [redacted] banding, 2) requested labeling statements – rationale, space limitations and equipment availability, 3) alternate product name, and 4) implementation for selected items.

Meeting Discussion:

- Carton Design [redacted] Wyeth described the carton as proposed in the original [redacted]



- Labeling statements: Wyeth stated a concern regarding the additional information requested by FDA on the vial labels, and the corresponding FDA recommendation that a flag label be used (comments 30 & 40 of the IR letter). The contract manufacturer has had difficulty in the past applying flag labels to vials and then subsequently putting the vials into cartons without damaging the labels.

  Wyeth stated that the intention to globally market the product. Therefore, adding an English statement to the ferrule (comment 25 of the IR letter) would pose a logistical problem for them. Currently, Wyeth is planning on printing the lot number on the ferrule. FDA stated that the comments provided in the IR letter were based on extensive internal discussion and acknowledged that it would be a challenge. FDA stated that there are safety concerns based on the product's complexity and the complex reconstitution instructions and encouraged Wyeth to incorporate the changes into the vial labels in order to address these concerns. Wyeth could consider making their carton larger and not include a divider in order to better accommodate a flag label.

  In regards to comments 26 & 39 of the IR letter, Wyeth stated that the current proposal is to have a green flip cap for the active vial and a white flip cap for the diluent vial. FDA stated that since the flip caps can be removed, the two vials need to be better distinguished from one another. The vial label is a more permanent solution to distinguishing between the two vials. Wyeth, however, can continue to use the color coded flip caps. Wyeth agreed to explore different colors for the labels.

- Alternate product names: Wyeth proposed for the carton the name "TORISEL

[redacted]

Wyeth then proposed "TORISEL (temsirolimus) injection" for the carton, and "TORISEL [redacted] ' for the active vial. FDA replied that, per USP, if a product is a solution intended for injection, then it must be called an injection. The recommendation to use the word 'Kit' was to differentiate the vial as packaged from the product that is ready to be infused in a patient.

- Implementation: Wyeth asked whether, after agreement was reached on the carton and vial labels, certain items concerning the label could be implemented after product launch (within the first year of launch). Wyeth expressed concern that extensive changes to the label and design of carton could delay the product getting to the market. Additionally, Wyeth proposed the concept of including a separate "instructions for use" as an insert. FDA stated that it was premature at this point to determine what types of changes could be done pre- or post- approval.
- In regard to comments 4 & 5 of the IR letter, Wyeth asked FDA to verify that FDA is recommending that the strength appear as 25mg on the carton and 25mg/mL on the active vial. FDA said yes that was correct. This recommendation is because the concentration of the solution changes with every dilution.
- [redacted]

[redacted]

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Amy Bertha
Regulatory Health Project Manager

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/s/

Amy Bertha
4/30/2007 12:38:49 PM
PROJECT MANAGER FOR QUALITY

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: April 5, 2007

To: Robert Justice, M.D., Director
Division of Drug Oncology Products (DDOP)

Through: Ellis Unger, M.D., Acting Deputy Director
Office of Surveillance and Epidemiology (OSE)

From: OSE Temsirolimus Risk Management Team

Subject: Review of proposed Risk Management Plan

Drug Name: TORISEL™ (temsirolimus, [redacted] Injection 25 mg

NDA#: 22-088

Sponsor: Wyeth Research

OSE RCM#: 2006-702

Title: Review of proposed Risk Management Plan dated August 30, 2006 submitted October 5, 2006

1 INTRODUCTION/BACKGROUND

This review follows a request from the Division of Drug Oncology Products (DDOP) for the Office of Surveillance and Epidemiology (OSE) to review and comment on the proposed Risk Management Plan (RMP) for TORISEL™ (temsirolimus) [redacted] Injection 25 mg dated August 30, 2006, submitted October 5, 2006.

Temsirolimus is a targeted cell-cycle inhibitor with anti-tumor properties. Temsirolimus is being developed as a non-cytotoxic agent to delay the time to tumor recurrence/progression and to increase survival in patients with advanced renal cell carcinoma (RCC).

Of note, temsirolimus is the ester analog of sirolimus and sirolimus is the major active metabolite. Briefly, sirolimus (Rapamune,[1] Wyeth [FDA approved in 1999]) is indicated for the prevention of organ rejection in renal transplant recipients aged 13 years or older who are at low to moderate risk of acute rejection. Rapamune is available as a tablet and oral solution. Rapamune is currently marketed without a risk minimization action plan and, in general, these two products appear to have similar identified risks.

2 MATERIAL REVIEWED

The following materials were reviewed:

- "Risk Management Plan for: Temsirolimus" submitted by Wyeth dated August 30, 2006.
- Email correspondence dated March 21, 2007, from Debra Segal, Manager in Wyeth Global Regulatory Affairs to DDOP. Response to questions regarding the drug interaction reference guide.
- Drug Interaction Reference Guide [*DRAFT submitted by Wyeth dated March 21, 2007*].
- Temsirolimus physician labeling [*DRAFT dated March 29, 2007*].
- Prowell, T. Review and evaluation of the temsirolimus safety data [*DRAFT dated March 15, 2007].*
- Holquist C. ODS Consult 2007-311, TORISEL (Temsirolimus Injection) 25 mg/mL, signed March 16, 2007.

2.1 Safety Risks

2.1.1 Sponsor's Safety Concerns

Wyeth specifically identified the following risks associated with temsirolimus:

- **Interstitial Lung Disease (ILD)** - In one study (3066K1-304-WW, n=209), pneumonitis was reported in four patients with one fatality.
- **Dyspnea** - In two temsirolimus studies (total n=244, including patients from study 3066K1-304-WW), 30% of patients experienced dyspnea (all grades) and 9% experienced grades 3 and 4. Dyspnea and cough appear to be the most common treatment emergent adverse events.
- **Hyperglycemia** - In two temsirolimus studies (n=244, including patients from study 3066K1-304-WW), 26% of patients experienced hyperglycemia and 11% experienced grades 3 and 4.
- **Off-label use** - Given the mechanism of action of temsirolimus, Wyeth anticipates significant interest in evaluating temsirolimus in other tumor types.
- **QT interval prolongation** - The effect of temsirolimus on QT/QTc interval was evaluated for 31 patients in study 3066K1-304-WW and 53 patients (n=27 temsirolimus 175/25mg and n=26 temsirolimus 175/75mg) in an ongoing phase 3

[1] Rapamune (sirolimus) Package Insert. Wyeth. 2007.

study for mantle cell lymphoma. Analysis of within-group and between group changes in QT/QTc interval did not reveal any clinically important trends. Five of 84 patients tested had a clinically noteworthy value for QT interval at 1 or more post-baseline timepoints. Four of the five patients did not have clinical signs or symptoms. The one patient with a treatment emergent adverse event (TEAE) associated with a prolonged QT was a [redacted] patient receiving temsirolimus at a higher dose, 175/25mg. The patient had an increased QT interval coinciding with a cardiac arrhythmia approximately 1 week after the last dose of temsirolimus. The investigator judged the TEAE to be probably not related to treatment. No other follow-up information on this patient was provided. Given the limited number of patients tested, Wyeth states that a potential effect on QT cannot be ruled out at this time.

- **Infection** - In two temsirolimus studies (total n=244, including patients from study 3066K1-304-WW), 25% of patients experienced infection (i.e., general infections and other infections such as cellulitis, herpes zoster, herpes simplex, bronchitis, and abscess). Infection not otherwise specified and pneumonia were the only infection-related TEAEs reported for at least 5% of patients in the temsirolimus arm. Per the investigators, most of these infections were not considered related to treatment.
- **Drug-Drug Interactions** - Temsirolimus is primarily metabolized by CYP3A4, thus there is a wide potential for drug interactions including interactions with other drugs that may be administered for treatment, in particular, paclitaxel and doxorubicin. Increasing and decreasing levels of temsirolimus blood concentration may pose increased risks and/or diminished efficacy to the patient.

2.1.2 DDOP Safety Concerns

The DDOP has identified additional safety concerns as follows:[2]

- Pancreatitis (potential consequence of hypertriglyceridemia)
  - No cases of pancreatitis were diagnosed during study 3066K1-304-WW. However, amylase and lipase were not routinely tested. Grade 3 and 4 hypertriglyceridemia occurred in 44% of patients.
- Bowel perforation secondary to mucositis
  - During study 3066K1-304-WW, there was one case in the temsirolimus arm, one case in the combination temsirolimus/interferon arm. There were two cases in a Phase II study of temsirolimus in combination with 5-FU/Leucovorin. Three out of the four cases were fatal.
- Renal failure
  - The medical officer (or study investigator) identified 7 patients whose deaths may have been due to temsirolimus in which acute renal failure appeared to be a contributing factor.

[2] Prowell, T. Review and evaluation of the temsirolimus safety data [*DRAFT dated March 15, 2007*].

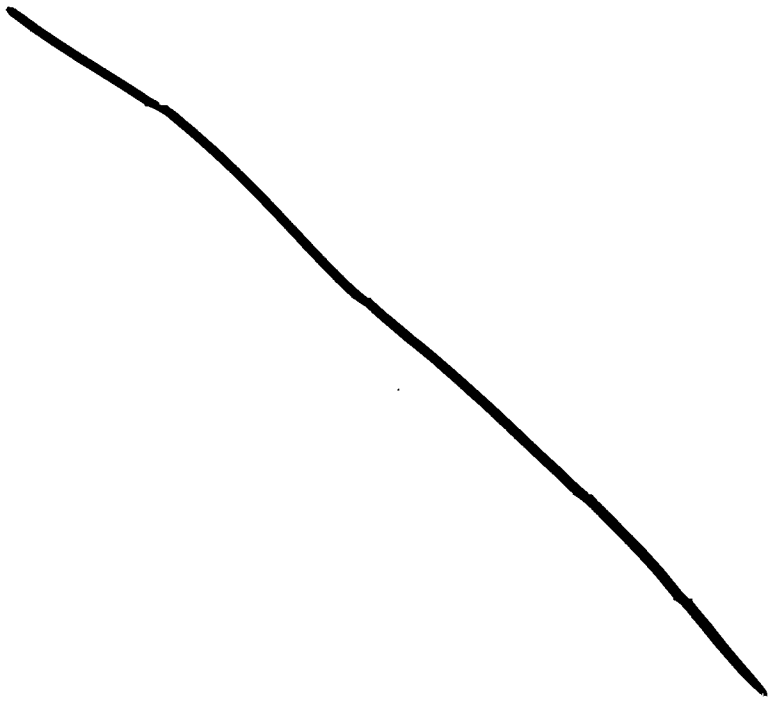
Further, abnormal electrolytes and other metabolic derangements in addition to hyperglycemia were common in the pivotal study (3066K1-304-WW; temsirolimus, interferon alfa, and combination arm, respectively) – hypercholesterolemia (25%, 5%, 26%), hyperlipemia (27%, 14%, 38%), hypophosphatemia (8%, 2%, 10%) and hypokalemia (9%, 4%, and 6%).

2.1.3 DMETS Safety Concerns

DMETS has identified additional safety concerns outlined in a consult response to DDOP on March 16, 2007, regarding the package labeling and potential for medication dosing errors. Specifically, the complexity of the product preparation for administration, absence of dilution instructions on the vial, and misleading information regarding the drug amount in the vial on the container and carton labeling need to be addressed.[3]

2.2 Sponsor's Proposed Risk Management Plan

Wyeth describes the goals and objectives of their proposed risk management plan as follows:



[3] Holquist C. ODS Consult 2007-311, TORISEL (Temsirolimus Injection) 25mg/mL, signed March16, 2007.

1 Page(s) Withheld

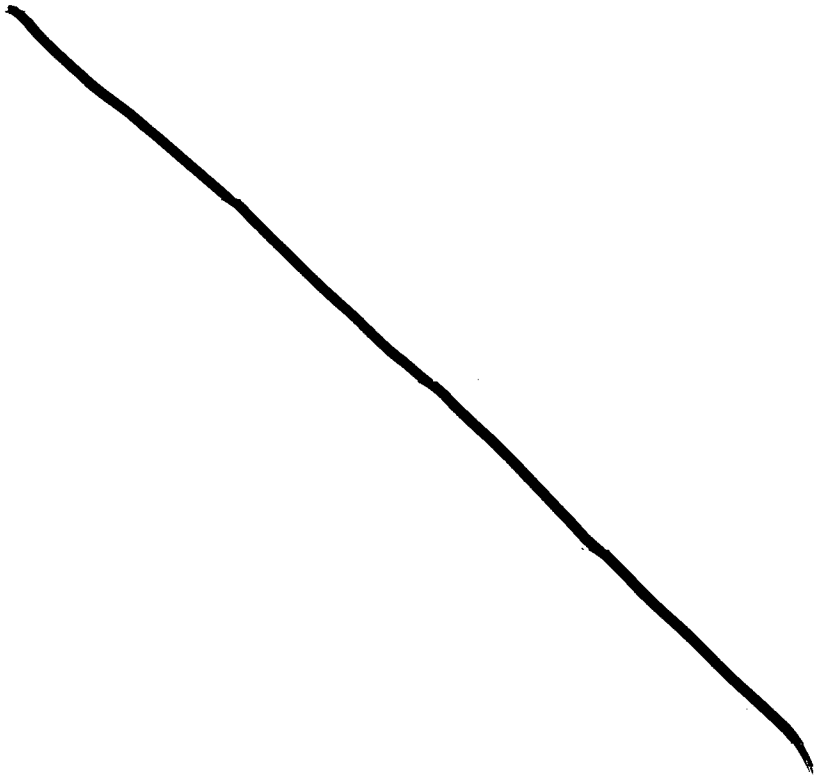
✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 3

3 COMMENTS



4 CONCLUSIONS AND RECOMMENDATIONS

Based on the information provided at this time and considering the patient population, severity of RCC, mortality of RCC, limited treatment options[5] (Proleukin,[6] Nexavar,[7] interferon alfa), comparable level of risks associated with other treatment options and with other chemotherapeutic agents in general, along with the limited scope of the prescribing population; it appears that the Sponsor's proposal is a reasonable approach to manage the risks at this time. The use of education (e.g., drug interaction reference guide) may be beneficial and can occur outside of a risk minimization action plan. At present, the current initiatives proposed by Wyeth do not constitute a formal risk minimization action plan.

We have recommendations on the draft labeling, medication error reporting, and the drug interaction reference guide provided below for your consideration. Should DDOP raise

[5] Cohen HT, McGovern FJ. Renal-cell carcinoma. [Review article]. NEJM 2005.353(23):2477-2490.
[6] Proleukin (aldesleukin) Package Insert. Chiron. September 2000.
[7] Nexavar (sorafenib) Package Insert. August 2006.

further concerns with the risks outlined above or identify additional risks associated with temsirolimus warranting more extensive risk minimization activities, please send a consult to OSE and notify the OSE-IO Project Manager, Mary Dempsey at 301.796.0147.

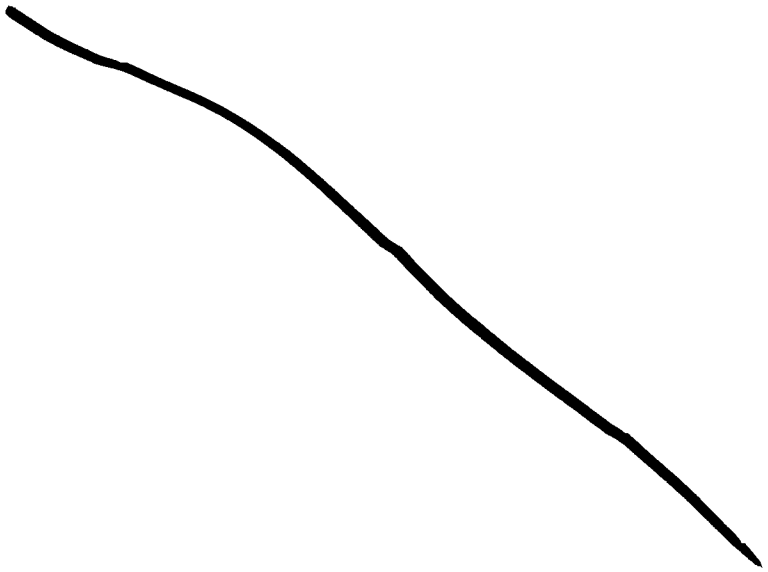
Recommendations for DDOP:

- Regarding draft Temsirolimus labeling [redacted]

- Medication Error Recommendations - Due to the complex dilution required for Torisel, we anticipate errors during product preparation. We recommend expedited reporting of any medication errors involving product preparation. This type of error will affect the final concentration of the drug product and may result in under or overdose.

Recommendations for the Sponsor Regarding the Drug Interaction Reference Guide:

[redacted]



OSE Risk Management Team
Boris Aponte, MPH, PhD, CHES, Health Education Specialist, DSRCS
Suzanne Berkman, PharmD, Senior Risk Management Analyst (detail), OSE-IO
Mary Dempsey, Risk Management Program Coordinator, OSE-IO
Jodi Duckhorn, MA, Patient Information and Research Team Leader, DSRCS
Carol Holquist, RPh, Director, DMETS
Claudia Karwoski, PharmD, Risk Management Team Leader, OSE-IO
Susan Lu, RPh, Safety Evaluator Team Leader, DDRE
Robert Pratt, PharmD, Safety Evaluator, DDRE
Joyce Weaver, PharmD, BCPS, Senior Risk Management Analyst, OSE-IO
Mary Willy, PhD, Senior Risk Management Analyst, OSE-IO

DDMAC Reviewer
Kathy Oh, PharmD, Regulatory Reviewer, DDMAC

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/s/

Suzanne Berkman
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DDMAC REVIEWER

Ellis Unger
4/5/2007 04:14:44 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-088

INFORMATION REQUEST LETTER

Wyeth Pharmaceuticals Inc.
Attention: Donald Esherick
500 Arcola Road
Collegeville, PA 19426

Dear Mr. Esherick:

Please refer to your October 5, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Torisel™ (temsirolimus) injection. We also refer to your CMC amendments dated December 5, 2006, January 26, 2007, and February 23, 2007.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submissions and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Carton label comments:

1. Revise wording of "TORISEL™" to TORISEL™ *Kit*", where the word "Kit" is differentiated from the word "TORISEL".
2. Delete all references to '
3. Revise ' ' to "(temsirolimus) injection".
4. Revise to "25 mg".
5. Place the statement ' before the statement "For intravenous infusion only".
6. Remove
7. Revise to "Each carton contains". Revise ' to "1 vial TORISEL™ (temsirolimus) injection 25 mg/mL" and ' to "1 vial DILUENT for TORISEL™".
8. The word "DILUENT" must be more prominent than the word "TORISEL". This can be accomplished thru the use of size, color, type face, etc.
9. The word "refrigerate" should be prominently displayed.
10. Revise wording of ", ' to "Refrigerate at 2° to 8°C (36° to 46°F)".
11. Include wording "Retain in carton until time of use" on the side panel.

12. If more space is needed, the addresses of Pierre Fabre and Ben Venue can be removed.

13. The white type is hard to read on blue background- revise accordingly.

14. [redacted]

TORISEL™ (temsirolimus) injection vial label comments:

15. Revise wording of [redacted] ' to read "TORISEL™ (temsirolimus) injection."

16. Remove all references to [redacted]

17. Revise [redacted] to "25 mg/mL [redacted]

18. Add ' [redacted]

19. Add [redacted]

20. Add ' [redacted]

21. Remove [redacted] '" and replace with "single use".

22. Remove . [redacted] el.

23. Insert "USAGE: See Insert". Remove [redacted]

24. Increase size of established name.

25. On the vial ferrule, print the following statement: [redacted]

26. Revise the colors used in the vial labels to significantly differentiate between "TORISEL™ (temsirolimus) injection" and "DILUENT for TORISEL™."

27. The word "DILUENT" must be more prominent than the word "TORISEL". This can be accomplished through the use of size, color, type face, etc.

28. Insert ' [redacted]

29. Indicate that the vial must be refrigerated for storage, by incorporating "refrigerate" in prominent type and/or color.

30. Due to the additional information required on the label, consider using a flag label for this vial.

31. Clearly indicate the placement of lot number and expiration dating period on the label.

Diluent vial label comments:

The word "DILUENT" must be more prominent than the word "TORISEL". This can be accomplished through the use of size, color, type face, etc.

32. Remove all references to [redacted]

33. Remove [redacted] and replace with "single use".
34. Remove [redacted] and replace with [redacted] injection vial".
35. Insert "USAGE: See Insert". Remove [redacted] ".
36. Add "refrigerate".
37. Remove [redacted]
38. In order to prevent direct injection of the diluent, insert "Not for direct administration" on the label.
39. Revise the colors used in the vial labels to significantly differentiate between "TORISEL™ (temsirolimus) injection" and "DILUENT for TORISEL™."
40. If additional space is needed for the above required information, consider using a flag label for the diluent vial.
41. Clearly indicate the placement of lot number and expiration dating period on the label.

If you have any questions, call Amy Bertha, Regulatory Health Project Manager, at 301-796-1647.

Sincerely,

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Chi-wan Chen, Ph.D.
Deputy Director
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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Chi Wan Chen
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Office of Surveillance and Epidemiology/Sam Chan, Mary Dempsey			FROM: HFD-150/Carl Huntley	
DATE March 15, 2007	IND NO.	NDA NO. 22-088	TYPE OF DOCUMENT New NDA Submission	DATE OF DOCUMENT October 5, 2006
NAME OF DRUG Torisel (temsirolimus i.v.)	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG Inhibitor of mTOR, anticancer drug	DESIRED COMPLETION DATE PDUFA date = April 5, 2007

NAME OF FIRM: Wyeth Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please see the postmarketing safety concerns for the following issues regarding Torisel, NDA 22-088.

The electronic submission is in the edr. \\CDSESUB1\evsprod\NDA022088\0000

1. Pancreatitis--no cases were reported in the phase III study, but there was a very high incidence of elevated triglycerides on study (including a 44% incidence of grade 3/4 elevations). High triglycerides, especially of that severity, are a well-established risk factor for pancreatitis, so to see zero cases is extremely surprising. There was an increased incidence of unexplained abdominal pain and grade 3/4 abdominal pain in the Torisel arm compared with the IFN arm---it's possible that some of that was due to undiagnosed pancreatitis since amylase and lipase were not routinely checked on study.

2. Pneumonitis/Interstitial Lung Disease--presented variably as cough/dyspnea/fever/hypoxia in some patients,

radiographic abnormalities (usually bilateral infiltrates) in others. There were 5 cases in the 208 patients in the safety population on the Torisel arm in the phase III trial.

3. Bowel Perforation--this appears likely to be due to severe drug-induced mucositis; there was one case in the Torisel arm and one case in the combination Torisel/Interferon arm in the phase III trial, as well as 2 cases in a Phase II study of Torisel + 5FU/Leucovorin. Three out of four of these cases were fatal.

SIGNATURE OF REQUESTER Thanks!, Carl Huntley	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND X ELECTRONIC
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/s/

Carl Huntley
3/15/2007 09:44:57 AM

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PHONE: (301) 796-1372 FAX: (301) 796-9845

TO: Patricia Johnson, Director I Worldwide Regulatory Affairs
Wyeth Pharmaceuticals

FAX: (617) 665-8039

FROM: Carl Huntley

DATE: March 8, 2007

Total number of pages, including cover sheet: 2

Re: NDA 22-088 Torisel®; Statistical questions.

COMMENTS:
The statistical review team is not able to reproduce the efficacy results presented in Table 9.4.4-1. We used Kaplan-Meier estimates of the distributions implemented using PROC LIFETEST in SAS for duration of response (investigator's assessment) and obtained the following results:

	IFN	TEMSR 25mg
Median duration in months (95% CI)	5.01 (4.0, 11.1)	7.5 (5.6, 9.2)

TEMSR 15mg/IFN

7.7 (5.8, 9.3)

Please provide us with the SAS outputs for table 9.4.4-1 and explain the differences.

Thanks

Regards,
-carl

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/s/

Carl Huntley
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PHONE: (301) 796-1372 FAX: (301) 796-9845

TO: Patricia Johnson, Director I Worldwide Regulatory Affairs
Wyeth Pharmaceuticals

FAX: (617) 665-8039

FROM: Carl Huntley

DATE: March 8, 2007

Total number of pages, including cover sheet: 1

Re: NDA 22-088 Torisel®; Statistical questions.

COMMENTS:
According to your email with an attached cover letter dated March 7th, 2007, it appears that some safety data sets, specifically Lab test, are missing data. Please submit these as soon as possible. Depending on the timing of the submission, this may result in a major amendment.

Thanks

Regards,
-carl

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/s/

Carl Huntley
3/8/2007 06:56:18 PM
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TO: Patricia Johnson, Director I Worldwide Regulatory Affairs
Wyeth Pharmaceuticals

FAX: (617) 665-8039

FROM: Carl Huntley

DATE: March 7, 2007

Total number of pages, including cover sheet: 2

Re: NDA 22-088 Torisel®; Statistical questions.

COMMENTS: This is to follow up with our telephone conference on March 6, 2007. The statistical review team would like to have the following information in order to complete the review for application of NDA 22088, Torisel.

1. Corresponding variables (in derived data sets) that represent the information of independent assessment to produce the efficacy results in tables 9.4.3-2 (Objective Response Rate in ITT Population), 9.4.4.-1 (Duration of Objective Response in ITT Population), and 9.4.5-1 (Clinical Benefit Rate in ITT Population).

2. SAS outputs for the results of Tables 9.4.3-2, 9.4.4-1 and 9.4.5-1.

Thanks

Regards,
-carl

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/s/

Carl Huntley
3/7/2007 04:49:10 PM
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Raquel Peat/ Study Endpoint and Labeling Development Team (SEALD)			FROM: HFD-150/Carl Huntley	
DATE March 7, 2007	IND NO.	NDA NO. 22-088	TYPE OF DOCUMENT New NDA Submission	DATE OF DOCUMENT October 5, 2006
NAME OF DRUG Torisel (temsirolimus i.v.)	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG Inhibitor of mTOR, anticancer drug	DESIRED COMPLETION DATE PDUFA date = April 5, 2007
NAME OF FIRM: Wyeth Pharmaceuticals				

REASON FOR REQUEST

I. GENERAL

☐ NEW PROTOCOL	☐ PRE--NDA MEETING	☐ RESPONSE TO DEFICIENCY LETTER
☐ PROGRESS REPORT	☐ END OF PHASE II MEETING	☐ FINAL PRINTED LABELING
☐ NEW CORRESPONDENCE	☐ RESUBMISSION	☐ LABELING REVISION
☐ DRUG ADVERTISING	☐ SAFETY/EFFICACY	☐ ORIGINAL NEW CORRESPONDENCE
☐ ADVERSE REACTION REPORT	☐ PAPER NDA	☐ FORMULATIVE REVIEW
☐ MANUFACTURING CHANGE/ADDITION	☐ CONTROL SUPPLEMENT	X OTHER *(SPECIFY BELOW)*:
☐ MEETING PLANNED BY		

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

☐ DISSOLUTION	☐ DEFICIENCY LETTER RESPONSE
☐ BIOAVAILABILTY STUDIES	☐ PROTOCOL-BIOPHARMACEUTICS
☐ PHASE IV STUDIES	☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	☐ SUMMARY OF ADVERSE EXPERIENCE
☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)	☐ POISON RISK ANALYSIS
☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP	

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please provide advice on the secondary endpoints: Quality Time Without Symptoms or Toxicity "Q-TWiST" and EuroQol questionnaire. The electronic submission is in the edr. \\CDSESUB1\evsprod\NDA022088\0000

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/s/

Carl Huntley
3/7/2007 11:49:34 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Rik Lostritto/ONDQA/DPAMS			FROM: HFD-150/Carl Huntley	
DATE March 6, 2007	IND NO.	NDA NO. 22-088	TYPE OF DOCUMENT New NDA Submission	DATE OF DOCUMENT October 5, 2006
NAME OF DRUG Torisel (temsirolimus i.v.)	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG Inhibitor of mTOR, anticancer drug	DESIRED COMPLETION DATE

NAME OF FIRM: Wyeth Pharmaceuticals

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- X OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Label and Nomenclature Committee consult. The electronic submission is in the edr.
\\CDSESUB1\evsprod\NDA022088\0000

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Carl Huntley
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PHONE: (301) 796-1372 FAX: (301) 796-9845

TO: Patricia Johnson, Director I Worldwide Regulatory Affairs
Wyeth Pharmaceuticals

FAX: (617) 665-8039

FROM: Carl Huntley

DATE: March 2, 2007

Total number of pages, including cover sheet: 2

Re: NDA 22-088 Torisel®; Office of Surveillance and Epidemiology (OSE), Risk Management Plan (RMP) Team information request.

COMMENTS: The OSE RMP Team has the following information request. We also ask when we can expect to receive the requested information.

1. Describe exactly how health care professionals will receive and utilize the proposed reference guide.

2. Submit the physician reference guide for review.

3. [redacted]

4. Describe exactly how health care professionals with receive and utilize the "support materials" (mentioned in 5.4, page 46). Besides the reference guide, explain what else is included in the support materials.

Thanks

Regards,
-carl

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/s/

Carl Huntley
3/2/2007 06:10:59 PM
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PHONE: (301) 796-1372 FAX: (301) 796-9845

TO: Patricia Johnson, Director I Worldwide Regulatory Affairs
Debra Segal, Manager, Worldwide Regulatory Affairs
Wyeth Pharmaceuticals
FAX: (617) 665-8039

FROM: Carl Huntley

Date: March 1, 2007

Total number of pages, including cover sheet: 1

Re: NDA 22-088 for Torisel®

COMMENTS: We have the following request/comments from Clinical Pharmacology.

How were the average AUC and average AUCsum calculated in the PK/PD (efficacy) analysis for report CSR-43942? Please explain in detail for both PK subgroup and non-PK subgroup.

Thank you.

Regards,
-carl

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/s/

Carl Huntley
3/2/2007 06:08:08 PM
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MEMORANDUM	Division of Medication Errors and Technical Support Office of Surveillance and Epidemiology HFD-420; WO 22, Mailstop 4447 Center for Drug Evaluation and Research

To: Robert Justice, M.D.
Director, Division of Oncology Drug Products
HFD-150

Through: Denise P. Toyer, Pharm.D., Deputy Director
Division of Medication Errors and Technical Support, HFD-420

From: Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, HFD-420

Date: February 16, 2007

Re: ODS Consult 2007-311, TORISEL (Temsirolimus Injection)
25 mg/mL (pending MO/chem)
NDA # 22-088

I. INTRODUCTION:

This memorandum is in response to a January 31, 2007 request from your Division for a review of the proposed container labels, carton and insert labeling for TORISEL submitted on October 5, 2006. At the time of the name review, container labels and labeling were not provided to DMETS. However, we note that the product information provided in this submission differs from that which was provided for use in the initial evaluation of the name. Specifically the Dosage and Administration section of the insert has been revised with respect to the instructions for drug preparation. This revision does not affect the decision on the acceptability of the proprietary name.

II. SAFETY EVALUATOR RISK ASSESSMENT

Following a systematic review of the container labels, carton and insert labeling submitted on October 5, 2006, DMETS has identified numerous ways in which the product design of Torisel, may lead to medication errors when introduced into the medication use system. Most notably DMETS believes that the complexity of product preparation for administration will lead to errors in dispensing of the product. Given these risks, DMETS believes that [redacted] product to lessen the complex preparation process or at a minimum modifications to the labels, labeling, packaging and healthcare provider education are needed to mitigate the potential for errors. The identified product preparation failure modes and causes are described below. Section III provides recommendations based upon these analyses.

1. Preparation Errors

[redacted]

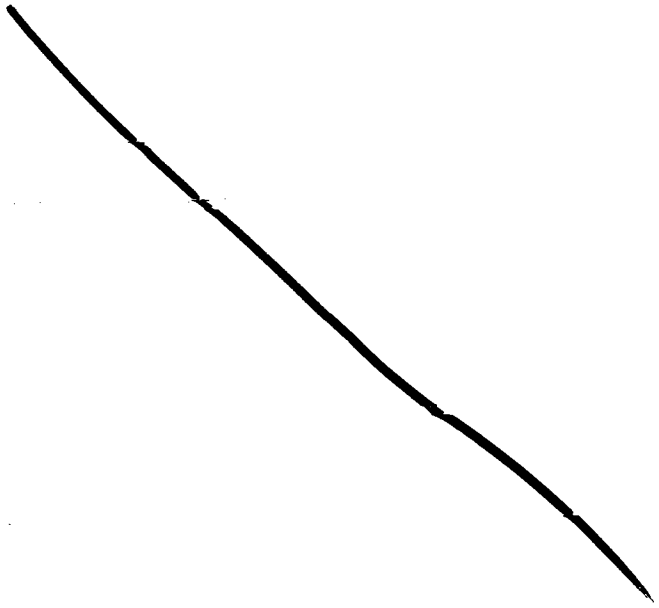
5 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 4



DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions, or need clarifications, please contact Sam Chan, project manager, at 301-796-2283.

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/s/

Carol Holquist
3/16/2007 10:55:45 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
3/16/2007 01:50:07 PM
DRUG SAFETY OFFICE REVIEWER

Bertha, Amy

From: Bertha, Amy
Sent: Friday, February 09, 2007 11:10 AM
To: 'Donald Esherick'
Subject: Microbiology comments- NDA 22-088, Temsirolimus

Don-
As a follow up to this morning's teleconference (9.Feb2007 9:30am) below is a list of microbiology comments in reference to NDA 22-088, Temsirolimus.

1. Provide the following information regarding [redacted] processing simulations conducted at Pierre Fabre:

2. [redacted]

   a)
   b)
   c)

   d)
   e)

   f)

3. Provide the model numbers and locations (building and room numbers) for [redacted] used in the manufacture the diluent for temsirolimus concentrate for injection at Ben Venue.

4. DMF 9642 was found to be inadequate with regard to information relating to [redacted] at Pierre-Fabre. These deficiencies should be resolved prior to the approval of NDA 22-088.

5. DMF 2315 was found to be inadequate with regard to information relating to [redacted] and holding times at Ben Venue. These deficiencies should be resolved prior to the approval of NDA 22-088.

As discussed in the teleconference, please contact me directly with any clarification questions you might have.

Responses to these comments should be sent to the NDA as an amendment. In addition, if you could please provide me with an electronic copy of your responses in a question and answer format, it would be appreciated.

A copy of this email will be placed in the NDA 22-088 administrative file.

Thank you, amy

Amy Bertha
Regulatory Health Project Manager
Office of New Drug Quality Assessment
OPS/ CDER/ FDA
tel: 301.796.1647
amy.bertha@fda.hhs.gov

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/s/

Amy Bertha
2/22/2007 02:24:07 PM
PROJECT MANAGER FOR QUALITY

MEMORANDUM OF TELECON

DATE: February 9, 2007

APPLICATION NUMBER: NDA 22-088, Temsirolimus

BETWEEN:

Name: Karl Blumberg, Senior Director, Drug Product Pharmaceuticals, External Supply
Parimal Desai,Vice President, Analytical and Quality Sciences, Pre-clinical Development
Donald Esherick, Director, Global Regulatory Affairs, Pharma CMC
Michael O'Brien, Senior Director, Chemical Development, Pre-clinical Development
John Roff, Associate Director, Microbiology, Analytical and Quality Sciences
Joe Rubino, Principle Research Scientist III, Pharm. Development, Pre-clinical Develop.
Warren Wezel, Sen. Director and Deputy Head Reg. Submissions and Stability Reference Standards, Analytical and Quality Sciences

Representing: Wyeth

AND

Office of New Drug Quality Assessment
Chi-wan Chen, Deputy Director
Sarah Pope, Pharm. Assessment Lead, Division of Pre-Marketing Assessment III
David Lewis, Pharm. Assessment Lead, Division of Post-Marketing Evaluation
Amit Mitra, Chemist, Manufacturing Science Branch
Mark Seggel, Chemist, Division of Pre-Marketing Assessment II
Amy Bertha, Regulatory Health Project Manager

Office of Pharmaceutical Sciences
Stephen Langille, Microbiologist, New Drug Microbiology Staff

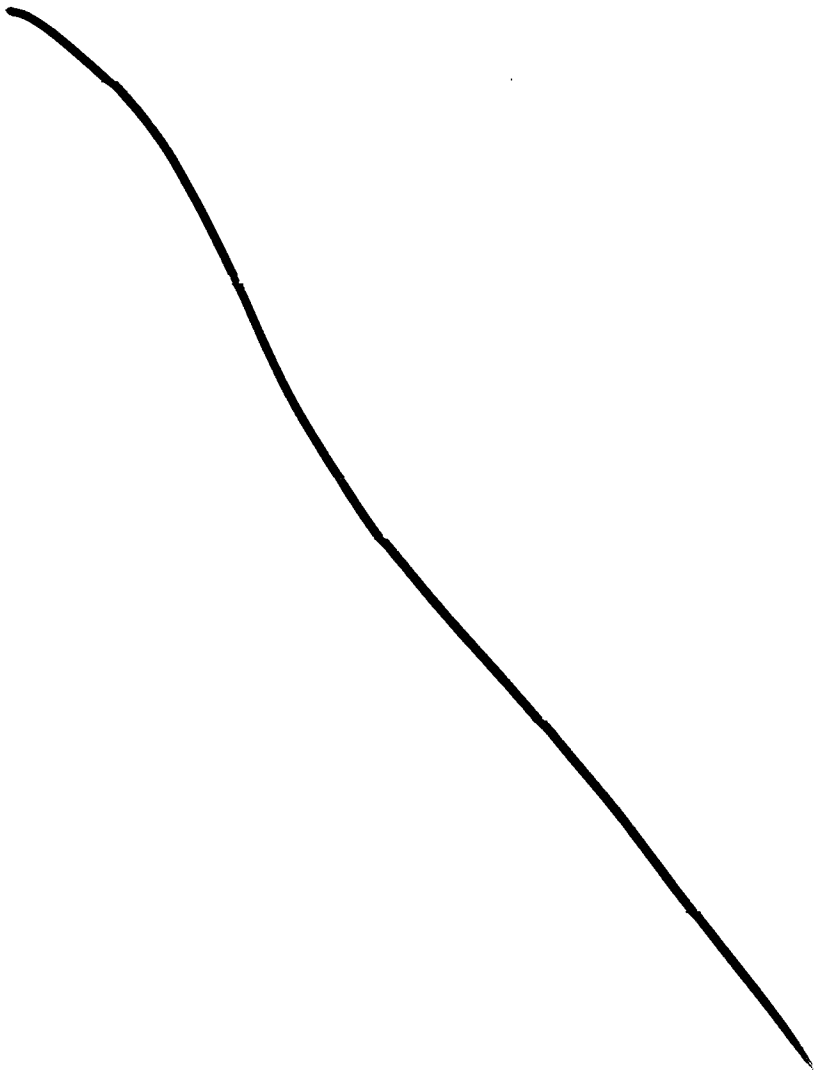
Representing: FDA

SUBJECT: CMC issues outstanding from December 19, 2006 IR letter

NDA 22-088 (temsirolimus) is for the treatment of patients with renal cell carcinoma [redacted] was submitted on October 5, 2006. The PDUFA user fee date is April 5, 2007. This NDA is part of the CMC pilot program. An IR letter was sent on December 19, 2007 and NDA amendments were submitted in response to the IR letter on January 19 and 26, 2007. FDA requested this brief teleconference in order to discuss the outstanding CMC issues from the December 19, 2007 IR letter, namely the proposed starting material, the expiry of the co-package product and microbiology issues.

Meeting Discussion:

- FDA had several microbiology comments for Wyeth, and it was decided that, due to the detailed nature of the questions, an email would be sent with the comments in writing. If after reading the micro comments, Wyeth determined a teleconference was necessary, they were advised to contact Amy Bertha. FDA also informed Wyeth that a DMF Deficiency letter would be sent to Ben Venue and Pierre Fabre.
- FDA asked Wyeth to clarify what the expiry is for the co-packaged products (drug product and diluent). Wyeth responded that the co-packaged product will have a 24 month expiry at 5°C. FDA said that the final decision on the storage conditions will be in the action letter.
- After reviewing Wyeth's response to the IR letter, FDA found Wyeth's starting material proposal still not acceptable.
-



{See appended electronic signature page}

Amy Bertha
Regulatory Health Project Manager

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/s/

Amy Bertha
3/29/2007 03:15:50 PM
PROJECT MANAGER FOR QUALITY

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TO: Patricia Johnson, Director I Worldwide Regulatory Affairs
Debra Segal, Manager, Worldwide Regulatory Affairs
Wyeth Pharmaceuticals
FAX: (617) 665-8039

FROM: Carl Huntley

Date: January 30, 2007

Total number of pages, including cover sheet: 2

Re: IND 55,830 and NDA 22-088 for Torisel®; proprietary name.

COMMENTS: We have the following request/comments from Pharmacology/Toxicology.

- Please provide a tabulated comparison of the batch analyses for all drug material used in the non-clinical and clinical studies conducted to date. The Table should include the name (or code name), concentration, and estimated exposure (based on administered dose) of all impurities/degradants.
- Please identify whether the impurities described as degradants in the clinical batches (e.g. [redacted] are detectable in biological specimens. If present, please indicate in which

species they were detected and provide all available data regarding the level of systemic exposure (including estimates of the % of the parent drug exposure).

- Please describe impurities that were present in temsirolimus and their levels, in the "Impurity Qualification" toxicology studies (Lot 76336-126, Batch 2001B0205, and Lot 24300-016). Also indicate how these impurities relate to those present in the clinical batches.

If the information is contained in your original application package, please provide information as to the exact location.

Thank you.

Regards,
-carl

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/s/

Carl Huntley
1/30/2007 10:36:10 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-088

INFORMATION REQUEST LETTER

Wyeth Pharmaceuticals Inc.
Attention: Donald Esherick
500 Arcola Road
Collegeville, PA 19426

Dear Mr. Esherick:

Please refer to your October 5, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Torisel (temsirolimus) injection. We also refer to your CMC amendment dated December 5, 2006.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submissions and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Since the proposed manufacturing facility for [redacted] temsirolimus (Wyeth, Rouses Point, NY) is scheduled for closing in 2007/8, clarify to what extent this facility will be used for the commercial launch of temsirolimus injection and describe your plans for establishing a new drug substance manufacturing site.

2. Your proposal for designating [redacted] as the starting material for the manufacture of temsirolimus is not acceptable. The starting material [redacted]. Thus, revise Section 3.2.S.2.2 of the NDA accordingly and provide the following information:

[redacted]

3. Provide the following information regarding the reference standard and/or working standard for [redacted] (key intermediate in the manufacture of temsirolimus): (a) lot number; (b) method of manufacture and purification; and (c) characterization and proof of structure.

4. [redacted]

[redacted]

5. Confirm, and provide the rationale for, the stability of bulk temsirolimus [redacted]), regarding its possible conversion [redacted] material, upon storage.

6. Provide proof of structure (or structural elucidation) for the specified, identified degradants in the drug product.

7. Table 12.3 of the Pharmaceutical Development report # RPT 65915 provides the [redacted] Data For CCI-779 [redacted] in Sodium Chloride Injection [redacted] Prepared With Various Diluent Formulas." The footnote suggests the [redacted] However, the text on page 29 of RPT 65915 suggests no drug related particles within the concentration ranges [redacted] Please clarify.

8. [redacted]

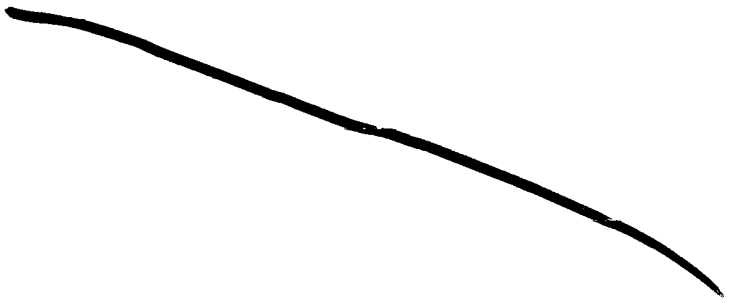
9. It appears from the stability Table 7.19 of report # RPT-66122 for temsirolimus injection that [redacted] is lost during processing. As an example, Batch # 2004B0276 was found to contain only [redacted] of theory during initial assay. Predict the reproducibility of the process loss during routine commercial manufacturing based on your current manufacturing experience. Also, elaborate on the calculation of excess of [redacted] needed to compensate for the process loss.

10. Clarify "Defects and Losses (vials) in Table 1.4-1: Filling Stage Parameters and Results" in Section 3.2.P.3.5. The clarification may include the type of defects and the criteria for locating and discarding the defective samples.

11. Section 3.2.P.4 states that the excipients are tested in accordance with the USP/NF and Ph. Eur monographs. However, the certificates of analyses for the excipients used in the primary stability studies comply with the USP/NF. Clarify whether you or your suppliers plan to test the excipients according to both USP/NF and Ph.Eur monographs during commercial manufacturing. Also, clarify whether the test for [redacted] is proposed to be conducted during commercial manufacturing to comply with the respective Ph.Eur monographs. If not justify.

12. Clarify whether [redacted] are to be used for [redacted] measurements of temsirolimus injection and the diluent. Provide a justification if only one specific method is used.

13. [redacted]



14. Your proposal to report the addition of an alternate drug product manufacturing site in an Annual Report unacceptable. Provided that your proposed comparability protocol is determined to be acceptable, a Special Report [21 CFR 314.81(b)(3)(ii)] may be an appropriate mechanism for reporting this information.

15. The following items are listed as "Tasks to be Performed" . As listed, the following items are quite qualitative in nature and do not appear to be directly substantiated by historical batch data and/or manufacturing experience. For each of the following tasks, provide a detailed explanation and justification of the proposed strategy. Please ensure that your discussion of these items also includes a data-driven correlation to your current process understanding presented in the Drug Product section of your NDA.

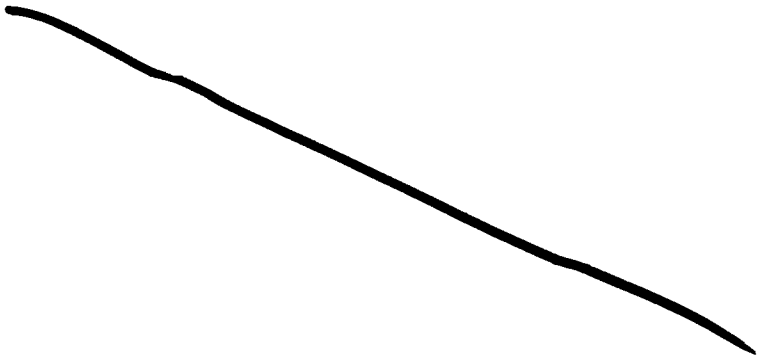
    a. The drug product manufacturing process between the proposed and the current site is comparable.
    b. The critical quality attributes for the drug product are within the proposed design space established by the design of experiments and therefore, the quality of the product is the same as that manufactured at the current site.
    c. The critical process parameters monitored during the manufacturing process at the alternate manufacturing site are comparable to that in the current manufacturing site and result in the manufacture of a product that has similar chemical and microbiological attributes as that of the drug product manufactured at the current site.
    d. The impurity profile of the drug product manufactured at the alternate site is comparable to that produced at the current site and no new impurities at or above the ICH qualification threshold are introduced as a result of the change to the alternate site.

16. Change the established name for Torisel on the vial, carton, and package insert from "(temsirolimus) " to "(temsirolimus) Injection."

17. Provide the expected introduction concentration (EIC) of the active moiety temsirolimus into the aquatic environment.

In reference to the Quality by Design aspects of your application, we have the following comments:

18. Provide the following regarding the manufacturing process of temsirolimus drug substance:



19. Provide data and conclusions to support the decision to manufacture the drug product and diluent using

20. As commercial experience is gained and as post-approval changes are implemented, the design space may change. Explain how the design space will be reassessed, verified, or redefined when a change is made in a unit operation, process parameter, in-process control, or manufacturing equipment. Propose and discuss a regulatory strategy for managing changes to the design space, including the potential expansion and contraction of the design space proposed in the current NDA for critical and non-critical parameters.

    We would suggest using degradation product control strategy in the drug product and reproducibility of [redacted] during processing as examples for initial discussion.

If you have any questions, call Amy Bertha, Regulatory Health Project Manager, at 301-796-1647.

Sincerely,

{See appended electronic signature page}

Chi-wan Chen, Ph.D.
Deputy Director
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Chi Wan Chen
12/19/2006 03:54:16 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-088

Wyeth Pharmaceuticals, Inc.
Attention: Patricia Johnson
Director, Global Regulatory Affairs
35 Cambridge Park Drive
Cambridge, MA 02140

Dear Ms. Johnson:

Please refer to your October 5, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Torisel® (temsirolimus) [redacted] Injection 25 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on November 27, 2006, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

1. Updated stability data should be provided as soon as possible, for both the drug substance and drug product.
2. Comments regarding Structured Product Labeling:

Highlights:

- Please maintain consistency between the highlights section (drug name, dosage form, route of administration) and section 3 of the FPI (Dosage Forms and Strengths).
- The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

  "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

  Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or rationale why pharmacologic class should be omitted from the Highlights.

- Regarding Contraindications, [redacted]. If the contraindication is not theoretical, then it must be reworded to explain the type and nature of the adverse reaction. The same applies to the Contraindications section in the FPI. [See 21 CFR 201.57(a)(9) and (c)(5)]
- Each statement under each heading must reference the section in the FPI. For example, the bullet concerning the recommended dose would have "(2)" after the statement.
- Under Warnings and Precautions, you list the subsection headings in the FPI. This information should be expanded.[See 21 CFR 201.57(a)(10)]
- The revision date is missing from Highlights and will be the month/year that the application is approved. [See 21 CFR 201.57(a)(15)] Also, delete "Revised Date" at the end of the FPI. The revision date at the end of Highlights replaces this information.

Full Prescribing Information (FPI): Contents:

- If there are no missing sections or subsections from the FPI, then there is no need to supply an asterisk referencing "Sections or subsections omitted from the Full Prescribing Information are not listed".
- Only include section and subsection headings. Delete all sub-sub headings from the Table of Contents (e.g., under 2.4 Dilution:, step1, 2)
- In the Table of Contents and FPI, avoid using caps on pronouns (or, of) in the heading titles. (e.g., section 2.4: Instructions for, not For).

Full Prescribing Information (FPI):

- The paragraphs in the full prescribing section should be indented under each section. Subsections should also be indented.

- The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, *[see Warnings and Precautions (5.1)]*, not [*see Hypersensitivity Reactions (5.1)*]. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Please fix all cross-references throughout the labeling. [See Implementation Guidance]
- Avoid using "trailing" zeros after whole numbers (e.g., see 2.4 Instructions for IV Administration). Please refer to the Institute for Safe Medication Practices website at http://www.ismp.org/Tools/abbreviationslist.pdf for a list of error-prone abbreviations, symbols, and dose designations.
- Delete unnecessary references. Include any references that are important to the prescriber. [21 CFR 201.5(c)(16)]
- Avoid using long lists of adverse reactions. See language below the table of adverse reactions. Please refer to the "Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biologcal Products – Content and Format," available at http://www.fda.gov/cder/guidance and revise the Adverse Reactions section accordingly.
- Under How Supplied/Storage and Handling, "U.S. Patent No. 5,362,718" appears out of place. Consider moving to end of labeling with manufacturer information.

- Regarding Patient Counseling Information, subsections 17.2 Increased Blood Glucose Levels and 17.7 Medications that can interfere with Torisel are written for the patient, not the prescriber. Please revise.
- At the end of the labeling, delete the company website address (www.wyeth.com). Also, do not include the telephone number as this information already appears in Highlights.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

We do not expect a response to this letter, and we may not review any such response during the current review cycle.

If you have any questions please call me at (301) 796-1372.

Sincerely,

{See appended electronic signature page}

Carl Huntley, R.Ph., MBA
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Carl Huntley
12/18/2006 02:32:40 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-088

NDA ACKNOWLEDGMENT

Wyeth Pharmaceuticals
Attention: Patricia Johnson, Director
Global Regulatory Affairs
35 CambridgePark Drive
Cambridge, MA 02140

Dear Ms. Johnson:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Torisel™ (temsirolimus) [redacted] injection 25 mg

Review Priority Classification: Priority (P)

Date of Application: October 5, 2006

Date of Receipt: October 5, 2006

Our Reference Number: NDA 22-088

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 4, 2006, in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be April 5, 2007.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please call me at (301) 796-1372.

Sincerely,

{See appended electronic signature page}

Carl Huntley, R.Ph., MBA
Regulatory Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Carl Huntley
12/18/2006 02:18:07 PM

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF ONCOLOGY DRUG PRODUCTS

DIVISION OF DRUG ONCOLOGY PRODUCTS

5901-B Ammendale Road
Beltsville, Maryland 20705

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PHONE: (301) 796-1372 FAX: (301) 796-9845

TO: Patricia Johnson, Director I Worldwide Regulatory Affairs
Wyeth Pharmaceuticals

FAX: (617) 665-8039

FROM: Carl Huntley

DATE: November 30, 2006

Total number of pages, including cover sheet: 2

Re: NDA 22-088 Torisel®; pharmacology requests/comments.

COMMENTS: The Pharmacology team has the following comments/questions.

1. Report # gtr-31709: acute i.v. toxicity study in rats.
    a. Please provide the tabulated summary and individual animal data for the gross pathology findings.
    b. Please indicate the method of i.v. administration, i.e. bolus or slow injection.

2. Report# RPT-43566: 39-week i.v. toxicity study in monkeys with a 13-week recovery.

a. The tabulated summary, page 32 (histopathology of testes), indicates 4 animals in each group were examined; however, the histopathology Table, page 375, indicates that testes of 3, 4, 3, and 4 animals were examined from the control, low-dose, mid-dose, and high-dose groups, respectively. Please clarify.

3. Report# gtr-31897: acute i.v. toxicity study in rats (addendum 1).
    a. Please submit the gross pathology data.

4. Please provide the historical data (uterine and embryo-fetal endpoints) for the species/strains used in the pivotal embryo-fetal toxicology studies.

Thanks

Regards,
-carl

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/s/

Carl Huntley
11/30/2006 02:36:33 PM
CSO

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF ONCOLOGY DRUG PRODUCTS

DIVISION OF DRUG ONCOLOGY PRODUCTS

5901-B Ammendale Road
Beltsville, Maryland 20705

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PHONE: (301) 796-1372 FAX: (301) 796-9845

TO: Patricia Johnson, Director I Worldwide Regulatory Affairs
Debra Segal, Manager, Worldwide Regulatory Affairs
Wyeth Pharmaceuticals
FAX: (617) 665-8039

FROM: Carl Huntley

DATE: November 30, 2006

Total number of pages, including cover sheet: 1

Re: NDA 22-088 Torisel®; request for clinical pharmacology information.
COMMENTS: Please provide the following information.

1. Final analysis data sets and all analysis codes for study 3066K1-200-US (population PK analysis, PK/PD for efficacy, PK/PD for safety).
2. Final analysis data sets and all analysis codes for study 3066K1-145-US (PK analysis, PK/PD-biomarker analysis).
3. Analysis codes for PK-safety relationship.

Thanks
Regards,
-carl

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/s/

Carl Huntley
11/30/2006 10:37:55 AM
CSO

MEMORANDUM OF MEETING MINUTES

MEETING DATE: November 22, 2006
TIME: 12:30 PM
LOCATION: Room 2376, WO
APPLICATION: NDA 22-088
DRUG NAME: Temsirolimus intravenous
TYPE OF MEETING: Type B, update of information from the hepatic impairment study
MEETING CHAIR: Brian Booth, Ph.D.

MEETING RECORDER: Carl Huntley, R. Ph., MBA

FDA ATTENDEES:

Brian Booth, Ph.D., Clin. Pharm. Team Leader, DCP5
Julie Bullock, Pharm.D., Clinpharm Reviewer, OCP/DCPI
Carl Huntley, R. Ph., MBA, Regulatory Project Manager, DDOP

EXTERNAL CONSTITUENT ATTENDEES:

Joseph Boni, PhD, Director, Clinical Pharmacology
Patricia M. Johnson, Director I, Regulatory Affairs
Debra Segal, Manager, Regulatory Affairs

BACKGROUND:

On May 11, 2006, a meeting was held regarding provision of data form the hepatic impairment study (NCI study 6813, under IND 61,010.
At that time an update of the study was provided:

- Hepatic Impairment Study (NCI Protocol 6813): This protocol is ongoing and filed under IND 60,010 (National Cancer Institute); Chris H. Takimoto, MD, PhD, FACP, Institute for Drug Development, Cancer Therapy and Research Center, San Antonio, TX is the principal investigator. The study was initiated March 2006; to date, 6 patients have been enrolled out of a total of 66 patients required for completion. The estimated completion date of the clinical study report is 3Q2007. Wyeth continues to monitor the progress of this study; however, study updates will be available by cross-reference to IND 60,010.

FDA Commented:

Ideally, the hepatic impairment study will be completed by the time of NDA filing and submitted in the NDA. If that timing cannot be met, submission of a completed study report during the review cycle is the next best alternative.

If a completed study report cannot be submitted, the NDA should be updated to the extent possible in order to construct the best package insert possible.

Discussion: Wyeth is proposing to submit all available safety and PK data from the hepatic impairment study at the time of the safety update. Wyeth will discuss with NCI what data can be provided (if any) with the original submission.

TELECON OBJECTIVES:

To provide an update to the discussion held on May 11, 2006

DISCUSSION:

The hepatic impairment study is ongoing and a safety update is expected on January 5, 2007. Wyeth won't be able to provide the pharmacokinetic (PK) data with this safety update. The study started in March, 2006 and has 9 active sites (IRB approved). The last NCI update included 14 patients but the data was not definitive enough with regard to drug disposition. Approximately a month ago, 38 were accrued; the accrual goal is 66 patients.

The Agency was asked what amount of data would be acceptable to permit labeling, if not all of the data was available. The Agency responded that it would depend on what data is available at the time of submission. Perhaps this could be carried into a phase 4 commitment. The next data set is due in December 2006. With the constraints of information, Wyeth will provide as much safety and pharmacokinetic (PK) information as they have. They currently have PK information on 24 patients but the safety narratives may not be ready with the planned January submission.

The Agency raised the question as to the stratification of the patient accrual. Wyeth stated that patients have been accruing across all group types.

With regards to the safety update in January, The Agency suggested that Wyeth should submit as much as they could. Wyeth asked if we had any questions on the PK review and there were no questions.

The meeting was adjourned at 12:45 PM

Submitted by:

_____

Carl Huntley, R.Ph., MBA
Regulatory Project Manager

Concurrence:

_____

Brian Booth, Ph.D.
Clinical Pharmacology Team Leader

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/s/

Brian Booth
12/6/2006 05:13:36 PM

2 Page(s) Withheld

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