CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-088

CHEMISTRY REVIEW(S)

OFFICIAL MEMORANDUM

TO: NDA 22-088 (DOCUMENT DATE 05-OCT-2006)

FROM: SARAH C. POPE, PH.D.

THROUGH: CHI-WAN CHEN, PH.D.

SUBJECT: CMC APPROVAL RECOMMENDATION FOR ORIGINAL NDA 22-088

DATE: 5/29/2007

NDA 22-088 for TORISEL Kit (temsirolimus) injection is currently under review. CMC Review #1 was finalized on 25-MAY-2007. CMC Review #1 states that NDA 22-088 is approvable pending the resolution of labeling (Package Insert and Container/Carton) issues. Final acceptable Container/Carton labeling was negotiated with the firm on 25-MAY-2007. Acceptable Container/Carton labels were submitted to the Agency on 25-MAY-2007. Final negotiations for the Package Insert were conducted in a 29-MAY-2007 teleconference; these additional negotiations were not captured in CMC Review #1 and are mentioned below.

Due to the Agency's concern that TORISEL be properly prepared in the clinical environment, the following language was inserted into the "Highlights" section (third bullet of the Dosage and Administration section) of the Package Insert:

"TORISEL (temsirolimus) injection vial contents must first be diluted with the enclosed diluent before diluting the result[redacted] solution with 250 mL of 0.9% Sodium Chloride Injection (2.4)."

Additionally, the Agency requested that all mentions of "sunitinib [redacted] in the TORISEL label be revised to "sunitinib" for the sake of clarity.

The Applicant agreed to both of these changes in a 29-MAY-2007 teleconference.

This memo serves as confirmation that there are no outstanding CMC approvability issues. From a Chemistry, Manufacturing and Controls standpoint, this application is recommended for approval.

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

/s/

Sarah Pope
5/29/2007 04:57:30 PM
CHEMIST

Chi Wan Chen
5/29/2007 05:13:42 PM
CHEMIST

CHEMISTRY REVIEW

NDA 22-088

Torisel™ *Kit*
(temsirolimus) injection

Wyeth Pharmaceuticals, Inc.

Office of New Drug Quality Assessment
Reviewed for the Division of Drug Oncology Products

CMC Review Team:
Sarah C. Pope, Ph.D.
Amit Mitra, Ph.D.
David Lewis, Ph.D.

Table of Contents

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Chemistry Review Data Sheet

1. NDA 22-088

2. REVIEW #1

3. REVIEW DATE: 25-MAY-2007

4. REVIEWERS: Sarah C. Pope, Ph.D.
Amit Mitra, Ph.D.
David Lewis, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA Submission	05-OCT-2006
Amendment (BC)	05-DEC-2006
Amendment (BC)	27-JAN-2007
Amendment (BC)	23-FEB-2007
Amendment (BC)	12-APR-2007
Amendment (BC)	04-MAY-2007
Amendment (BC)	25-MAY-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	Wyeth Pharmaceuticals, Inc.
Address:	35 CambridgePark Drive Cambridge, MA 02140
Representative:	Patricia Johnson, Director, Global Regulatory Affairs
Telephone:	617-665-8623

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: TORISEL™
b) Non-Proprietary Name (USAN): Temsirolimus
c) Code Name/# (ONDQA only):
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Temsirolimus is a first-in-class specific inhibitor of the mammalian target of rapamycin (mTOR), an enzyme which regulates cell growth and proliferation.

11. DOSAGE FORM: Concentrate for dilution and intravenous injection.

12. STRENGTH/POTENCY: 25 mg/mL. The diluent/concentrate solution is 10 mg/mL, which is then further diluted with normal saline prior to intravenous infusion.

13. ROUTE OF ADMINISTRATION: Intravenous infusion

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X__Not a SPOTS product

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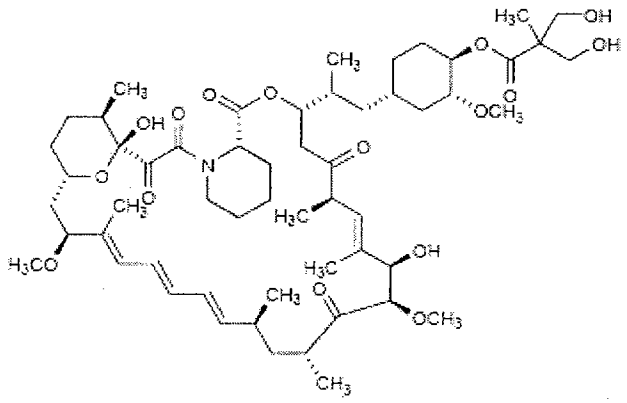
On Original

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



Temsirolimus (CCI-779, WAY-130779)
Rapamycin 42-[2,2-bis(hydroxymethyl)propionate
$C_{56}H_{87}NO_{16}$
MW = 1030.30 mg/mmol

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS[3]
9642	5	Pierre Fabre	Temsirolimus Concentrate	1	Adequate	06-MAR-2007	Review conducted by Microbiology reviewer (Dr. S. Langille).
2315	5	Ben Venue	Temsirolimus Concentrate	1	Adequate	06-MAR-2007	Review conducted by Microbiology reviewer (Dr. S. Langille).
[redacted]	3	[redacted]	[redacted]	1	Adequate	30-JAN-2007	Review conducted by Dr. A. Mitra.
	3			3	N/A	See attached review.	Sufficient information in the NDA; no separate review necessary.
	5			4	N/A	See attached review.	Sufficient information in the NDA; no separate review necessary.

[1] Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
[3] Include reference to location in most recent CMC review

B. Other Supporting Documents:
Not applicable

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	55,830	Wyeth Pharm.	Original IND, including treatment protocol approved in Sept/2006.
NDA	21-083	Wyeth Pharm.	Original NDA for Rapamune Oral Solution (approved Sept/1999)
NDA	21-110	Wyeth Pharm.	Original NDA for Rapamune Tablets (approved Aug/2000)

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			
EES	Site inspections	18-OCT-2006	J. D'Ambrogio	Overall acceptable received on 23-FEB-2007.
Pharm/Tox	Drug substance, drug product impurity qualification (organic and inorganic)	21-MAR-2007	Dr. H. Saber	Pending as of 13-MAR-2007.
Biopharm	N/A	05-OCT-2006	Dr. J. Bullock	Acceptable – see review dated 20-MAR-2007.
ODS/DMETS	Labeling consult	26-OCT-2006	C. Holquist	Completed 16-MAR-2007; trade name acceptable.
Methods Validation	To be submitted post-approval			
EA	N/A	N/A	Dr. A. Mitra	Categorical exclusion granted (see attached review).
Microbiology	Consulted to the Office of Microbiology	13-OCT-2006	Dr. S. Langille	See Microbiology Review dated 02-MAR-2007, by Dr. S. Langille.

The Chemistry Review for NDA 22-088

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing and Controls standpoint, this New Drug Application is approvable, pending the submission of acceptable container/carton labeling, including the Patient Information and Physician's Package Insert.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The following comments and risk management statements regarding CMC should be included in the action letter:

1. As stated in the 05-APR-2007 meeting, your proposed Chemistry, Manufacturing and Controls (CMC) Regulatory Agreement, submitted as part of the CMC Pilot program, was not reviewed and is not part of this approval action. Existing regulations and guidances should be followed, as appropriate, for all post-approval CMC changes. We remind you that you must comply with the reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).
2. We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified during this process.

We remind you of our agreements that were made in the 05-APR-2007 teleconference and in your submission dated 12-APR-2007. These agreements are listed below:

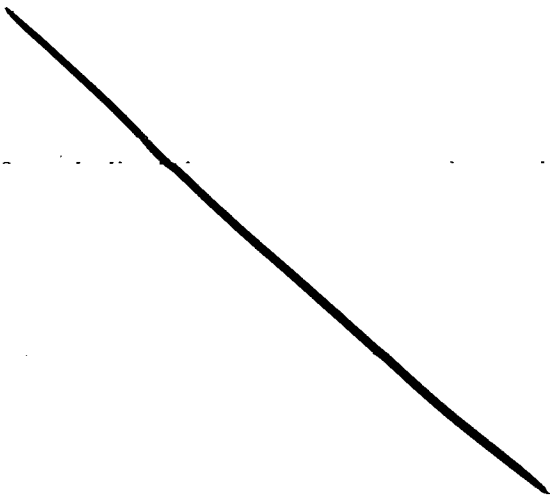
1. You have agreed to investigate the use of a flag label, or a suitable alternative, in order to incorporate additional information in the container labels for both the diluent and active vials.
2. You have agreed to submit the developed strategy for the above agreement in a Prior Approval supplement.
3. You have agreed to further discussions with the Agency regarding packaging technology options available, to ensure the physical connection of the two co-packaged vials.

II. Summary of Chemistry Assessment

A. Description of the Drug Substance(s) and Drug Product

Drug Substance (temsirolimus)
Temsirolimus is a New Molecular Entity. It is a non-hygroscopic, white to off-white powder which possesses minimal solubility ([redacted] in water. There are no definable [redacted] for temsirolimus, as there are no ionizable functionalities in the physiological pH range [redacted]

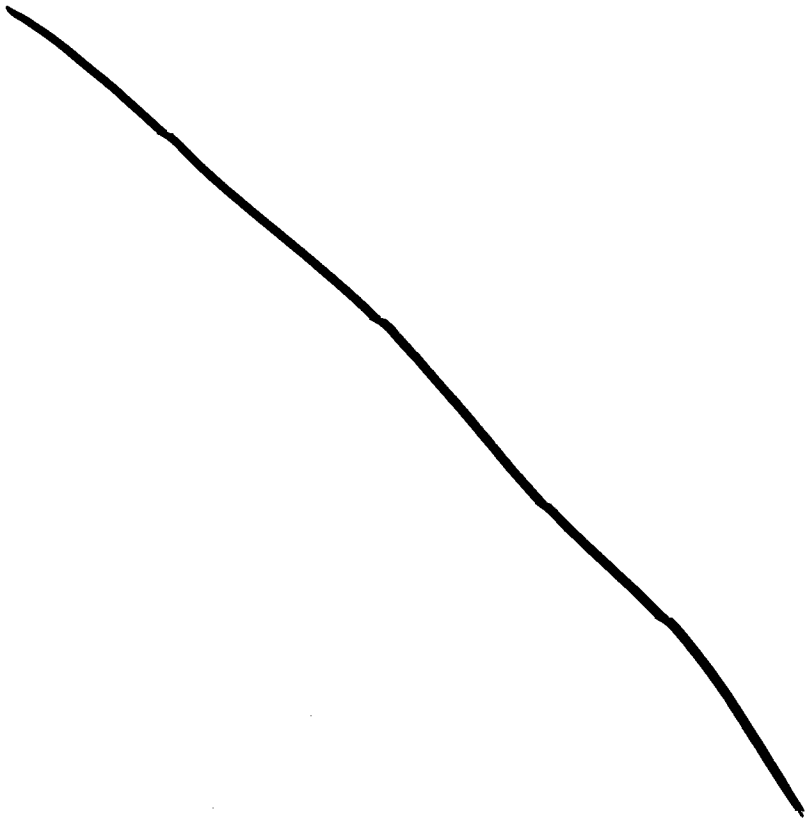
[redacted]



The Applicant proposed two drug substance manufacturing sites: Wyeth Pharmaceuticals, Inc. (Rouses Point, NY) [redacted]

Two reviewers from the current review team (Dr. S. Pope and Dr. D. Lewis) accompanied field investigators (Dr. P. Mouris and Ms. U. Inokon) on a pre-approval inspection of the drug substance manufacturing site (Rouses Point, NY; CFN 1310337; 08-JAN-2007 through 12-JAN-2007). This inspection resulted in an

"acceptable" recommendation from the field, and consequently, the same recommendation was issued by the Office of Compliance.



Temsirolimus was accepted as a United States Adopted Name (USAN) in 2004. Additional terminology may reference the Applicant's laboratory codes "CCI-779" and "WAY-130779". The CAS number for temsirolimus is 162635-04-3.

The amount of submitted stability data for the drug substance was based on agreements reached at the 17-APR-2006 pre-NDA meeting. The applicant provided long term and accelerated stability data for three commercial-scale batches of temsirolimus. The applicant provided months of long term and accelerated stability data for three commercial-scale batches of temsirolimus. All six primary stability batches were manufactured using the proposed commercial process, scale, and manufacturing equipment. Supportive stability data were provided for six additional batches of temsirolimus manufactured using the proposed commercial process, but prior to parameter optimization.

A [redacted] month retest period was granted for the [redacted] drug substance, when stored at 2-8°C.

Drug Product (temsirolimus injection)

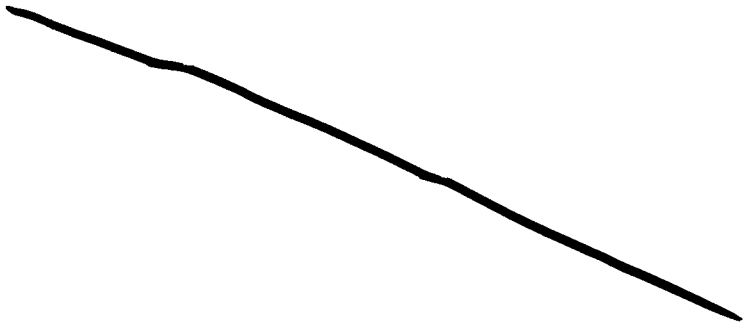
Torisel (temsirolimus) injection is formulated as a 25 mg/mL sterile solution co-packaged with a specific diluent for reconstitution. The diluent/concentrate combination results in a 10 mg/mL solution that is suitable for further dilution with 0.9% Sodium Chloride Injection for intravenous administration. The concentrate formulation includes the following excipients: *dl*-alpha tocopherol, dehydrated alcohol (ethanol anhydrous), anhydrous citric acid, and propylene glycol. The diluent contains polysorbate 80, dehydrated alcohol (ethanol anhydrous), and polyethylene glycol 400.

[redacted]

During the Chemistry, Manufacturing, and Controls review, the Agency determined that the Applicant's proposed descriptor for the active vial [redacted] was not correct. Therefore, the name of the active vial was revised to "TORISEL (temsirolimus) injection." In this review, all references to the [redacted] " specifically refer to the contents of the active vial. This discrepancy was handled during the labeling negotiations that occurred following the completion of the bulk of this review.

[redacted]

The Applicant proposed several critical quality attributes for the drug product including: quality of raw materials including the API, sterility, freedom from pyrogens, freedom from particulate matter, consistent fill volume, strength, and purity. [redacted] The Applicant proposed appropriate controls for critical quality attributes not specifically addressed via the drug substance manufacturing process (see the above discussion).



The applicant proposed two drug product manufacturing sites. The active concentrate will be manufactured at Pierre Fabre (France), while the diluent for reconstitution will be manufactured at Ben Venue Laboratories (Bedford, OH). An overall "acceptable" EES recommendation was issued by the Office of Compliance on 23-FEB-2007.

The amount of submitted stability data for the drug product was based on agreements reached at the 17-APR-2006 pre-NDA meeting. The applicant provided long term and room temperature stability data for three commercial-scale batches of the active concentrate, when stored in an inverted position. Photostability conditions (ICH Option 2) were studied using one of the primary stability batches. All three primary stability batches were manufactured using the proposed commercial process; however, the proposed commercial site was not used for production of the primary stability batches. Site-specific stability data for three process validation batches manufactured at the proposed drug product manufacturing site (Pierre Fabre) was updated in a 05-DEC-2006 amendment to this NDA.

The applicant provided long term and room temperature stability data for three commercial-scale batches of Diluent for Temsirolimus Injection, when stored in an inverted position. Photostability conditions (ICH Option 2) were studied using one of the primary stability batches. All three primary stability batches were manufactured using the proposed commercial process; however, the proposed commercial site was not used for production of the primary stability batches. Site-specific stability data for three process validation batches manufactured at the proposed drug product manufacturing site (Ben Venue) was updated in a 05-DEC-2006 amendment to this NDA.

The final drug product includes the concentrate for injection (25 mg/mL) as well as the supplied diluent. Both components are packaged in glass vials fitted with gray butyl rubber stoppers and Complete Drug

Master File references have been provided for these proposed packaging components. Stability samples for the diluent and concentrate were packaged in each of the proposed marketing configurations.

The applicant proposed, and was granted, a 24-month expiration dating period for the concentrate, when stored under refrigerated conditions (5°C ± 3°C) and protected from light. The applicant also proposed a [redacted] month expiration dating period for the diluent when the material is stored under controlled room temperature for up to 12 months, followed by storage under refrigerated conditions (5°C ± 3°C) for the remainder of the [redacted] month shelf life.

Due to the discrepancy in expiration dating periods for the concentrate and diluent, the approved expiration dating period for the co-packaged drug product is the lesser of the two proposed expiries (24 months), when stored under refrigerated conditions (5°C ± 3°C) and protected from light.

B. Description of How the Drug Product is Intended to be Used

Torisel (temsirolimus) injection is formulated as a 25 mg/mL sterile solution co-packaged with a specific diluent for reconstitution. The diluent/concentrate combination results in a 10 mg/mL solution that is suitable for further dilution with 0.9% Sodium Chloride Injection for intravenous administration.

C. Basis for Approvability or Not-Approval Recommendation

This NDA is recommended for Approval from a Chemistry, Manufacturing, and Controls standpoint. There are no outstanding Chemistry, Manufacturing, and Controls issues.

III. Administrative

This NDA was submitted electronically as a 505(b)(1) application. A Quality Overall Summary is included in the application. The CMC information in this NDA was accepted for review under the CMC pilot program (FR Vol. 70, No. 134, pp. 40719-40720, July 14, 2005). This program proposes innovative approaches to ensuring product quality.

The CMC section of this application was reviewed by a team. The review team members selected for the quality assessment and their individual responsibilities are listed below:

Review Team	Assessment Responsibility
Sarah C. Pope, Ph.D.	Administrative Information, Executive Summary, Comparability Protocol, Labeling
David Lewis, Ph.D.	Drug Substance, Labeling
Amit Mitra, Ph.D.	Manufacturing Sciences/Drug Product, Labeling
Steve Langille, Ph.D.	Microbiology Evaluation (separate review)

158 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 1

A. Reviewer's Signature
See appended electronic signature page.

B. Endorsement Block
C.-W.Chen/ONDQA/Deputy Director

C. CC Block
R. Lostritto/ONDQA/Div. 3/Director
R. Harapanhalli/ONDQA/Branch 5/Branch Chief
C. Huntley/OND/DDOP/Regulatory PM
A. Bertha/ONDQA/PM for Quality

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

/s/

Sarah Pope
5/25/2007 11:49:31 AM
CHEMIST
signing off for David Lewis, Ph.D. also

Amit K. Mitra
5/25/2007 01:58:48 PM
CHEMIST

Chi Wan Chen
5/25/2007 02:20:32 PM
CHEMIST