DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-088

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

Dear Ms. Johnson:

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

We acknowledge receipt of your submissions dated October 18, 2006; November 16, 21, and 22, 2006; December 5, and 13, 2006; January 19, and 26, 2007; February 20, 22, and 23, 2007; March 7, and 9, 2007; April 5, 12, 17, and 30, 2007, and May 4, 2007.

This new drug application provides for the use of TORISEL™ (temsirolimus) injection, for the treatment of advanced renal cell carcinoma.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission "SPL for approved NDA 22-088."

The final printed labeling (FPL) for immediate container and carton labels must be identical to the enclosed labeling. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 22-088**". Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated May 24, 2007.

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These commitments are listed below.

1. Submit the completed report and data sets for the thorough QT prolongation evaluation 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

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Commitment Protocol**", "**Postmarketing Study Commitment Final Report**", or "**Postmarketing Study Commitment Correspondence**."

We have the following comments and risk management statements regarding CMC.

1. As stated in the April 5, 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 postapproval 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 April 5, 2007 teleconference and in your submission dated April 12, 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.

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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 copackaged vials.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send two copies of both the promotional materials and the package insert directly to:

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

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

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

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Office of Oncology Drug Products
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

Enclosure

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/s/

Richard Pazdur
5/30/2007 03:06:27 PM

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TORISEL™ safely and effectively. See full prescribing information for TORISEL.

TORISEL™ *Kit* (temsirolimus) injection, for intravenous infusion only
Initial U.S. approval: 2007

----------INDICATIONS AND USAGE ----------
TORISEL™ is a kinase inhibitor indicated for the treatment of advanced renal cell carcinoma. (1)

----------DOSAGE AND ADMINISTRATION ---------- ----
- The recommended dose of TORISEL is 25 mg infused over a 30-60 minute period once a week. Treat until disease progression or unacceptable toxicity. (2.1)
- Antihistamine pre-treatment is recommended. (2.2)
- TORISEL (temsirolimus) injection vial contents must first be diluted with the enclosed diluent before diluting the resultant solution with 250 mL of 0.9% sodium chloride injection. (2.5)

----------DOSAGE FORMS AND STRENGTHS ----------
TORISEL injection, 25 mg/mL supplied with DILUENT for TORISEL. (3)

---------- CONTRAINDICATIONS ----------
- None. (4)

----------WARNINGS AND PRECAUTIONS ----------
- To treat hypersensitivity reactions stop TORISEL and treat with an antihistamine. TORISEL may be restarted at physician discretion at a slower rate. (5.1)
- Hyperglycemia and hyperlipemia are likely and may require treatment. Monitor glucose and lipid profiles. (5.2, 5.5)
- Infections may result from immunosuppression. (5.3)
- Monitor for symptoms or radiographic changes of interstitial lung disease (ILD). If ILD is suspected, discontinue TORISEL, and consider use of corticosteroids and/or antibiotics. (5.4)
- Bowel perforation may occur. Evaluate fever, abdominal pain, bloody stools, and/or acute abdomen promptly. (5.6)
- Renal failure, sometimes fatal, has occurred. Monitor renal function at baseline and while on TORISEL. (5.7)
- Due to abnormal wound healing, use TORISEL with caution in the perioperative period. (5.8)
- Live vaccinations and close contact with those who received live vaccines should be avoided. (5.12)
- Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant. (5.13)

----------ADVERSE REACTIONS----------
The most common adverse reactions (incidence ≥ 30%) are rash, asthenia, mucositis, nausea, edema, and anorexia. The most common laboratory abnormalities (incidence ≥30%) are anemia, hyperglycemia, hyperlipemia, hypertriglyceridemia, elevated alkaline phosphatase, elevated serum creatinine, lymphopenia, hypophosphatemia, thrombocytopenia, elevated AST, and leukopenia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Wyeth Pharmaceuticals Inc. at 1-800-934-5556 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Strong inducers of CYP3A4/5 and inhibitors of CYP3A4 may affect concentrations of the primary metabolite of TORISEL. If alternatives cannot be used, dose modifications of TORISEL are recommended. (7.1, 7.2)

See 17 for PATIENT COUNSELING INFORMATION.
Revision date: 5/2007

FULL PRESCRIBING INFORMATION: CONTENTS [*]

***Sections or subsections omitted from the full prescribing information are not listed.**

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