DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022088

WRITTEN REQUEST – AMENDMENT 4

Wyeth Pharmaceuticals, Inc.
Attention: Michelle J. Yu, MS, RAC
Manager, WW Regulatory Strategy
10646 Science Center Drive
San Diego, CA 92121

Dear Ms. Yu:

Please refer to your correspondence dated February 16, 2011, requesting changes to FDA's January 12, 2001, Written Request for pediatric studies for temsirolimus.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on January 12, 2001, and as amended on September 30, 2004, September 28, 2007 and September 29, 2010, remain the same. (Text added is underlined. Text deleted is ~~strikethrough~~.)

- **Timeframe for submitting reports of the study(ies):**

  Reports of the above studies must be submitted to the Agency on or before ~~September 30, 2010;~~ ~~February 25, 2011;~~ May 31, 2012. Please keep in mind that pediatric exclusivity only extends existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated September 30, 2004, as amended by this letter and by previous amendment(s) dated September 28, 2007 and September 29, 2010, must be submitted to the Agency on or before May 31, 2012, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

- In accordance with section 505A(e)(2), if:

    1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
    2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
    3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

- Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that temsirolimus is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies).

- In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

    - the type of response to the Written Request (i.e., complete or partial response);
    - the status of the application (i.e., withdrawn after the supplement has been filed or pending);
    - the action taken (i.e., approval, approvable, not approvable); or
    - the exclusivity determination (i.e., granted or denied).

- If your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

If you have any questions, call Modupe Fagbami, Regulatory Project Manager, at 301-796-1348.

Sincerely,

{See appended electronic signature page}

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

Attachment:
Complete Clean Copy of Written Request as amended

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 022088

WRITTEN REQUEST

Wyeth Pharmaceuticals, Inc.
Attention: Michelle J. Yu, MS, RAC
Manager, WW Regulatory Strategy
10646 Science Center Drive
San Diego, CA 92121

Dear Ms. Yu:

Please refer to your New Drug Application (NDA) for TORISEL® (temsirolimus) injection. The Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal, Food, Drug and Cosmetic Act (the Act), that you submit specific pediatric studies, detailed later in the letter. These studies investigate the potential use of Temsirolimus in the treatment of children with brain tumors or other solid tumors.

BACKGROUND

The development of pediatric oncology drugs merits special consideration. Compared to adult malignancies, pediatric cancers afflict small numbers of patients. Because the majority of pediatric patients receive their cancer therapy as participants in clinical research protocols, participation in Phase 3 oncology trials has become the *standard of care* in pediatric oncology. Children with cancer are usually treated at specialized centers by pediatric oncologists who are members of a national pediatric cooperative study group. One of the highest priorities of these groups is to develop improved novel therapies. Early access to new drugs is one mechanism to achieve this goal.

Known and potential differences in the biology of pediatric and adult tumors usually will not permit the extrapolation of clinical activity from adults to children. Therefore, it is usually impossible to rely on pharmacokinetic and safety data alone to guide the use of these drugs in children. It is imperative that we evaluate the effectiveness and safety of new drugs in pediatric populations. In most cases, in the absences of available therapies to treat refractory stages of most pediatric cancers, the FDA expects to be able to use flexible regulatory approaches in developing and approving drugs for pediatric tumors [e.g., basing approval on an effect on tumor size or other surrogate marker likely to predict clinical benefit (Subpart H), and/or based on safety in small numbers of patients (Subpart E)].

The intent of designing studies for development of drugs for pediatric oncology is to proceed in the context of an overall development program. Drugs that lack dosing and pharmacokinetic information should begin with Phase 1 studies. Drugs that have dosing and pharmacokinetic data in pediatric patients should be tested in Phase 2 or pilot studies. If appropriate, a specific disease may be targeted; otherwise, several studies in a variety of tumor types, such as brain tumors, solid tumors, or

hematologic tumors should be planned. Depending upon the outcome of the Phase 2 studies, Phase 3 studies may be initiated. See the **Guidance for Industry Pediatric Oncology Studies in Response to a Written Request** located on the web at www.fda.gov/cder/guidance/3756dft.htm for circumstances when it may be appropriate to request an exclusivity determination or advisory opinion at the end of either Phase 1 or 2. The FDA recommends that the rationale for the drug development plan and context in an overall pediatric oncology drug development program be included with each study.

Protocols for each of your studies should be submitted to the FDA for review, but they need not be submitted simultaneously. For example, if you begin with a Phase 1 study, initially a Phase 1 protocol should be submitted for review, but the submission of Phase 2 or pilot study protocols may be deferred.

REQUESTED STUDIES

Please submit the information from the following types of studies:

- Type of studies:

  A Phase I/II Safety and Exploratory Pharmacogenomic/Pharmacodynamic Study of Intravenous Temsirolimus in Pediatric Subjects with Relapsed/Refractory Solid Tumors. The study will consist of two parts and will include evaluation of pharmacogenomic and pharmacodynamic information. Pharmacokinetic analyses will include single and multiple-dose pharmacokinetics of temsirolimus in this population.

  Part 1: An ascending-dose study in subjects ages 1-21 years with advanced solid tumors. At least 3 to 6 subjects will be entered at each dose level. Dose escalation to the next level will occur based on safety evaluation for at least 3 weeks after the first dose of temsirolimus for all subjects at a particular dose level. A minimum of 6 subjects will be treated with the highest dose of temsirolimus.

  Part 2: This portion will be conducted in three groups of children with refractory or relapsed pediatric solid tumors. Subjects with the following tumor types will be enrolled: neuroblastoma, rhabdomyosarcoma and high-grade gliomas. Approximately 60 subjects, 20 per tumor group, will be enrolled. The study design of Part 2 is based on the Simon Two-Stage Design. For each group, the sample size for the first stage is at least 8 evaluable subjects and the sample size for the second stage is at least 12 evaluable subjects. All subjects in Part 2 will be treated with the dose level previously determined in Part 1. All clinical sites selected to participate in the temsirolimus pediatric studies will have the experience, support and expertise to care for children with cancer.

- Indication(s) to be studied (i.e., objective of each study):

  Pediatric Refractory Solid Tumors, including neuroblastoma, rhabdomyosarcoma and high-grade gliomas

- Age group in which study(ies) will be performed:

  Pediatric subjects aged 1 year to 21 years

- Study endpoints:

  Phase 1

  Objectives include:

  - Evaluation of the safety of IV temsirolimus administered once weekly to children with solid tumors with disease that is recurrent or refractory to standard therapy or for whom standard therapy is not appropriate.
  - Identification of the maximum tolerated dose or a biologically effective dose of IV temsirolimus when administered once weekly.
  - Collection of preliminary information on the anti-tumor activity of IV temsirolimus.
  - Determination of the single- and multiple-dose pharmacokinetics of temsirolimus in children with once-weekly IV treatment.

  Phase 2

  Objectives include:

  - Collection of preliminary information on the anti-tumor activity of IV temsirolimus in children with neuroblastoma, high-grade gliomas, and rhabdomyosarcoma. Anti-tumor activity will be assessed by determining the percentage of subjects exhibiting objective response (CR + PR).
  - Freedom from progression (disease stabilization defined as CR+PR+MR+SD) at 3 months may be used as a secondary endpoint.
  - Verification of the safety of the selected dose.
  - Determination of the single- and multiple-dose pharmacokinetics of temsirolimus in children with once weekly IV treatment.

- Drug information:

  Dosage form: *Solution*

  Route of administration: *Intravenous Injection*

  Regimen: *Once weekly intravenous infusion until disease progression as long as temsirolimus is well tolerated.*

- Drug specific safety concerns:

  Serious adverse events considered possibly related to single-agent use of temsirolimus include the following:

  leucopenia, thrombocytopenia, anemia, decreased hemoglobin, decreased platelet count, abnormal clot retraction, increased international harmonized ratio, hemorrhage, epistaxis, gingival bleeding, intracranial hemorrhage, abdominal pain, nausea, vomiting, hematemesis, diarrhea, constipation, mucosal inflammation, stomatitis, mental impairment, confusional state, depression, sedation, depressed consciousness, coma, convulsions, mania, psychotic disorder, chest pain, dyspnea, pharyngitis, alveolitis, allergic alveolitis, lung infiltration, pleural effusion, hemoptysis, lower respiratory tract infection, pneumonitis, pneumonia, primary atypical pneumonia, respiratory failure, pericardial effusion, pulmonary hypertension, hypotension, right ventricual failure, tachycardia, pulmonary embolism, thrombosis, deep vein thrombosis, abnormal hepatic function, cholangitis, pancreatitis, increased blood urea, increased blood creatinine, dysuria, renal failure, hypersensitivity, anaphylactic reaction, rash erythematous, pruritus, urticaria, urticaria vesiculosa, abscess, skin and subcutaneous tissue abscess, infection, gingival infection, paronychia, candidal infection, sepsis, dehydration, hot flushes, pyrexia, asthenia, fatigue, lethargy, malaise, ataxia, rigors, decreased appetite, reduced dietary intake, decreased weight, hyperglycemia, cellulitis, metabolic acidosis, and glioma.

- Statistical information, including power of study and statistical assessments:

  Formal inferential statistics will be provided for Part 2 data only. The emphasis of the statistical analyses will be placed on estimation and exploratory data analysis. The primary endpoint is response rate (CR + PR). The proportion of subjects achieving a complete or partial response in each tumor group and the 95% confidence for the true proportion will be calculated for all subjects.

  Safety data will be summarized for all subjects who receive at least one dose of study medication. These data (adverse events, laboratory data and vital signs) will be summarized for all subjects.

  Pharmacokinetic parameters including clearance (CL), volume of distribution (Vd), area under the concentration-time curve (AUC), and half-life ($t_{1/2}$) will be estimated for all subjects.

- Labeling that may result from the study(ies):

  Appropriate sections of the label may be changed to incorporate the findings of the studies.

- Format of reports to be submitted:

  Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. Include other information as appropriate. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity one of the following designations must be used: Hispanic/Latino or Not Hispanic/Latino.

- Timeframe for submitting reports of the study(ies):

  Reports of the above studies must be submitted to the Agency on or before May 31, 2012. Please keep in mind that pediatric exclusivity only extends existing patient protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY"** in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

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- In accordance with section 505A(e)(2), if:

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  6) you have not marketed the formulation within one year after the Agency publishes such notice,

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We hope you fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, call Modupe Fagbami, Regulatory Project Manager, at 301-796-1348.

Sincerely,

{See appended electronic signature page}

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

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

/s/

RICHARD PAZDUR
02/25/2011