DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST – AMENDMENT #1

IND 58,546

Bristol-Myers Squibb Company
Attention: Meenal Pai, Pharm.D.
Manager, Global Regulatory Science
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Pai:

Please refer to your correspondences dated December 12, 2007, requesting changes to FDA's June 22, 2007, Written Request for pediatric studies for IXEMPRA™ (ixabepilone BMS-247550).

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 June 22, 2007, remain the same.

- *Study endpoints:*
  Study 1:
  1. Determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of BMS-247550 (ixabepilone) administered as a one-hour infusion daily for 5 consecutive days every 21 days in children with cancer.
  2. Define the toxicity spectrum of ixabepilone on the daily x 5 schedule every 21 days in children with cancer.
  3. Determine the plasma pharmacokinetics of ixabepilone.
  4. Evaluate the pharmacodynamics of ixabepilone using an assay that measures the relative amounts of endogenous tubulin in peripheral blood mononuclear cells that exists in the polymerized versus the unpolymerized state.
  5. Measure nerve growth factor levels before and after the start of treatment with ixabepilone as a potential surrogate marker for the development of peripheral neuropathy.
  6. Measure responses to ixabepilone.
  7. Measure the time to disease progression in patients with objective responses.
  8. Compare the tolerance, toxicity profile, MTD, DLT, pharmacokinetics and pharmacodynamics of ixabepilone in children treated on this study and adults who were treated with the same schedule of treatment.

  Study 2: The primary endpoint is objective response rate (CR + PR) using RECIST criteria. The secondary endpoint is the time to disease progression and for patients with measurable chest disease a comparison of automated volumetric tumor measurement with standard RECIST and WHO methods.

- *Statistical information, including power of study and statistical assessments:*
  Study 1: This trial uses a conventional dose-escalation design to establish the MTD of ixabepilone based on severity of toxicity. Four dose levels are planned.

At least 3 patients will be treated at each dose level (cohort) and if a DLT is observed in 1 of 3 patients, the cohort will be expanded up to 6 patients. MTD is defined as the dose level immediately below the level at which ≥ 2 patients in a cohort of 2 to 6 patients experienced a DLT. Patient accrual will be expanded at the MTD to at least 6 and as many as 12 patients, including at least 2 who are ≤ 5 years of age. In the expanded cohort at the recommended dose, < 25% of patients (3/12) should have experienced DLT attributable to ixabepilone.

Study 2: Evaluation of activity will be carried out by a standard procedure as follows. Within each category (stratum) of tumors, approximately 10 patients will be entered. If there are no patients with responses, the trial for this stratum will be terminated because the agent is ineffective. If ≥ 1 patient responds in a stratum, 10 additional patients will be entered. If there are ≤ 2 responses, the trial will be terminated for this stratum because the agent is inactive. If there are ≥ 3 patients with responses, the trial will be terminated for this stratum because the agent is active. The responses will be categorized by type (CR, PR or PD) according to protocol specified criteria. Response rate and time to progression will be described. Toxicity information recorded will include the type, severity, time of onset, time of resolution and the probable association with the study regimen.

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 June 22, 2007, as amended by this letter, must be submitted to the Agency on or before December 28, 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 (301-827-5911) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 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:

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 in accordance with section 505A(e)(2).

Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that IXEMPRA™ ixabepilone (BMS-247550) 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 circumstances:

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

Finally, please note that, 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, please call Frank Cross, Regulatory Project Manager, at (301) 796-0876.

Sincerely,

{See appended electronic signature page}

Karen D. Weiss, M.D.
Deputy Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Attachment

IND 58,546

Bristol-Myers Squibb Company
Attention: Meenal Pai, Pharm.D.
Manager, Global Regulatory Science
5 Research Parkway
Wallingford, CT 06492

Dear Dr. Pai:

Reference is made to your November 20, 2006 Proposed Pediatric Study Request submitted to IND 58,546 for Ixabepilone (BMS-247550).

To obtain needed pediatric information on ixabepilone, 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 information from the following studies:

We hope you fulfill this pediatric request.

- *Type of studies*:
  Study 1: A phase 1, open-label, dose-finding, safety and pharmacokinetic study of intravenous ixabepilone in pediatric patients with advanced, refractory solid tumors including brain tumors.

  Study 2: A phase 2 single-arm, safety and efficacy study of ixabepilone (BMS-247550) in children and young adults with refractory solid tumors.

- *Populations to be studied:*
  Study 1: Advanced, refractory, histologically confirmed solid tumors, which include but are not limited to rhadomyosarcoma and other soft tissue sarcomas, Ewing's sarcoma family of tumors, osteosarcoma, neuroblastoma, Wilms' tumor, hepatic tumors, germ cell tumors, and primary brain tumors. In patients with brain stem or optic gliomas the requirement for histological confirmation may be waived.

  Study 2: The target tumors are distributed into the following categories: (1) embryonal or alveolar rhabdomyosarcoma, (2) osteosarcoma, (3) Ewing's sarcoma/peripheral neuroectodermal tumor (PNET), (4) synovial sarcoma or malignant peripheral nerve sheath tumor (MPNST), (5) Wilms' tumor, and (6) neuroblastoma.

- *Age group in which studies will be performed*:
  Study 1: Patients of $\geq$ 1 year and $\leq$ 18 years of age.
  Study 2: Patients must be $\geq$ 1 year and $\leq$ 21 years of age at trial entry.

- *Study endpoints:*
  Study 1:
  1. Determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of BMS-247550 (ixabepilone) administered as a one-hour infusion daily for 5 consecutive days every 21 days in children with cancer.
  2. Define the toxicity spectrum of ixabepilone on the daily x 5 schedule every 21 days in children with cancer.

3. Determine the plasma pharmacokinetics of ixabepilone.
4. Evaluate the pharmacodynamics of ixabepilone using an assay that measures the relative amounts of endogenous tubulin in peripheral blood mononuclear cells that exists in the polymerized versus the unpolymerized state.
5. Measure nerve growth factor levels before and after the start of treatment with ixabepilone as a potential surrogate marker for the development of peripheral neuropathy.
6. Measure responses to ixabepilone.
7. Measure the time to disease progression in patients with objective responses.
8. Compare the tolerance, toxicity profile, MTD, DLT, pharmacokinetics and pharmacodynamics of ixabepilone in children treated on this study and adults who were treated with the same schedule of treatment.

Study 2: The primary endpoint is objective response rate (CR + PR) using RECIST criteria. The secondary endpoint is the time to disease progression and for patients with measurable chest disease a comparison of automated volumetric tumor measurement with standard RECIST and WHO methods.

- *Drug information*
  - **Dosage form:** ixabepilone 15mg, 20mg and 30mg lyophile per single-use vial. The Vehicle for Constitution is comprised of an ethanol plus polyoxyethylated castor oil (Cremaphor® EL) mixture (1:1 by volume). The diluent is Lactated Ringer's Injection (USP).
  - **Route of administration:** intravenous
  - **Regimen:**
    Study 1: Ixabepilone will be administered IV daily as a one-hour infusion for 5 consecutive days every 21 days. The starting dose for this trial will be 3 mg/m²/dose, which represents 50% of the adult MTD. The same dose levels will be tested in children as were studied in the adult trial – 3, 6, and 8 mg/m²/dose. In addition, a 4.5 mg/m²/dose level will be added, as the 6 mg/m²/dose was the MTD in adults treated on the same schedule. If the 8 mg/m²/dose is tolerable, subsequent dose levels will be at 30% increments.

    Study 2: Ixabepilone will be administered as a one-hour infusion on Days 1 to 5 every 21 days at the recommended phase 2 dose determined from study 1.

- *Drug specific safety concerns*:
  Neutropenia, peripheral neuropathy, hypersensitivity reactions, cardiovascular events.

- *Statistical information, including power of study and statistical assessments:*
  Study 1: This trial uses a conventional dose-escalation design to establish the MTD of ixabepilone based on severity of toxicity. Four dose levels are planned. At least 3 patients will be treated at each dose level (cohort) and if a DLT is observed in 1 of 3 patients, the cohort will be expanded up to 6 patients. MTD is defined as the dose level immediately below the level at which ≥ 2 patients in a cohort of 2 to 6 patients experienced a DLT. Patient accrual will be expanded at the MTD to at least 6 and as many as 12 patients, including at least 2 who are ≤ 5 years of age. In the expanded cohort at the recommended dose, < 25% of patients (3/12) should have experienced DLT attributable to ixabepilone.

  Study 2: Evaluation of activity will be carried out by a standard procedure as follows. Within each category (stratum) of tumors, approximately 10 patients will be entered.

If there are no patients with responses, the trial for this stratum will be terminated because the agent is ineffective. If ≥ 1 patient responds in a stratum, 10 additional patients will be entered. If there are ≤ 2 responses, the trial will be terminated for this stratum because the agent is inactive. If there are ≥ 3 patients with responses, the trial will be terminated for this stratum because the agent is active. The responses will be categorized by type (CR, PR or PD) according to protocol specified criteria. Response rate and time to progression will be described. Toxicity information recorded will include the type, severity, time of onset, time of resolution and the probable association with the study regimen.

- *Labeling that may result from the studies*:
  Appropriate sections of the label may be changed to incorporate the findings of the studies.

- *Format of reports to be submitted*:
  Full study reports and data sets 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. All pediatric patients enrolled in the studies 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 should be used: Hispanic/Latino or Not Hispanic/Latino.

- *Timeframe for submitting reports of the studies:*
  Reports of the above studies must be submitted to the Agency on or before December 28, 2012. Please keep in mind that pediatric exclusivity attaches only to 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.

- *Response to Written Request:*
  As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

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. 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.

Reports of the studies should be submitted as a New Drug Application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please 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. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

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If you have any questions, please call Frank Cross, Project Manager, at (301) 796-1994.

Sincerely,

{See appended electronic signature page}

Karen D. Weiss, MD
Deputy Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Linked Applications	Sponsor Name	Drug Name
IND 58546	BRISTOL MYERS SQUIBB CO	BMS 247550

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

/s/

KAREN D WEISS
04/22/2008