DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

IND 58,546

Bristol-Myers Squibb Company
Attention: Heather Knight-Trent, PharmD
Director, Global Regulatory Sciences
5 Research Parkway
Wallingford, CT 06492

Dear Ms. Knight-Trent:

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:

- *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. Secondary endpoints are 1) 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 and 2) plasma pharmacokinetics of ixabepilone.

  Relevant pharmacokinetic endpoints include clearance, volume of distribution and AUC that may be derived through approaches such as optimal sparse sampling in all patients with rich sampling in a sub-group. Such data should then be appropriately analyzed using methods such as nonlinear mixed effects modeling.

  Data from the Phase 1 and Phase 2 studies are to be combined to develop pharmacokinetic and pharmacodynamic (PK-PD) models to explore exposure-response relationships for measures of safety and effectiveness.

- *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 3 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, 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.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (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).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and

optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

If you have any questions, call Sharon Thomas, Regulatory Project Manager, at (301) 796-1994.

Sincerely,
{See appended electronic signature page}
Karen D. Weiss, MD
Deputy Director
Office of Oncology Drug Products
Office of New Drugs
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/

Karen Weiss

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