DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST – AMENDMENT 2

NDA 19-785

Bristol-Myers Squibb Medical Imaging
Attention: Heather V. Nigro
331 Treble Cove Road
North Billerica, MA 01862

Please refer to your correspondence dated February 23, 2007, requesting changes to FDA's June 1, 2005 Written Request for pediatric studies for Kit for Preparation of Technetium Tc99m Sestamibi.

We have reviewed your proposed changes and are amending the Written Request. For convenience, the full text of the Written Request, as amended, follows. This Written Request supersedes the Written Requests dated December 17, 2004 and June 1, 2005.

To obtain needed pediatric information on Technetium Tc99m Sestamibi, 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:

Background:
Technetium Tc99m Sestamibi has been utilized for myocardial perfusion imaging (MPI) in adults since its approval in 1990. Technetium Tc99m Sestamibi is used as a diagnostic cardiac imaging agent to evaluate pediatric patients with congenital cardiac abnormalities, Kawasaki disease, myocardial ischemia from hypertrophic cardiomyopathy, and heart damage from various chemotherapy agents. However there are no data available to assess the efficacy and safety of this agent in the pediatric population. Preclinical studies should be undertaken to supplement the safety information obtained in the clinical studies.

Type of studies:

Study 1: Pediatric Radiation Dosimetry Determination and Pharmacokinetic (Biodistribution) Study

Study 2: Pediatric Diagnostic Efficacy and Safety Study (Prospective Study)

Study 3: Pediatric Diagnostic Efficacy and Safety Study (Retrospective Study)

Objectives of Studies:

Study 1: To determine the dosimetry, pharmacokinetics (biodistribution in blood and urine) and safety of Technetium Tc99m Sestamibi including biodistribution, dosimetry and safety in pediatric patients

Study 2: To determine the diagnostic efficacy and safety of Technetium Tc99m Sestamibi in pediatric patients with Kawasaki disease, by using clinical outcomes as the truth standard.

Study 3: To determine the diagnostic efficacy and safety of Technetium Tc99m Sestamibi in pediatric patients with Kawasaki disease, by using X-ray angiography as the truth standard.

Study design:

Study 1: The study may be an open-label, non-randomized multi-center trial in pediatric patients who have been scheduled to undergo rest or exercise stress Technetium Tc99m Sestamibi cardiac imaging. All patients will undergo either whole body nuclear imaging to determine dosimetry or assessment of pharmacokinetics (biodistribution in blood and urine), or both. All patients will be assessed for safety. If sedation is required, the sponsor will need to provide sedation parameters and monitoring protocols. If both rest and stress Technetium Tc99m Sestamibi cardiac imaging studies will be done in the same patient then the studies will need to be done on separate days except at sites where the standard clinical practice is to perform a one day study.

Results of study 1 may be used to inform the dose selected for study 2. If dose adjustments are found to be necessary, the Division should be notified prior to proceeding with a new dose.

Study 2: This study may be an open-label, non-randomized multi-center diagnostic efficacy and safety trial in pediatric patients with Kawasaki disease (based on criteria for the diagnosis of “classical” or “incomplete” Kawasaki disease: Newburger JW, et al. Circulation 2004; 110:2747-71) who are under evaluation for suspected myocardial perfusion abnormalities. Patients will undergo rest and exercise stress testing using imaging with Technetium Tc99m Sestamibi. The protocol should specify if sedation is required and, as applicable, provide sedation administration procedures and monitoring plans. The predictive value of Technetium Tc99m Sestamibi to define pediatric Kawasaki patients at high and low risk of developing cardiac events will be determined. The clinical protocol will, in addition to any other details, include analytical plans for determination of the categorical classifications of patients as either "high" or "low" risk for cardiac events based upon pre-specified imaging results and pre-specified composite cardiac outcomes (the truth standard, specified below). The primary endpoint will consist of a summary determination of the sensitivity and specificity for the imaging detection of patients at high risk for cardiac events. All patients will be followed for short-term cardiac outcomes at 6 months and followed yearly to evaluate long-term cardiac outcomes over a 10 year period. The assessment of cardiac outcomes at 6 months will be considered an interim study report). A 10 year follow up plan will be developed that describes: calculation of sensitivity and specificity based on 10 year cardiac outcomes and the measures to limit the number of patients lost to follow-up. A final study report will be submitted upon completion of the 10 year period for all patients, exclusive of premature discontinuations due to death or any subject's termination of participation.

Study 3: This study should retrospectively collect data from multiple clinical sites to evaluate the performance (sensitivity and specificity) of Tc99m Sestamibi cardiac imaging in patients with known Kawasaki disease, by using X-ray angiography as the truth standard. Pediatric patients with known or suspected Kawasaki disease (“classical” or “incomplete”) from the proposed clinical sites should be screened for enrollment. The search should cover a period of 10 years prior to initiation of the study (defined as the date of amended protocol: June 30, 2006). All Technetium Tc99m Sestamibi cardiac images from the identified patients must be screened. Studies from patients who have undergone both rest and stress MPI (rest-stress, stress-rest, or stress only) and X-ray angiography within 3 months of each other must be sent to a core laboratory for blinded evaluation. Both exercise and pharmacologic stress procedures are acceptable. In addition, medical records should be carefully reviewed. A plan must be provided for the collection and evaluation of adverse events that occurred during or within 3

days post myocardial perfusion imaging (MPI) procedure. Additional data collected should include demographics, medical history and vital signs. Statistical analysis will be done on images from patients who have had both stress (exercise or pharmacological) and rest MPI in addition to X-ray angiography.

Age Groups to be studied:

Study 1: Two independent groups of pediatric patients:

- 4 years to < 12 years
- ≥ 12 years to < 17 years

Study 2: Two independent groups of pediatric patients:

- 4 years to < 12 years
- ≥ 12 years to < 17 years

Study 3: Pediatric patients:

- 1 month to < 17 years

Number of Patients:

A sufficient number of patients of both sexes to detect a clinically meaningful treatment effect must complete the studies. Pediatric patients must be approximately evenly distributed between sexes based on the prevalence of the disease within the sexes. There must be reasonably equal numbers of patients in the age groups and patients must be reasonably distributed within the age ranges and race/ethnic groups. Gender, age and race/ethnic enrollment should reflect the prevalence of the disease.

Study 1: A minimum of 24 patients will be evaluated for safety and for either dosimetry, or pharmacokinetics (biodistribution in blood and urine). This will include at least 12 patients in each group (children aged 4-11 years; adolescents aged 12 to < 17 years). Of these, at least 6 patients in each age group will be studied at rest and at least 6 will be studied during stress (four cohorts-child rest, child stress, adolescent rest, adolescent stress). Approximately 6 patients in each of these cohorts should be evaluable for dosimetry or pharmacokinetics. At least 10 patients will be evaluated for both, dosimetry and pharmacokinetics. All patients will be assessed for safety.

Study 2: There must be a minimum of 60 evaluable patients in the study with at least 20 in each age group. In addition, a minimum of 20 patients need to have Technetium Tc99m Sestamibi cardiac imaging scans with demonstrated myocardial perfusion abnormality(ies).

Study 3: Based on the medical record system at each proposed clinical site, the sponsor must develop a plan (search strategy) to identify all known or suspected Kawasaki disease patients aged <17 years who have been evaluated with Technetium Tc99 Sestamibi cardiac imaging procedures and x-ray angiography (within 3 months of each other) within 10 years prior to initiation of the study (defined as the date of amended protocol: June 30, 2006). The plan must be designed to meet all three of the following criteria:

1. A minimum of 300 patients with any Technetium Tc99 Sestamibi cardiac imaging procedures (rest, exercise stress, or pharmacological stress) must be screened;

2. A minimum 60 eligible patients (KD; rest-stress, stress-rest, or stress only Tc99m sestamibi cardiac MPI; and X-ray angiogram within 90 days) must be enrolled;
3. All available X-ray angiography and rest-stress, stress-rest, or stress-only images from eligible patients must undergo a Blinded Read.

Patient Evaluation and Study Endpoints:

Dosimetry and Pharmacokinetics (Biodistribution)

Study 1: The following dosimetry and PK parameters must be calculated.

For each dosimetry patient, time-activity curves must be obtained for liver, spleen, lungs, heart, kidneys, urinary bladder, GI tract, the whole body and any other organ that may be identified visually, as well as for the appropriate background regions. Time-dependent image counts must be derived based on a region-of-interest (ROI) analysis of imaging data. Corrections must be applied for overlapping organs and for background counts. Data must be converted to fractional injected Technetium Tc99m Sestamibi radioactivity values at each time point for each organ using the assayed radioactive source and appropriate correction for attenuation. In addition, blood and urine samples must be counted to assess Technetium Tc99m Sestamibi radioactivity levels.

The radiation dose to various organs must be estimated using the medical internal radiation dose (MIRD) method. Absorbed radiation dose must be determined for the lungs, heart, liver, spleen, kidney, bone marrow, skeletal muscle, thyroid, gonads, bladder wall, GI tract, whole body and other organs included in age-appropriate MIRD pediatric phantoms. The effective dose equivalent (EDE) and effective dose per unit administered activity must also be calculated.

For each pharmacokinetic patient, blood and urine samples must be counted to assess technetium Tc99m Sestamibi radioactivity levels. The blood area under the curve (AUC, presented as percent injected dose (%ID-hours), and the terminal phase elimination half-life and mean residence time must be calculated for technetium Tc99m Sestamibi.

Efficacy

Study 2: Technetium Tc99m Sestamibi images must be graded by blinded independent readers using an established scoring system to be defined by the protocol. The scans must be compared to a composite event endpoint of hospitalization of cardiac etiology, coronary intervention, development of congestive heart failure, myocardial infarction or cardiac death. The predictive value of Technetium Tc99m Sestamibi imaging will be based upon comparison to the occurrence of the composite cardiac endpoint. Additionally, exploratory analyses will describe performance characteristics relative to any available angiographic data.

Study 3: The primary endpoints are sensitivity and specificity, by using X-ray angiography as the truth standard. For the primary analysis, the criterion for a positive X-ray angiography result must be defined prior to initiating the Blinded Read. Alternative definitions of a positive angiogram may be used in exploratory analyses to determine sensitivity and specificity with respect to the MPI images. These exploratory analyses should be specified in the study statistical analysis plan. X-ray angiograms may be evaluated by only one board-certified radiologist or cardiologist with relevant pediatric

experience. MPI images, however, must be independently evaluated by three qualified physicians with experience in reading Tc99m Sestamibi cardiac perfusion images. All MPI and angiogram image evaluation must be performed in a blinded fashion at a core laboratory. There must be an independent review charter that describes how the blinded read will be performed. Sensitivity and specificity, using X-ray angiography as the truth standard, in the patients with Technetium Tc99 Sestamibi reported for the entire group and the rest-stress, stress-rest, and stress only subgroups cardiac imaging and X-ray angiography must be presented.

Safety

For all studies, safety must be assessed with collection of adverse events and serious adverse events and, for studies 1 and 2, hematologic, chemistry, and routine urinary laboratory parameters must be documented.

After administration of Technetium Tc99m Sestamibi in adults, cases of angina, chest pain and death have occurred. Adverse events that have been reported at a rate of 0.5% or greater include headache, chest pain/angina, ST segment changes, nausea, taste perversion and parosmia. Less frequently reported adverse events include seizure, transient arthritis, angioedema, arrhythmia, dizziness, syncope, abdominal pain, vomiting, and severe hypersensitivity. A few cases of flushing, edema, injection site inflammation, dry mouth, fever, pruritis, rash, urticaria, and fatigue have been reported. Patients in these studies must be monitored for these potential adverse events.

In studies 1 and 2, all patients must be contacted within 12-36 hours of the procedure. In study 2, the sponsor must submit short-term cardiac outcome data at 6 months and plans for routine follow up of all patients over the course of 10 years. The sponsor must submit plans for monitoring and contacting patients for long-term assessment including measures to limit the number of patients lost to follow-up.

Statistical information, including power of study and statistical assessments:

Study 2: Appropriate Statistical methods of analysis must be clearly indicated, consistent with the study design outlined above and consistent with that stated in the FDA Guidance for Industry, Developing Medical Imaging Drug and Biological Products. The point estimates with 95% CI should be provided. . There is no requirement for hypothesis testing in this study.

Study 3: The sensitivity and specificity calculation must be consistent with that stated in the FDA Guidance for Industry, Developing Medical Imaging Drug and Biological Products. The point estimates with 95% CI should be provided. There is no requirement for hypothesis testing in this study. The demographics, including the length and severity of Kawasaki disease, of those patients who are excluded from the primary analysis due to missing images, must be compared to that of those who are included in the analysis.

Drug information

Dosage: One day studies 0.1-0.2 mCi/kg for rest, 0.3 mCi/kg for stress

Two day studies 0.2 mCi/kg for rest and 0.2 mCi/kg for stress on day two

Route of Administration: Intravenous

- Use an age-appropriate formulation in the study(ies) described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.

  Development of a commercially marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.

  If you cannot develop a commercially marketable age-appropriate formulation, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product label upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

  Bioavailability of any formulation used in the studies should be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *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. 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 should 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 December 17, 2007. 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.

Please 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.

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 (301-594-0183) 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, 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 Alice Kacuba, Regulatory Project Manager Team Leader, at 301-796-1381.

Sincerely,

{See appended electronic signature page}

Karen Weiss, M.D.
Deputy 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/

Karen Weiss

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