DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21797
NDA 21798

WRITTEN REQUEST - AMENDMENT #3

Bristol-Myers Squibb Company
Attention: Katherine Takaki, Ph.D.
Director, Global Regulatory and Safety Sciences
5 Research Parkway
Mail Stop 2CW-507
Wallingford, CT 06492

Dear Dr. Takaki:

Please refer to your correspondence dated November 5, 2012, requesting changes to FDA's November 28, 2006 Written Request for pediatric studies for BARACLUDE® (entecavir).

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 November 28, 2006, and as amended on April 23, 2007 and June 28, 2010, remain the same. (Text added is underlined. Text deleted is ~~strikethrough~~.)

Type of studies:

1. Study (or studies) to assess the multiple dose pharmacokinetic (PK) profile of multiple dose levels of BARACLUDE™ (entecavir) in pediatric patients with chronic HBV infection.

2. Randomized, controlled Phase 3 study of safety and efficacy of BARACLUDE™ (entecavir) in pediatric patients with chronic HBV infection treated for 48 to 96 weeks. Dose selection should be based on discussions with the Agency following review of the PK data. Study subjects should have evidence of chronic hepatitis B disease as documented by hepatitis B surface antigen (HBsAg) positivity, hepatitis B e antigen (HBeAg) positivity, measurable HBV DNA in the blood, and evidence of liver inflammation documented by abnormal liver transaminases or liver biopsy. Long-term follow-up to obtain safety data must be included in the study design.

Unless otherwise specified, ~~both~~ treatment-naïve ~~and treatment-experienced~~ patients should be evaluated and ~~randomization~~ randomized in the Phase 3 study~~ should be stratified according to prior treatment status~~.

Resistance

Collect and submit information regarding the resistance profile (genotypic~~ and phenotypic)~~ of clinical isolates at baseline and during treatment from pediatric patients receiving

BARACLUDE™ (entecavir) who experience loss of virologic response. Data pertaining to the development of HBV mutants resistant to BARACLUDE™ (entecavir) should be analyzed for correlates to loss of efficacy, cross-resistance with other drugs, and hepatitis "flares". Submit data in the HBV Resistance Format provided by the Division of Antiviral Products.

Statistical information, including power of study and statistical assessments:

1. Descriptive analyses of pharmacokinetics at all doses, safety, and activity data in HBV-infected pediatric patients. A minimum number of pediatric patients (as stated below) must complete the pharmacokinetic study (or studies) conducted to characterize pharmacokinetics for dose selection. Final selection of sample size for each age group should take into account all potential sources of variability. As study data are evaluated, the sample size should be increased as necessary for characterization of pharmacokinetics across the intended age range.

≥2 years to ≤ ~~<~~6 years: ~~12~~ 10

≥6 years to ≤~~<~~12 years: 8

≥12 years to ≤18 years: 8

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Studies must include an adequate number of patients to characterize pharmacokinetics across the age ranges studied, taking into account inter-subject and intra-subject variability. The number of patients should be approximately evenly distributed across the age ranges studied.

2. A Phase 3 clinical study with a placebo control group should have sufficient power to detect clinically meaningful differences in efficacy between drug and placebo in patients completing 48 weeks of treatment. An active-controlled non-inferiority trial should have sufficient power to rule out significant difference(s) in virologic efficacy between the treatment arms. This number of pediatric patients should also provide an adequate sampling to assess safety of the drug as noted above.

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 November 28, 2006, as amended by this letter and by previous amendments dated April 23, 2007 and June 28, 2010, must be submitted to the Agency on or before November 30, 2013, 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 BARACLUDE® (entecavir) 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, please contact Elizabeth Thompson, M.S., Regulatory Project Manager, at (301) 796-0824 or via email at elizabeth.thompson@fda hhs.gov.

Sincerely,

{See appended electronic signature page}

Edward M. Cox, MD, MPH
Director
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Attachment: Amended Written Request

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Bristol-Myers Squibb Company
Attention: Katherine Takaki, Ph.D.
Director, Global Regulatory and Safety Sciences
5 Research Parkway
Mail Stop 2CW-507
Wallingford, CT 06492

Dear Dr. Takaki:

To obtain needed pediatric information on BARACLUDE™ (entecavir), 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. This revised Written Request supersedes any and all earlier versions.

Type of studies:

1. Study (or studies) to assess the multiple dose pharmacokinetic (PK) profile of multiple dose levels of BARACLUDE™ (entecavir) in pediatric patients with chronic HBV infection.

2. Randomized, controlled Phase 3 study of safety and efficacy of BARACLUDE™ (entecavir) in pediatric patients with chronic HBV infection treated for 48 to 96 weeks. Dose selection should be based on discussions with the Agency following review of the PK data. Study subjects should have evidence of chronic hepatitis B disease as documented by hepatitis B surface antigen (HBsAg) positivity, hepatitis B e antigen (HBeAg) positivity, measurable HBV DNA in the blood, and evidence of liver inflammation documented by abnormal liver transaminases or liver biopsy. Long-term follow- up to obtain safety data must be included in the study design.

Unless otherwise specified, treatment-naïve patients should be evaluated and randomized in the Phase 3 study.

Indication to be studied:
Treatment of chronic HBV infection in pediatric patients

The objective of these studies will be to determine the pharmacokinetic and safety profile of BARACLUDE™ (entecavir) across the age range studied, identify an appropriate dose (or doses) for use in HBV-infected pediatric patients, and evaluate the efficacy of this dose (or doses) in patients receiving treatment.

Age group in which studies will be performed:
Pediatric patients from 2 years through 16 years

Study Endpoints:

Pharmacokinetics

Parameters including: C_{max}, C_{min}, T_{max}, t1/2, AUC, and apparent oral clearance.

Safety and tolerability

Safety will be assessed in all studies including those designed primarily to assess PK profile. HBV- infected pediatric patients will be followed for safety for a minimum of 48 weeks at the recommended dose. Patients discontinuing treatment with BARACLUDE™ (entecavir) will be followed for at least 24 weeks.

Evaluation of long-term safety endpoints related to the use of BARACLUDE™ (entecavir) in pediatric patients including assessment of growth, renal function, and the potential for development of cirrhosis and/or hepatocellular carcinoma over a period of 5 years following initiation of treatment must be incorporated into study follow-up. The Division would expect that at least 50% of eligible patients will have data over 5 years of follow-up (on and off treatment). Confirmation that patients are continuing in long-term follow-up will be required, however, submission of these long-term data is not required for fulfillment of this written request."

Efficacy

Virologic efficacy will be determined for each subject after 48 to 96 weeks of treatment with BARACLUDE™(entecavir) using virologic and serologic markers of chronic HBV infection. Efficacy may be measured using a composite endpoint that includes decline in serum HBV DNA ("undetectable" by PCR assay) plus normalization of ALT and/or the proportion of patients who become HBeAg negative during the study period. Any liver biopsy data obtained during the course of the study should be submitted for review.

Resistance

Collect and submit information regarding the resistance profile (genotypic) of clinical isolates at baseline and during treatment from pediatric patients receiving BARACLUDE™ (entecavir) who experience loss of virologic response. Data pertaining to the development of HBV mutants resistant to BARACLUDE™ (entecavir) should be analyzed for correlates to loss of efficacy, cross-resistance with other drugs, and hepatitis "flares". Submit data in the HBV Resistance Format provided by the Division of Antiviral Products.

Drug Information

Dosage form: Age appropriate formulations including 0.5 mg tablets, 1 mg tablets, and oral solution containing 0.05 mg/mL

Route of administration: oral

Regimen: to be determined by development program

Use an age-appropriate formulation in the study (or studies) 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.

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.

Drug specific safety concerns:

Based on available toxicity information with your product, please provide specific safety parameters that your pediatric program will address, including but not limited to:

1. Renal or hepatic toxicity arising during dosing

2. Possible hepatitis “flares” during or following therapy

3. Development of resistance mutations in HBV leading to loss of efficacy of BARACLUDE™ (entecavir) and/or other drugs or to a "flare" of disease

4. Long-term safety issues including growth and development, progression of liver disease, hepatocellular carcinoma, and development of other malignancies.

Safety of BARACLUDE™(entecavir) must be studied in an adequate number of pediatric patients to characterize adverse events across the age range. The safety database must include at least 100 pediatric patients who have received BARACLUDE™(entecavir) for at least 48 weeks.

Statistical information, including power of study and statistical assessments:

1. Descriptive analyses of pharmacokinetics at all doses, safety, and activity data in HBV-infected pediatric patients. A minimum number of pediatric patients (as stated below) must complete the pharmacokinetic study (or studies) conducted to characterize pharmacokinetics for dose selection. Final selection of sample size for each age group should take into account all potential sources of variability. As study data are evaluated, the sample size should be increased as necessary for characterization of pharmacokinetics across the intended age range.

≥2 years to ≤6 years: 10

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2. A Phase 3 clinical study with a placebo control group should have sufficient power to detect clinically meaningful differences in efficacy between drug and placebo in patients completing 48 weeks of treatment. An active-controlled non-inferiority trial should have sufficient power to rule out significant difference(s) in virologic efficacy between the treatment arms. This number of pediatric patients should also provide an adequate sampling to assess safety of the drug as noted above.

Labeling that may result from the study (or studies):

Appropriate sections of the label may be changed to incorporate the findings of the study (or studies), including information regarding dosing, safety, and efficacy of BARACLUDE™ (entecavir) in pediatric patients with chronic HBV infection.

Format of reports to be submitted:

You must submit 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 (or 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 study (ies):

Reports of the above studies must be submitted to the Agency on or before November 30, 2013. 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. Please 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 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 (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.

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 (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).

FDA will post the medical, statistical, and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm328603.htm and publish in the Federal Register 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.

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 entecavir 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:

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- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
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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.

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

/s/

EDWARD M COX
05/31/2013