DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

sNDA 21797/S-18
sNDA 21798/S-19

SUPPLEMENT APPROVAL

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

Dear Dr. Takaki:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received September 20, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for BARACLUDE® (entecavir) 0.5 and 1 mg tablets and BARACLUDE® (entecavir) oral solution, 0.05 mg/mL.

We also refer to your amendments dated:

October 16, 2013	December 24, 2013	March 7, 2014	March 19, 2014
October 24, 2013	January 2, 2014	March 10, 2014	
December 9, 2013	January 30, 2014	March 11, 2014	
December 11, 2013	February 14, 2014	March 17, 2014	

These Prior Approval supplemental new drug applications propose to expand the patient population for treatment to include pediatric subjects two years of age and older with chronic hepatitis B virus infection.

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for the patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for these NDAs, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the carton and immediate-container labels submitted on March 17, 2014, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 21798/S-19**." Approval of this submission by FDA is not required before the label is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement from birth to 2 years because the necessary studies are impossible or highly impracticable. This is because treatment of chronic HBV in patients less than 2 years of age is rarely required.

We note that you have fulfilled the pediatric study requirement for ages 2 years to 16 years for this application.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since BARACLUDE® (entecavir) was approved on March 29, 2005, we have become aware of the potential impact that even relatively minor amino acid resistance-associated substitutions that may emerge during treatment with BARACLUDE® (entecavir) can have on treatment outcomes and future treatment options. Given that the worldwide population of HBV-infected individuals is in the hundreds of millions with a large number living in the US, a relatively minor resistance pathway in a small percentage of those receiving BARACLUDE® (entecavir) could affect a large number of individuals. Infrequently occurring amino acid substitutions were observed in resistance data submitted for pediatric trial AI463189 as well as trial AI463028 and in resistance data submitted for trials AI463085, AI463048, AI463050, AI463085, AI463901, AI463110, and AI463111 in multiple NDA supplements. The impact of these amino acid substitutions has not been fully evaluated. They potentially represent substitutions negatively impacting treatment with BARACLUDE® (entecavir) as well as future treatment options and represent a serious safety risk. Combining resistance data from these clinical trials will strengthen our ability to evaluate the clinical impact these infrequently occurring amino acid substitutions have on treatment outcomes. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of development of clinically significant resistance mutations during treatment with BARACLUDE® (entecavir).

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

2136-1 Submit integrated analyses for genotypic and phenotypic resistance for studies AI463048, AI463050, AI463085, AI463901, AI463110, and AI463111, and

integrated phenotypic resistance analyses for studies AI463028 and AI463189 in SAS format. The virology data should be submitted following the guidance format.

The timetable you submitted on March 10, 2014 states that you will conduct this study according to the following schedule:

Final Report Submission: 12/31/2015

Submit the final reports to your NDAs. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Nina Mani, Regulatory Project Manager, at (240) 402-0333 or the Division's main number at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Jeffrey S. Murray, M.D., MPH
Deputy Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

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

/s/

JEFFREY S MURRAY
03/20/2014