DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-797/S-001
NDA 21-798/S-001

Bristol-Myers Squibb Pharmaceutical Company
Attention: Joan C. Fung-Tomc, PhD
Director, Global Regulatory Affairs
5 Research Parkway
PO Box 5100
Wallingford, CT 06492

Dear Dr. Fung-Tomc:

Please refer to your new drug applications (NDA) dated February 23, 2006, and received February 24, 2006, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BARACLUDE® (entecavir) 0.5 mg and 1.0 mg Film-Coated Tablets and BARACLUDE® (entecavir) 0.05 mg/mL Oral Solution.

We acknowledge receipt of your submissions dated June 8, 2006, June 23, 2006, August 4, 2006, August 14, 2006, August 17, 2006, October 18, 2006, October 25, 2006, November 17, 2006, November 27, 2006, December 1, 2006, December 6, 2006, December 7, 2006, December 8, 2006, December 8, 2006, December 13, 2006, December 15, 2006, January 12, 2007, January 19, 2007, January 26, 2007, January 29, 2007, February 6, 2007, February 12, 2007, and February 13, 2007, and received June 9, 2006, June 26, 2006, August 4, 2006, August 15, 2006, August 18, 2006, October 19, 2006, October 26, 2006, November 20, 2006, November 28, 2006, December 4, 2006, December 7, 2006, December 8, 2006, December 11, 2006, December 15, 2006, December 18, 2006, January 16, 2007, January 22, 2007, January 29, 2007, January 30, 2007, February 7, 2007, February 12, 2007, and February 15, 2007.

These supplemental new drug applications provide for the use of BARACLUDE® (entecavir) 0.5 mg and 1.0 mg Film-Coated Tablets and BARACLUDE® (entecavir) 0.05 mg/mL Oral Solution the treatment of chronic hepatitis B virus infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.

These supplemental new drug applications support inclusion of the following new information:

- 96-week safety and efficacy data of entecavir compared to lamivudine;
- 48-week date in HIV-1/HBV co-infected subjects;
- 96-week resistance data; and
- Data on the susceptibility of entecavir and adefovir to substitutions at rtI169.

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

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and text for the patient package insert.)

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions "**FPL for approved supplement NDA 21-797/S-001 and NDA 21-798/S-001**." Approval of these submissions by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in the original NDA approval letter dated March 29, 2005.

The following new postmarketing commitments were agreed to in your submission dated February 12, 2007. The statuses of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

1. Provide study reports describing anti-HIV activity in cell culture (and PMCs) of entecavir against multiple clinical and laboratory isolates including the RF strain using several different assay systems. Provide plots of the concentration-response data. Provide study reports describing the inhibitory activity of entecavir triphosphate against HIV-1 reverse transcriptase in a biochemical assay. Determine and provide study report of the susceptibility of NL4-3 M184V variant to ETV.

   Final Study Report Date: by May 1, 2007

2. If entecavir is determined to have anti-HIV activity, cell culture combination activity relationships of entecavir with approved NRTIs for HIV should be re-evaluated.

   Final Study Report Date: by July 1, 2007

3. Please check the substitution [redacted] alone without M204V/L180M for entecavir susceptibility.

   Final Study Report Date: by May 1, 2007

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

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 Marsha S. Holloman, BS Pharm, JD, Regulatory Project Manager, at (301) 796-0731.

Sincerely,

{See appended electronic signature page}

Debra B. Birnkrant, MD
Director
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Final agreed-upon package insert and patient package insert

---

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

/s/

Debra Birnkrant
2/23/2007 04:04:00 PM
NDA 21-798, 21-797