

021797 & 021798 - Original Approval - Package. PDF

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Approval Package for:

APPLICATION NUMBER:

21-797

21-798

Trade Name: BARACLUDE

Generic Name: Entecavir 0.5 and 1.0 mg Film-Coated Tablets and 0.05 mg/ml Oral Solution

Sponsor: Bristol-Myers Squibb Pharmaceutical Company

Approval Date: March 29, 2005

Indications: Provides 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 for 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.

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APPROVAL LETTER(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-797
NDA 21-798

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

Dear Dr. Fung-Tomc:

Please refer to your new drug applications (NDA) dated and received September 30, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BARACLUDGE™ (entecavir) 0.5 mg and 1.0 mg Film-Coated Tablets and BARACLUDGE™ (entecavir) 0.05 mg/mL Oral Solution.

We acknowledge receipt of your submissions, including pre-submissions, dated:

June 17, 2004	November 29, 2004	March 4, 2005
July 1, 2004	November 30, 2004	March 7, 2005
July 14, 2004	December 2, 2004	March 8, 2005
July 27, 2004	December 22, 2004	March 15, 2005
August 2, 2004	December 29, 2004	March 18, 2005
August 6, 2004	January 6, 2005	March 21, 2005
August 23, 2004	January 10, 2005	March 22, 2005
September 2, 2004	January 21, 2005	March 23, 2005
September 9, 2004	February 8, 2005	March 24, 2005
September 10, 2004	February 9, 2005	March 25, 2005
September 29, 2004	February 11, 2005	March 28, 2005
November 19, 2004	February 15, 2005	
November 22, 2004	February 25, 2005	

These new drug applications provide for the use of BARACLUDGE™ (entecavir) 0.5 mg and 1.0 mg Film-Coated Tablets and BARACLUDGE™ (entecavir) 0.05 mg/mL Oral Solution for 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.

We have completed the review of these applications, as amended, and have concluded that adequate information has been presented to demonstrate that these drug products are safe and effective for use as recommended in the attached agreed-upon labeling text. Accordingly, the applications are approved effective on the date of this letter.

This approval includes both the 30-count and 90-count packages of oral tablets, even though you do not plan to market the 90-count packages at this time. When you begin to market the 90-count bottle,

please provide the revised labeling (package insert, patient package insert, and immediate container label, *etc.*) in the next annual report.

The final printed labeling (FPL) must be identical to the attached agreed-upon labeling (text for the package insert, text for the patient package insert, and immediate container and carton labels). Marketing these products with FPL that are not identical to the approved labeling text may render the products misbranded and an unapproved new drugs.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January, 1999). 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. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-797" and "FPL for approved NDA 21-798". Approval of these submissions by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric subjects unless this requirement is waived or deferred. We are deferring submission of your pediatric studies ages from birth to 16 years of age until such studies can be conducted.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

1. Deferred pediatric study/substudy under PREA for the treatment of chronic hepatitis B with evidence of active liver inflammation in pediatric subjects ages from birth to 16 years of age. This study will determine the entecavir exposure (pharmacokinetics profile) for pediatric subjects ages from birth through 16 years of age to support dose-selection for the efficacy and safety assessment.

Protocol submission: by December, 2005

Final report submissions: by July, 2007

2. Deferred pediatric study under PREA for the treatment of chronic hepatitis B with evidence of active liver inflammation in pediatric subjects ages from birth to 16 years of age. Using doses selected based on study/substudy in postmarketing commitment 1, conduct a pediatric safety and efficacy study of entecavir with efficacy based on the results of a variety of virologic, biochemical, serologic, and composite endpoints over at least 48 weeks of dosing and safety monitored over 48 weeks.

Protocol submission: by July, 2007

Final report submissions: by December, 2009

Submit final study reports to this NDA. For administrative purposes, all submissions related to this/these pediatric postmarketing study commitment(s) must be clearly designated "**Required Pediatric Study Commitments**".

We remind you of the remaining postmarketing study commitments as agreed to in your submission dated March 29, 2005. These commitments are listed below:

3. Conduct and submit a final study report for a large simple safety study to assess the major clinical outcomes of death, progression of liver disease, and cancer in a broad population of HBV-infected patients using entecavir compared to standard of care over a period of 5 to 10 years of follow-up. The study should be randomized, stratified according to prior treatment, and of sufficient size to detect a 30% difference in cancer outcomes between the two groups. Monitoring by an independent Data Safety Monitoring Board is recommended. Given the anticipated length of the study, it is recommended that the protocol include plans to assess the adequacy of enrollment and submit interim reports of results at yearly intervals.

Protocol submission: by July, 2005

Final report submission: by July, 2016

4. Complete and submit the final study report for Study 048 comparing the efficacy and safety of entecavir to adefovir in patients with chronic HBV and decompensated liver disease.

Protocol submission: Study ongoing

Final report submission: by October, 2008

5. Conduct and submit a final study report for a larger study of efficacy and safety of entecavir in patients who are post-liver transplant. This study should enroll 50 to 100 patients and include analysis of virologic, biochemical, and serologic endpoints, evaluation of safety, and evaluation of HBV resistance.

Protocol submission: by December, 2005

Final report submission: by December, 2008

6. Complete and submit the final study report for Study 038 evaluating the safety, efficacy, and resistance profile of entecavir in patients with HIV/HBV co-infection.

Protocol submission: Study ongoing

Final report submission: by July, 2006

7. Complete and submit the final study reports for Studies 022, 027, and 026 and evaluate the safety and efficacy of entecavir compared to lamivudine during the second year of continued blinded study drug dosing.

Protocol submission: Studies ongoing

Final report submissions: by October, 2006

8. Complete and submit the final study reports for Studies 901 and 049 to obtain long-term dosing (> five-years for some subjects) and follow-up data (> five-years for some subjects) on entecavir use in subjects rolled-over from the Phase-2 and Phase-3 clinical trials to address the following issues:

- maintenance of virologic suppression;
- durability of HBeAg seroconversion and the rate of new events;
- risk of drug-related adverse events including malignancy; and
- risk for development of resistance to entecavir.

Protocol submission: *Studies ongoing*

Final report submission: *by July, 2011*

9. Continue to perform genotypic and phenotypic analyses of HBV DNA from patients receiving long-term entecavir therapy in ongoing clinical trials 022, 026, 027, 038, 048, and 901. Provide 96-, 144-, and 240-week data on the genotypic and phenotypic analyses of isolates from entecavir-treated patients with chronic HBV who experienced virologic rebound in serum HBV DNA levels in both the nucleoside-naïve and the lamivudine-resistant studies.

Protocol submissions: *Studies ongoing*

Report submissions: *by March 29, 2006 and submitted annually, thereafter,
summary reports of overall consecutive resistance analyses.*

10. Conduct and submit a final study report for a study to evaluate the safety, efficacy, and resistance profile of entecavir used in combination with another oral anti-HBV therapy in treatment-naïve and treatment-experienced patients with chronic HBV to determine if there is any added benefit of combination therapy.

Protocol submission: *December, 2005*

Final report submission: *December, 2009*

11. Determine the *in vitro* susceptibility to entecavir and adefovir of substitutions at rtI169 alone and in the context of lamivudine- and entecavir-associated resistance mutations. Also, determine the *in vitro* susceptibility to entecavir of tenofovir-associated resistance substitutions at rtA194 in a lamivudine-resistant background.

Final report submission: *July, 2006*

12. Conduct and submit a final study report to evaluate the use of entecavir in treatment of chronic HBV infection in minority racial/ethnic groups that were under-represented in the pivotal clinical trials (Blacks/African Americans, Hispanics).

Protocol submission: *by December, 2005*

Final report submission *by December, 2008*

Submit clinical protocols to your IND for this product. Submit non-clinical and chemistry, manufacturing, and controls protocols, and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing**

**Study Commitment Protocol”, “Postmarketing Study Commitment Final Report”, or
“Postmarketing Study Commitment Correspondence.”**

During a January 25, 2005, teleconference with DAVDP, you agreed to submit Periodic Safety Update Reports (PSURs) every 6 months for the first 5 years of marketing as well as Periodic Adverse Drug Event Reports (PADERs) every 3 months for the first 3 years of marketing. A summary and analysis of reported malignancies, serious hepatic events, and post-treatment exacerbations of hepatitis from ongoing clinical trials, observational studies, and spontaneous reporting should be included every 6 months in the PSUR.

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 electronic copy to DAVDP and two electronic copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, (DDMAC) HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of each drug product when it is available to both DAVDP and DDMAC.

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

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call Marsha S. Holloman, BS Pharm, JD, Regulatory Health Project Manager at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Mark J. Goldberger, MD, MPH
Director
Office of Drug Evaluation IV
Office of New Drugs
Center of Drug Evaluation and Research

Enclosure: Attached Agreed-upon Labeling [PI, PPI, Carton and Container starting on next page.]

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

/s/

Edward Cox
3/29/05 04:52:46 PM
for Mark J. Goldberger, MD MPH