DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-567/SE-002

Bristol-Myers Squibb
Attention: Margo Heath-Chiozzi, M.D.,
Executive Director, Regulatory Science
5 Research Parkway
PO Box 5100, Mailstop 3Sig-515
Wallingford, CT 06492

Dear Dr. Heath-Chiozzi:

Please refer to your new drug application (NDA) dated October 30, 2003, received October 30, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for atazanavir (REYATAZ) 100mg, 150mg, 200mg tablets.

We acknowledge receipt of your submissions dated:

October 30, 2003, December 23, 2003, January 21, 2004, January 26, 2004, January 29, 2004, February 5, 2004, February 10, 2004, February 18, 2004, March 9, 2004, March 30, 2004, April 9, 2004, April 26, 2004, May 7, 2004, June 18, 2004, July 1, 2004, and July 2, 2004.

This supplemental NDA is being approved for a new dosing regimen of REYATAZ 300mg/ritonavir 100mg once daily for treatment in HIV-infected antiretroviral-experienced patients.

We completed our review of this application as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text with the minor editorial revision listed below:

Table 11, entry for "Oral contraceptives" changed to "Hormonal contraceptives," as follows:

Hormonal contraceptives: ethinyl estradiol and norethindrone	↑ ethinyl estradiol ↑ norethindrone	Coadministration of REYATAZ/ritonavir with hormonal contraceptives has not been studied. However, higher doses of ritonavir, without REYATAZ, decrease contraceptive steroid concentrations. Because contraceptive steroid concentrations may be altered when REYATAZ or REYATAZ/ritonavir is coadministered with oral contraceptives or with the contraceptive patch, alternate methods of nonhormonal contraception are recommended.

Except for the additional revision noted above, the final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, text for the patient package insert, immediate container and carton labels) and submitted labeling (package insert submitted July 1, 2004, patient package insert

submitted July 1, 2004) and must be formatted in accordance with the requirements of 21 CFR 201.66. These revisions are terms of the approval of this application. Marketing the product with FPL that is not identical to the approved labeling text and the agreed upon editorial revision as stated above may render the product misbranded and an unapproved new drug.

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 this submission "**FPL for approved NDA 21-567/SE-002**." Approval of this submission 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 patients unless this requirement is waived or deferred. We are waiving the pediatric study requirement for ages < 3 months and deferring pediatric studies for ages ≥ 3 months to 18 years for this application.

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

1. A pediatric study or studies under PREA for the treatment of HIV infection in pediatric patients ages ≥ 3 months to 18 years to determine safe and appropriate dosing.

   Final Report Submission: October 31, 2006

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 your postmarketing study commitments in your submission dated July 1, 2004. This commitment is listed below.

1. Submit an integrated safety review of the following events:

   - Hematological events including anemia, hemolytic anemia, thrombocytopenia, thrombic thrombocytopenic purpura (TTP), thrombocytopenic purpura (TP), pancytopenia. For these events please include the subjects with laboratory abnormalities not otherwise classified as an adverse event.
   - Allergic reaction, hypersensitivity
   - Depression, suicide
   - Cardiac events and ECG abnormalities not otherwise classified as an adverse event.
   - Renal abnormalities. The review will include a summary of events by subjects who received or did not receive concomitant tenofovir

   This safety review will include both serious and nonserious adverse events reported in phase I/II and III clinical trials, in the early access program, and serious adverse events

identified in the first year of marketing approval. The review will include a patient narrative for each case, a completed table as described in the January 21, 2004 correspondence, and a summary of events in patients receiving atazanavir compared to atazanavir and ritonavir.

Protocol submission: Not applicable
Study start: Not applicable
Final report submission within 6 months of the date of this letter

We also remind you of your open postmarketing study commitments referenced in the corrected approval letter for atazanavir (REYATAZ) dated June 20, 2003.

Submit clinical protocols to your IND for this product. Submit nonclinical 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 Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. 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:

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

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, please call Anthony DecCicco, R.Ph., Chief, Project Management, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Jeffrey Murray, M.D.
Deputy Director
Division of Antiviral Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

Jeffrey Murray
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