CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-567

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-567

Bristol-Myers Squibb
Pharmaceutical Research Institute
5 Research Parkway
P.O.Box 5100
Wallingford, CT 06492-7660

Dear Ms. Piccirillo:

Please refer to your new drug application NDA 21-567 dated December 20, 2002, received December 20, 2002 submitted under section 505(b)/pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for REYATAZ (atazanavir) 100mg, 150mg and 200mg capsules.

We acknowledge receipt of your submissions dated December 20, 2002, January 17, 2003, February 3, 2003, February 19, 2003, February 26, 2003, February 27, 2003, February 28, 2003 (4), March 4, 2003, March 5, 2003, March 6, 2003, March 7, 2003, April 1, 2003, April 3, 2003, April 8, 2003, April 10, 2003, April 11, 2003 (2), April 14, 2003, April 24, 2003, May 1, 2003, May 5, 2003, May 6, 2003, May 15, 2003, May 23, 2003, May 30, 2003, June 6, 2003 (2), June 9, 2003, June 13, 2003 (3), June 17, 2003, and June 19, 2003.

This new drug application provides for the use of REYATAZ (atazanavir) 100mg, 150mg and 200mg capsules in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults.

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

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert and the patient package insert), also submitted on June 19, 2003, and submitted immediate container and carton labels submitted on December 20, 2002. 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.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submission 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 ten submissions as "FPL for approved NDA 21-567." Approval for this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing study commitments in your submission dated June 19, 2003. These commitments are listed below.

1. Submit analysis of protease cleavage sites in ATV- resistant patients from ongoing studies 034, 043 and 045.

   Protocol submission - Not Applicable
   Study start - Ongoing
   Final report submission within 12 months of the date of this letter.

2. Test the activity in vitro of atazanavir against multiple clinical isolates of non-clade B subtypes of HIV-1 and HIV-2.

Protocol submission - Not Applicable
Study start - Ongoing
Final report submission within 12 months of the date of this letter.

3. Complete ongoing carcinogenicity studies in mice and rats and submit final reports.

Protocol submission - Completed
Study start - Ongoing
Final reports submission within 9 months of the date of this letter.

4. Conduct a drug-drug interaction study to explore dosing recommendations for the coadministration of atazanavir and nevirapine and of atazanavir/ritonavir and nevirapine.

Protocol submission within 6 months of the date of this letter.
Study start within 10 months of the date of this letter.
Final report submission within 30 months of the date of this letter.

5. Evaluate the pharmacokinetics of atazanavir when co-administered with histamine H2 receptor antagonist.

Protocol submission within 3 months of the date of this letter.
Study start within 7 months of the date of this letter.
Final report submission within 24 months of the date of this letter.

6. Evaluate the pharmacokinetics and safety of atazanavir when coadministered with interferon and ribavirin in patients infected with hepatitis C virus.

Protocol submission within 13 months of the date of this letter.
Study start within 18 months of the date of this letter.
Final report submission within 36 months of the date of this letter.

7. Determine, in vivo, the extent to which atazanavir inhibits CYP1A2 or CYP2C9, preferably with warfarin, or with theophylline.

Protocol submission within 9 months of the date of this letter.
Study start within 12 months of the date of this letter.
Final report submission within 27 months of the date of this letter.

8. Conduct a pharmacokinetic study of atazanavir in subjects with renal impairment to allow the determination of dosing for this population.

Protocol submission within 4 months of the date of this letter.
Study start within 8 months of the date of this letter.
Final report submission within 39 months of the date of this letter.

9. Assess the long term antiviral efficacy and safety of atazanavir in ARV treatment naive and stable switch patients through the conduct of studies -034, -044, -041 and -067.

Protocol submission - Completed
Study start - Ongoing
Final reports submission within: 12 months of the date of this letter for study -034; 24 months for studies -044, -041; 27 months for study -067.

10. Assess the efficacy and safety of atazanavir when pharmacokinetically boosted with low dose ritonavir in protease inhibitor treatment naive patients.

    Protocol submission within 3 months of the date of this letter.
    Study start within 6 months of the date of this letter.
    Interim 24 week report submission within 24 months of the date of this letter.

11. Using objective measurements (e.g., DEXA and CT scanning, etc.) evaluate the role of atazanavir in fat redistribution through 96 weeks of therapy through the conduct of studies -034/-077 (DEXA and CT scan) and -043 (CT scan).

    Protocol submission - Completed
    Study start - Ongoing
    Final report submission within 39 months of the date of this letter.

12. Evaluate the suspected protease inhibitor class-associated effects of fat redistribution and metabolic abnormalities through the conduct of studies -034/-077 and -043.

    Protocol submission - Completed
    Study start - Ongoing
    Final report submission within 12 months of the date of this letter.

13. Follow a cohort of patients who failed on ATV treatment and developed the I50L mutation on new physician-selected PI regimens for 48 weeks compared to an NNRTI-failure/PI-naïve patient cohort and determine treatment response, baseline genotypes and phenotypes, and genotypes and phenotypes of virologic failures.

    Protocol submission within 9 months of the date of this letter.
    Study start within 12 months of the date of this letter.
    Final report submission within 36 months of the date of this letter.

14. A test (USP<781>) for optical rotation will be developed by fourth quarter 2003. Data will begin to be collected for all commercial batches. Once sufficient data are generated, the data will be reviewed to determine a numerical acceptance criterion and drug substance specification will be updated accordingly.

    Final submission: Within 24 months of the date of this letter (with the annual report)

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."

Furthermore, please note that although the FDA recognizes the following intentions are not postmarketing study commitments, the completion and submission of these agreements are highly encouraged.

- Conduct a drug-drug interaction study to determine dosing recommendations for the coadministration of atazanavir and methadone.
- Conduct a drug-drug interaction study to determine dosing recommendations for the coadministration of atazanavir with tenofovir.
- Evaluate pregnancy outcomes through review of the ARV Pregnancy Registry for three years.

- Evaluate, in vitro, the potential for atazanavir to inhibit CYP2B6.
- Evaluate, in vitro, the extent that ≤1 μM ketoconazole inhibits atazanavir metabolism.
- Develop educational materials for patients and healthcare workers regarding the avoidance of drug interactions and the management of hyperbilirubinemia in atazanavir treated patients.
- Provide a final safety report for the Study AI424900 after study closure.
- Perform genotypic and phenotypic monitoring of isolates from patients in ongoing studies -034, -044, -041, -067, -097, -100 (ARV treatment naïve) who experience loss of virologic response.
- Perform genotypic and phenotypic monitoring of isolates from patients in ongoing studies -043, and -045 (previously ARV experienced) who experience loss of virologic response.

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

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

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

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

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 Vasavi Reddy, RPh., Regulatory Project Manager at 301-827-2413.

Sincerely,

{See appended electronic signature page}

Mark J. Goldberger, M.D., MPH
Director/ODEIV
Center for Drug Evaluation and Research
Food and Drug Administration

Attached Files
1. FPL
2. PPI

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

/s/

Mark Goldberger
6/20/03 02:00:00 PM