

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-822

OTHER ACTION LETTER(s)



NDA 21-822

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Nancy L. McKay, P.E.
Senior Associate Director, Drug Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368

Dear Ms. McKay:

Please refer to your new drug application (NDA) 21-822 dated December 21, 2004, received December 22, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aptivus® (tipranavir) oral solution, 100 mg/mL.

We acknowledge receipt of your submissions dated: May 10, 2005, May 11, 2005, May 13, 2005 (2), May 16, 2005, June 3, 2005 and June 7, 2005.

We completed our review of this application, as amended, and it is approvable. Neither the single-dose relative bioavailability Study 1182.45 nor the Phase I/IIa study in pediatric patients (Study 1182.14) contained in your application provide adequate data to support approval of NDA 21-822 for tipranavir oral solution.

Approval of this application could be supported by evaluating the relative bioavailability of the two dosage forms after multiple doses at steady-state. The single dose relative bioavailability study contained in your application is inadequate. Tipranavir is a dual substrate of CYP3A and P-gp and steady state concentrations of tipranavir depend on the net effect (induction or inhibition) on CYP3A and P-gp. The capsules and oral solution contain different excipients that may have different effects on CYP3A and P-gp; the capsules contain Cremophor EL and the solution contains vitamin E polyethylene glycol succinate. Thus, it is difficult to predict relative bioavailability of these two dosage forms from single-dose data due to the complex enzyme/transporter interactions during absorption.

In the absence of adequate bioequivalence data or relative bioavailability data, the approval of this NDA could be supported with additional clinical data. However, NDA 21-814 (tipranavir capsules) does not include sufficient data to recommend a clinically effective dose of tipranavir oral solution. Although your application includes data from pediatric patients receiving the oral solution in ongoing Study 1182.14, the study results are limited and incomplete. The application does not include adequate exposure data, safety data, or efficacy data to recommend a clinically effective dose of the tipranavir solution for use in pediatric patients.

Therefore, before the application may be approved, you must address the requests listed below to resolve the deficiencies described in this letter.

1. Provide steady-state relative bioavailability or bioequivalence data for the oral solution compared to the capsules.
2. In the absence of acceptable bioequivalence or relative bioavailability data for tipranavir oral solution compared to the capsules, provide adequate exposure data in the relevant patient population that demonstrate that the selected dose of the oral solution achieves tipranavir concentrations similar to those achieved following administration of tipranavir capsules at a dose of 500 mg with 200 mg ritonavir twice daily in adult patients. We note that if you choose to provide exposure data from pediatric patients, you also need to provide data on the safety and activity of Aptivus (tipranavir) in HIV-infected pediatric patients. Additional data from your study 1182.14 may possibly provide such information on the safety and activity of tipranavir overall in the pediatric population.

We encourage you to discuss your plans to address the above deficiencies with the Division of Antiviral Drug Products.

In addition, it will be necessary for you to submit draft labeling to incorporate information from these studies. If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

In addition, as required by 21 CFR 314.550, submit three copies of all promotional materials including promotional labeling and advertisements that you intend to use within 120 days following approval of this product. Submit all proposed materials in draft or mock up form, not final print. Send one copy to the Division of Antiviral Drug Products and two copies of both the promotional materials and the proposed package insert directly to:

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

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Antiviral Drug Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

NDA 21-822

Page 3

If you have any questions, please contact Tanim Sinha, M.S., Regulatory Health Project Manager, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Mark Goldberger, M.D., M.P.H.
Director
Office of Drug Evaluation IV
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/

Edward Cox
6/22/05 05:07:52 PM
for Mark J. Goldberger, MD, MPH