

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-822

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-822

Boehringer Ingelheim Pharmaceuticals, Inc.
Attention: Mr. Charles Mazzarella
Associate Director, Drug Regulatory Affairs
900 Ridgebury Rd
P.O. Box 368
Ridgefield, CT 06877-0368

Dear Mr. Mazzarella:

We acknowledge receipt on December 20, 2007, of your resubmission, with letter date of December 20, 2007 to your new drug application for APTIVUS (tipranavir) Oral Solution.

We consider this a complete, class 2 response to our June 22, 2005 action letter. Therefore, the user fee goal date is June 21, 2008.

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 note that you have submitted pediatric studies with this application for pediatric patients > 2 years to 18 years of age. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

If you have any questions, call Jaewon Hong, PharmD, Regulatory Project Manager, at (301) 796-2013.

Sincerely,

{See appended electronic signature page}

Anthony DeCicco, R.Ph.
Chief, Project Management Staff
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Tony DeCicco
2/26/2008 01:50:56 PM



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIV

FACSIMILE TRANSMITTAL SHEET

DATE: May 17, 2006

To: Nancy L. McKay	From: Anne Marie Russell
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Antiviral Products
Fax number: 203-791-6262	Fax number: 301-796-9883
Phone number: 203-791-6759	Phone number: 301-796-2014
Subject: Response to March 27, 2006 pre-sNDA teleconference request for NDAs 21-814 and 21-822	

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service
Division of Antiviral Drug Products
Food and Drug Administration
Silver Spring, MD 20903

MEMORANDUM OF TELEPHONE FACSIMILE CORRESPONDENCE

Date: May 19, 2006
To: Nancy McKay, Senior Associate Director, Drug Regulatory Affairs
Address: Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road
PO Box 368
Ridgefield, CT 06877

From: Anne Marie Russell, Ph.D., Regulatory Project Manager

Through: Andrea James, M.D., Medical Reviewer
Derek Zhang, Ph.D., Clinical Pharmacology Reviewer

Concur: Debra Birnkrant, M.D., Division Director
Kendall Marcus, M.D., Medical Team Leader
Kellie S. Reynolds, Pharm.D., Clinical Pharmacology Team Leader
Virginia Behr, Chief Project Management Staff
David Roeder, Associate Director for Regulatory Affairs

NDA: 21-812 (capsules) and 21-822 (oral solution)
Drug: tipranavir
Subject: Response to March 27, 2006 pre-sNDA teleconference request

The following comments are being conveyed on behalf of the Division of Antiviral Products and are directed towards your March 27, 2006 submission. Your submission included your proposal to respond to DAVP's approvable letter for NDA 21-822 issued on June 22, 2005 and your plan to submit additional supplements to both NDAs.

1. Your proposed plan for submission of an efficacy supplement to NDA 21-814 for the use of tipranavir capsules in the pediatric population is acceptable.
2. Your proposed plan for submission of an efficacy supplement to NDA 21-822 for use of tipranavir oral solution in the pediatric population does not follow the Guidance for Industry: "Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fee." As per this guidance, "If the original application is not yet approved, a request for approval of other new indications or claims should be submitted in a separate, original application." Because your original NDA 21-822 application (that is considered pending due to the June 22, 2006 approvable letter) was intended for an

adult indication, your proposal to resubmit the NDA with a pediatric indication is considered a new indication and thus must be submitted as a new NDA application.

3. We acknowledge your plan to submit a supplement in the fourth quarter of 2006 to NDA 21-822 for use of the oral solution in adults. Following the explanation in #2 above, it is most appropriate for you to submit your application for the use of tipranavir oral solution in adults as your response to the NDA 21-822 approvable letter (a Class 2 resubmission).
4. There appears to be a discrepancy in your submissions; the interim analyses submitted with your accelerated approval package indicated that the PK data was collected and analyzed from Week 2 but the March 27, 2006 submission presents the PK data collected and analyzed from Week 4. Please clarify if all of the pharmacokinetic (PK) information in the pediatric population was collected from pediatric patients dosed with the oral solution. Also, were the interim analyses performed on the PK data from Week 2 or Week 4?
5. As per the protocol, subjects 12-18 years old were to remain on the oral solution until after the Week 4 PK assessments, at which time they were allowed to switch to the capsule. How many of the 52 patients ages 12-18 were still being dosed with the oral solution at the time of the Week 4 PK assessment?

If our response in this telephone facsimile correspondence is clear to you and you determine that further discussion is not required, you have the option of canceling the teleconference currently scheduled for May 22, 2006 (contact the RPM). Please note that if there are any major changes to the purpose of the teleconference based on our responses herein, we may not be prepared to discuss or reach agreement on such changes during the teleconference.

We are providing the above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at (310) 796-2014 if you have any questions regarding the contents of this transmission.

Anne Marie Russell, Ph.D.
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

Anne Marie Russell
5/19/2006 03:35:56 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-814
NDA 21-822

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

Dear Ms. McKay:

Please refer to your December 21, 2004 new drug applications (NDAs) received December 22, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tipranavir (TPV) capsules (NDA 21-814) and oral solution (NDA 21-822.)

We acknowledge that these applications were originally submitted on October 22, 2004 and were consequently withdrawn and resubmitted in December 2004.

The following submissions refer to the first submission of the NDAs:

Oct. 27, 2004	Nov. 30, 2004
Oct. 29, 2004	Dec. 03, 2004 (2)
Nov. 01, 2004	Dec. 05, 2004
Nov. 03, 2004	Dec. 06, 2004 (2)
Nov. 12, 2004	Dec. 09, 2004
Nov. 17, 2004	Dec. 17, 2004
Nov. 18, 2004	

The following submissions refer to the resubmission of the NDAs:

Dec. 29, 2004	Feb. 03, 2005
Jan. 04, 2005	Feb. 09, 2005
Jan. 12, 2005	Feb. 10, 2005 (2)
Jan. 13, 2005	Feb. 16, 2005
Jan. 25, 2005 (2)	Feb. 22, 2005
Feb. 02, 2005	

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 22, 2005 in accordance with 21 CFR 314.101(a).

Your applications have been given priority review. The PDUFA user fee goal date is June 22, 2005.

However, in our filing review, we have identified the following potential review issues:

Clinical/Statistical Comments:

1. As you are aware, the FDA reviewers independently analyze datasets as part of the multi-disciplinary and comprehensive review of an NDA. The importance of the FDA reviewers' ability to independently verify the data submitted by the applicant is paramount, and thus reviewability of submitted datasets are essential to the integrity of the NDA review. The FDA clinical and statistical reviewers for your NDA 21-814 have already forwarded numerous queries and comments to you regarding the reviewability of your submitted datasets. We reference our multiple queries sent to you via email and/or facsimile on 11/17/04, 11/23/04, 11/30/04, 12/01/04, 12/02/2004, 12/06/04, 12/08/04, 12/28/04, 01/07/05, 01/11/05, 01/31/05, 02/02/05, 02/08/05, 02/14/05, 02/18/05 which all pertain to dataset reviewability issues. We are in receipt of your responses to our queries/comments and your multiple revised submissions with the latest revised datasets being submitted on February 16, 2005. These subsequently submitted, format-revised and definition-clarified datasets are currently under review. We will continue to forward you our queries/comments regarding the datasets and will expect a timely response to facilitate this priority review of your application. Please keep in mind that periodically, we will not only request to review raw datasets, but also selective source data to clarify, verify, and expand upon the information in the datasets.
2. Starting with the FDA team's realization that deaths of subjects in the TPV pre-approval clinical trials were not being reported in an expedited manner (November 2003), there has been an extensive dialogue between FDA and the members of BIPI regarding deaths of subjects on study. Inconsistencies and missing information with dates of reports, dates of treatments, dates of deaths, reasons for deaths, follow-up information, as well as uncertain attribution of drug-relatedness have contributed to this extensive dialogue. We reference our queries and comments sent to you via email and/or facsimile on 10/20/04 and 11/05/2004, as well as the minutes from the face-to-face meeting between FDA and BIPI on 11/22/2004. We are in receipt of your responses to our queries/comments which include clarifications regarding inconsistencies, retrieval of missing information from source data, and submission of individual case report files for each fatal case. We have also received your recent submission which updates subjects who died on TPV clinical trials as part of your 2-month safety report. In taking a first look at the recent death cases, we have the following additional comments at this time.

- a. There appear to be 8 new deaths in Resist 1; 2 new deaths in Resist 2 (1 was approximately 63 days after discontinuing TPV, so in actuality only 1 on study death for Resist 2); and 3 new deaths on the naive trial, 1182.33 since the June 11, 2004 database cutoff through December 31, 2004. TDF was a background ARV in 10 of the 13 deaths. Renal failure was a part of the clinical picture in 6 of the 13 deaths.
 1. Please conduct a safety analyses examining TDF + TPV given concurrently in your controlled TPV trials.
 2. Please examine possible safety issues with the renal system as follows:
 - Perform the following survival analyses using the Kaplan-Meier method on all subjects in the two RESIST trials through time of safety cutoff date: Time to confirmed increase in serum creatinine ≥ 0.5 mg/dL from baseline (confirmed by laboratory values at two consecutive visits). Please compare and contrast between subjects on TPV vs. control arms and all subjects on TDF + TPV vs. all subjects on no TDF + TPV.
 - b. In your February 22, 2005 submission you state that not all clinical report forms (CRFs) for the fatal cases were included. These CRFs should be submitted to FDA for review at the earliest possible date. Please provide an estimate of when the missing CRFs will be submitted for our review.
3. Extensive drug interactions between tipranavir and other concomitant medications including multiple antiretrovirals have been determined via the review of your pharmacokinetic studies. Please see comments from FDA's clinical pharmacology reviewer included in this letter. In light of these drug interaction issues, we recommend that you perform the following analyses in your RESIST trials.
- a. Please perform subgroup analyses on the primary efficacy endpoint of treatment response at Week 24 for RESIST 1 and RESIST 2 trials for the following subgroups. Use the Intent-to-Treat population (i.e., your FASS24 population) data for the analyses.

Background antiretroviral regimen containing:

1. abacavir (ABC) or no abacavir (ABC)
2. zidovudine (ZDV) or no zidovudine (ZDV)
3. NNRTI or no NNRTI
4. additional non-study PI added (i.e., dual-boosted PI) or no additional non-study PI (i.e., no dual-boosted PI). We recognize that subjects on dual-boosted PI during study will be considered as non-responders by definition.

Present the above subgroup analyses in the following two formats

1. As shown in Table 3.2.1:1 in the Summary of Clinical Efficacy for the ITT population (FASS24)
2. As shown in Table 3.2.1:3 in the Summary of Clinical Efficacy for the ITT population (FASS24)

4. Due to the nature of the study design in your Phase 3 pivotal trials (i.e. open-label study in a salvage population), introduction of systemic bias at all levels from the investigators to subjects is inevitable. Our concern regarding bias in these studies was accentuated when our initial review of your application revealed the post randomization events during the “optimization period” as well as our difficulties in assessing background switch drug regimens via your datasets. We reference our queries/comments which were forwarded to you via email and/or facsimile on 01/07/05, 01/11/05, 01/31/05, 02/02/05, and 02/18/05. We are in receipt of your responses to our queries/comments including revised datasets. We have also held multiple teleconferences with you to clarify some of these issues that are currently under review by the Division. We recommend that as we are undergoing our review, you also re-examine the data for possible sources of systemic bias. In particular, we ask that you verify all subjects who deviated from protocol conduct/specifications were captured using your pre-specified definitions for protocol violation.
5. You state in your cover letter for the 27-volume two month safety update submission on February 22, 2005 that a revised proposed package insert will be submitted to the FDA shortly. Changes to the proposed package insert will include (b) (4) from the Precautions section to WARNINGS. Your safety analyses that provide the rationale for this change are under review by the Division. Furthermore, we recommend that as you revise your proposed package insert, you further consider the following query that was forwarded to you on 02/14/05: “In the original protocol for 1182.22, TPV is classified as a sulfonamide. There is no warning of the sulfonamide component in the current investigator’s brochure or proposed labeling. Please clarify your position on TPV as a sulfonamide and how you propose to instruct subjects with sulfa allergies on TPV use.” We are in receipt of your initial response to this query which you submitted on 02/28/05. We recommend further dialogue regarding this matter before the finalization of your revised proposed package insert. Also, given the extensive drug-interaction issues with TPV, we recommend that you dialogue with our reviewers regarding the Clinical Pharmacology section of your proposed package insert.
6. The safety findings of study 1182.22 are concerning. This study enrolled 51 healthy females who received at least one dose of TPV. Nineteen subjects (37%) prematurely discontinued due to adverse events and the study terminated early due to a concern about possible serum sickness. Since your safety database thus far contains a low percentage of females, it is difficult to determine what the concerning safety signals of 1182.22 in healthy young females translate to in the HIV-infected females of varying immunodeficiency. We recommend that you
 - a. propose an analysis plan that examines gender-related safety differences as thoroughly as possible both from the controlled trials and from your whole current TPV safety database.
 - b. take steps to ensure that female subjects are enrolled into the current treatment naïve trial (please discuss with the Division what these steps will be).

Pharmacology/Toxicology Comment:

7. Please include information on cell viability in the final report on the Sheep Red Blood Cell Plaque Forming Assay study to determine the potential for tipranavir to cause immune suppression.

Clinical Pharmacology Comments:

8. Based on your *in vitro* drug interaction assessment (Report # U03-3576), I/K_i ratios are much greater than 1 for CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Note that for the calculation of I/K_i, we use *in vivo* C_{max} (bound plus unbound) to represent inhibitor concentrations (I). Follow-up *in vivo* evaluations to determine the drug interaction potential with CYP1A2, CYP2C9, CYP2C19 and CYP2D6 drugs are needed. The label will describe the absence of such information. Please provide us with your interpretation of the significance of the *in vitro* findings and describe your plans for *in vivo* evaluations.
9. Based on cross study comparisons, multiple doses of efavirenz administration (600 mg QD) decreased the steady-state tipranavir exposure by about 30-40% compared to tipranavir/ritonavir alone (at either 500/100 or 750/200 mg dose combinations). The current proposed label does not address the potential significance of this interaction. Please update the wording in the label to provide useful instructions to health care providers. Provide your plans for further evaluation of this interaction.
10. Further study may be needed to fully characterize the extent of the interaction between didanosine and tipranavir/ritonavir at the proposed dose level, 500 mg/200 mg, due to the insufficient number of patients in the study conducted. The need for further evaluation will be considered during our review.
11. Study 1182.44 evaluated the effect of single dose rifabutin on the steady-state PK of tipranavir/ritonavir. Since rifabutin is also a CYP3A inducer, the multiple dose administration of rifabutin might shift the balance of induction and inhibition of CYP3A towards more induction, and thus reduce the tipranavir exposure. Please provide us with your interpretation of this potential interaction. Also, indicate whether you plan further evaluations of the interaction between tipranavir/ritonavir and multiple doses of rifabutin.
12. Please update the drug metabolism and drug interaction information in your proposed label. You can refer to the latest Kaletra and Reyataz labels for the both content and format. Areas to address include the following:
 - a. Update Table 1 to include the effects of co-administered drugs on tipranavir exposure, for all drugs evaluated. If the comparison is based on a cross study comparison, that fact should be noted clearly in the table.
 - b. Update Table 10, to include a more complete list of potential interactions. The table needs to include useful information regarding dosing and clinical significance.

NDA 21-814

NDA 21-822

Page 6

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

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

Sincerely yours,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Debra Birnkrant
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NDA 21-822, 21-814



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-814
NDA 21-822

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

Dear Ms McKay:

Please reference your New Drug Applications (NDAs) 21-814 and 21-822 for tipranavir capsules and oral solution and the teleconference between you and your colleagues at Boehringer Ingelheim, Pharmaceuticals and the Division of Antiviral Drug Products on December 17, 2004.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the teleconference outcomes.

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

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF TELECONFERENCE MINUTES

T-CON DATE: December 17, 2004

TIME: 11:00 a.m. EST

APPLICATION: NDA 21-814
NDA 21-822

DRUG NAME: Tipranavir capsules and oral solution

FDA ATTENDEES:	Debra Birnkrant, M.D.	Division Director
	Rosemary Johann-Liang, M.D.	Team Leader
	Andrea James, M.D.	Medical Reviewer
	Neville Gibbs, M.D.	Medical Reviewer
	Rafia Bhore, Ph.D.	Statistics Reviewer
	Tanima Sinha, M.S.	Regulatory Project Manager
	Elizabeth Thompson	Regulatory Project Manager

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC. (B.I.) ATTENDEES:

Dr. Burkhard Blank
Dr. Mike Tianco
Dr. Martin Kaplan
Dr. Chris Corsico
Ms. Nancy McKay

BACKGROUND/DISCUSSION:

This teleconference was held at the request of Boehringer-Ingelheim Pharmaceuticals, Inc. to discuss their NDAs for tipranavir capsules and oral solution and the direction of these applications.

B.I. has decided to withdraw their NDAs on December 21, 2004, the day before the filing date of December 22, 2004.

The Division of Antiviral Drug Products understands their reasoning for withdrawal.

ACTION ITEMS:

B.I. will provide a draft press release to the Division prior to withdrawal of their NDAs

B.I. will withdraw their NDAs on December 21, 2004.

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/s/

Debra Birnkrant
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-814
NDA 21-822

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

Dear Ms McKay:

We have received your new drug applications (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Tipranavir Capsules and Oral Solution

Date of Application: October 21, 2004

Date of Receipt: October 22, 2004

Our Reference Numbers: NDA 21-814; NDA 21-822

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the applications on December 21, 2004 in accordance with 21 CFR 314.101(a).

We will review these applications under the provisions of 21 CFR 314 Subpart H (accelerated approval). Before approval of this application, you must submit copies of all promotional materials, including promotional labeling as well as advertisements, to be used within 120 days after approval.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

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 note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application. Once the application has been filed, we will notify you whether we have deferred the pediatric study requirement for this application.

Please cite the NDA numbers listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:

Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Division Document Room, N-115
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products, HFD-530
Attention: Document Room, N-115
9201 Corporate Boulevard
Rockville, Maryland 20850

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

Sincerely,

{See appended electronic signature page}

Debra Birnkrant, M.D.
Director
Division of Antiviral Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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/s/

Debra Birnkrant
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NDA 21-822, 21-814