

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 23, 2005
TO: HFD-530: Division File
FROM: HFD-530: Tanima Sinha, Regulatory Project Manager
SUBJECT: **Clinical Information Request**
NDA 21-814, (tipranavir) capsules

On Friday February 18, 2005, a clinical information request was sent to Boehringer Ingelheim Pharmaceuticals, Inc. via email on behalf of Dr. Melisse Baylor, a secondary clinical reviewer for this application. Below is the information that was requested.

We are unable to determine the first ARV regimen for subjects in study 1182.51 and 1182.52 from the RM dataset due to the large number of blank rows in the RMSTDY column, the even higher number of blank rows in the RMENDY column, and the vague reasons for ARV meds in the RMREASON column (such as HIV).

Please clearly label which ARVs were part of the OB regimen; one suggestion for doing this would be to use the term "optimized background" consistently in the RMREASON column. In addition, some ARVs were being used at enrollment and were continued after week 2. These should be identified as both prestudy regimen and OB.

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/s/

Tanima Sinha
2/24/05 11:28:42 AM
CSO
clin request 2-18-05

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 18, 2005
TO: Division File, HFD-530
FROM: Tanima Sinha, Regulatory Project Manager
SUBJECT: **Clinical Pharmacology Information Request**
NDA 21-814, Tipranavir Capsules

On February 16, 2005, the following information request was sent via email to Boehringer-Ingelheim Pharmaceuticals Inc., on behalf of Dr. D. Zhang, the primary clinical pharmacology reviewer for this application. The contents follow:

Dear Nancy,

I hope that you are doing well. I have the following request from Dr. Zhang, the PK reviewer for your application.

Thanks,
Tanima Sinha
Regulatory Project Manager
Food And Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products
301-827-2335

-----Original Message-----

From: Zhang, Derek Yuanchao
Sent: Wednesday, February 16, 2005 10:03 AM
To: Sinha, Tanima
Cc: Zheng, Jenny J
Subject: NDA 21-814

Tanima,

Please ask BIP1 to send us an electronic copy of the code (ctl file) for PPK analysis for Study 1182.52 alone. Thanks.

Derek

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/s/

Tanima Sinha
2/24/05 11:02:59 AM
CSO
clin pharm info request 2-16-05

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 16, 2005

TO: HFD-530: Division File

FROM: HFD-530: Tanima Sinha, Regulatory Project Manager

SUBJECT: **Clinical Information Request**
NDA 21-814, Tipranavir capsules

On Monday February 14, 2005, a clinical information request was sent to Boehringer Ingelheim Pharmaceuticals, Inc. via email on behalf of Drs Gibbs, James and Baylor, the clinical reviewers for this application. Below is the information that was requested.

Questions from Dr. Gibbs:

Trials 1182.4, 1182.6 and 1182.51

1. Please provide results of autopsy on Patient # 0215/BI case # 2001-BP-01639/Trial #1182.6. Patient expired []
2. Please provide the baseline hematology labs and post TPV labs on Pt #135. The subject arrested and died during Head CAT Scan on [] The Investigator reported the cause of death as "intracerebral hemorrhage" - (Clinical Narratives, Appendix 5, page 20 of 996). Did the CAT scan head reveal any lesions? Was an Autopsy performed? If so, please provide the autopsy report.
3. Pt #213 was hospitalized with Acute-on-Chronic Renal Failure. At what point of this patient's hospitalization were the ARV medications withheld? Your narrative summary states that "the patient was contacted to resume all medications at previous doses 16Feb01." How did the subject respond to this re-challenge with ARV medications?
4. Pt #1168: Case ID # 2001-BP-01871(0)
Please provide baseline and in- study labs for this subject. Please provide further details of the subject's diagnosis of "Gastrointestinal Hemorrhage NOS" and "Renal Impairment NOS."

5. Pt #212: Case ID No. 2001-BP- 02598(1)
Please provide dose of TPV that subject was started on 14th Jan 2000.
Please provide baseline and in-study hematology labs.
6. The following cohorts were used in study 1182.4:
- TPV 500 mg + RTV 100 mg bid
 - TPV 1250 mg + RTV 100 mg bid
 - SQV 400 mg + RTV 400 mg bid

Please provide a numerical analysis of the following parameters by cohort in 1182.4, expressing the following specific parameters as change from baseline to week 24 weeks, namely:

- Hb
 - Platelet count
 - Total WBC counts, neutrophil and lymphocyte count
 - BUN and creatinine
 - Liver function tests- GGT and triglyceride levels
7. Please provide information supporting the DSMB's decision to discontinue the TPV/r arm of the Study 1182.51.

Question from Dr. James:

8. In the original protocol for 1182.22 TPV is classified as a sulfonamide. There is no warning of the sulfonamide component in the current IB 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.

Question from Dr Baylor:

9. Since TPV is related to the sulfonamides, please provide any additional information on the adverse event of photosensitivity in study subject 2052 in study 1182.22.

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Tanima Sinha
2/24/05 11:20:30 AM
CSO
clinical request 2-14-05

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 09, 2005
TO: Division File, HFD-530
FROM: Tanima Sinha, Regulatory Project Manager
SUBJECT: **Clinical-Stats Information Request**
NDA 21-814, Tipranavir Capsules

On February 08, 2005, an information request for sent via email to Boehringer-Ingelheim Pharmaceuticals, Inc. on behalf of Drs Bhore and Baylor, the statistical and secondary medical reviewer respectively. The contents of that email follow:

Good Morning Nancy,

I hope that you are doing well. I am back for the rest of the month.

I have the following requests from Dr. Bhore and Dr. Baylor.

From Dr. Bhore:

The following request is in reference to RESIST 1 (Study 1182.12) and RESIST 2 (Study 1182.48).

Regarding Discontinuations/Additions/Switches of Antiretrovirals on Study:

In the dataset requested on February 2, 2005, please add the following variables.

Pre-determined T-20 stratum (i.e., assigned T-20 or not assigned T-20)

Actual T-20 stratum (i.e., actually used T-20 or not actually used T-20)

From Dr. Baylor:

TPV study 1182.22:

Please ask BI if they measured temperatures when they checked vital signs in this study.

Question for BI re study 1182.51

Please provide the meaning for code #9 in DSTERM. Only codes 1-8 are listed in the CRF.

Can you tell us where CRF for Patient #2052 in study 1182.22 is?

Please provide a response for Dr. Baylor as soon as possible.

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/s/

Tanima Sinha
2/24/05 01:23:39 PM
CSO
02-08-05' clin info request.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 7, 2005

TO: Division File, HFD-530

FROM: Tanima Sinha, Regulatory Project Manager

SUBJECT: **Clinical-Stats Information Request Clarification**
NDA 21-814, Tipranavir Capsules

On February 02, 2005, a clin-stats request was made to Boehringer Ingelheim, Pharmaceuticals, Inc., via email. Following that email communication, another request was generated to make some clarifications to the first request. Below outlines the clarifications made:

Please disregard request number 3 from the original email and replace it with the following:

3. The following two questions are regarding formats for two datasets in '\2004-12-29\crt\datasets\analysis datasets\PK data\1182_0052'.
 - a. In pk.xpt file, the formats for \$ANALY1F, \$PKQ1F, ACEA1F, SEX1F and YNIF were not found in 'DEFINE.pdf' (in the same sub-directory) or could not be loaded, respectively for variables ANALYTE, PKQ, RACEA, SEX and RANDEL. Please send these formats.
 - b. In nonmem.xpt file, the 'date' is between 37381 and 37459. Therefore, if format Date9. is used, these dates will go beyond year 2062 (SAS day 0 is Jan. 1, 1960). Please explain and specify the format for the variable 'date'.

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/s/

Tanima Sinha
2/24/05 01:18:54 PM
CSO
12-30-04 clin request.

Table 2: RESIST TWO TRIAL – “Optimization (OTMZ) Period”

| | Patient Unique ID# | Date Randomized (mo/date/yr) | Treatment Assignment (Include all drugs initially assigned) | Date Initial Drugs Started (mo/date/yr) | Optimization One Regimen Change (Include all changes) | Date OTMZ One | Optimization Two Regimen Change (Include all changes) | Date OTMZ Two | Optimization Three Regimen Change (Include all changes) | Date OTMZ Three (Add more Columns as needed for more changes) | Date OTMZ Period END S | FINAL Outcome Status of the Subject (Success or Failure) |
|-------|--------------------|------------------------------|---|---|---|---------------|---|---------------|---|---|------------------------|--|
| 1 | | | | | | | | | | | | |
| 2 | | | | | | | | | | | | |
| 3 | | | | | | | | | | | | |
| Et c. | | | | | | | | | | | | |

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Tanima Sinha
2/24/05 11:17:22 AM
CSO
clin info request 1-31-05



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-814

□ □

2-4-05

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) □ □

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 upgrading hepatic toxicity 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.

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 Tanim 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

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 2, 2005

TO: Division File, HFD-530

FROM: Monica Zeballos, Pharm.D. on behalf of Tanima Sinha, M.S.,
Regulatory Project Manager

SUBJECT: Clinical/Statistics Information Request
NDA 21-814, Tipranavir

On Wednesday, February 2, 2005, a clinical/statistical information request was sent to Boehringer Ingelheim, Pharmaceuticals, Inc. via email regarding their NDA 21-814 for tipranavir. The request was sent on behalf of Dr. Kim Struble, the medical reviewer, Dr Melisse Baylor, the medical reviewer, Dr. R. Bhore, the primary statistical reviewer and Dr Susan Zhou, statistical reviewer for this application. Below is the information that was requested.

1. Please clarify why you classified the following subjects responders. These subjects do not appear to have two consecutive 1 log decreases in HIV RNA.

PT ID Wk 8 change Wk 16 change Wk 24 change

Study 48

| | | | |
|------|------------|------------|------------|
| 1041 | -1.8352769 | 0.34697024 | -2.0282127 |
| 1245 | -1.1608897 | -0.7209138 | -1.3881669 |
| 3151 | -1.010991 | -0.6486007 | -1.0163661 |
| 3187 | -1.1846807 | -0.9478441 | -1.1949919 |
| 3274 | -1.0543168 | -0.7697907 | -1.1616309 |
| 4082 | -1.8531893 | -0.9479577 | -1.0001032 |
| 4291 | . | -0.7042988 | -1.6780143 |

Study 12

| | | | |
|------|------------|------------|------------|
| 1194 | -1.162354 | -0.9699694 | -1.1923913 |
| 1702 | -2.3091481 | -0.6303423 | -2.71867 |
| 1717 | . | -0.944017 | -1.1428617 |
| 1931 | -0.2172624 | -0.7796467 | -1.1859108 |
| 1960 | -1.6744018 | 0.15518572 | -1.413489 |
| 2121 | -1.1622839 | -0.8612539 | -1.1622839 |
| 3021 | -1.8090668 | -0.6941562 | -1.0226698 |

3038 -1.5828072 -0.9207183 -1.5495259
3120 -1.4873404 -0.9872048 -1.4873404

2. In addition you classified the following subjects as D/C Before Achieve Viral suppression; however it appears that all these subjects had a week 24 value. Please provide the discontinuation date and clarification regarding the classification.

PT ID #'s 4092, 6008, 1405, 1597 1924

3. The following two questions are regarding formats for two datasets in '\\2004-12-29\crt\datasets\analysis datasets\PK data\1182_0052'.
 - a. In pk.xpt file, the formats for \$ANALY1F, \$PKQ1F, ACEA1F, SEX1F and YN1F were not found in 'DEFINE.pdf' (in the same sub-directory) or could not be loaded, respectively for variables ANALYTE, PKQ, RACEA, SEX and RANDEL. Please send these formats.
 - b. In nonmem.xpt file, the 'date' is between 37381 and 37459. Therefore, if format Date9. is used, these dates will go beyond year 2062 (SAS day 0 is Jan. 1, 1960). Please explain and specify the format for the variable 'date'.

Statistical Queries on APTIVUS (tipranavir) NDA 21-814, N000.

The following Statistical comments/questions refer to RESIST 1 (Study 1182.12) and RESIST 2 (Study 1182.48).

Questions regarding Optimized Background Regimen

4. Were the background antiretrovirals (i.e., background regimen) determined prior to randomization for each patient?
5. If yes, which dataset(s) has(/have) the information on the pre-determined background regimen for each patient.
6. If yes to question 1, was the planned background regimen actually started for each patient at the start of the randomized protease inhibitor (PI)?
7. If no to question 3, how many of the patients in the RESIST 1 and RESIST 2 trials had a delayed start?
8. Please provide this information by treatment group and provide summary statistics on the median time to start of the optimized background regimen (OBR) in both groups.
9. Please provide us references within in the Protocol(s) and Statistical Analysis Plan (s), if any, on definition(s) of optimized background regimen.

Regarding Discontinuations/Additions/Switches of Antiretrovirals on Study:

10. Please provide us the following dataset with the following variables. This dataset may have multiple records per patient in the chronological order that drugs were discontinued, added, or switched.

- Study ID
- Patient ID
- Treatment Group
- PI Stratum
- Study Start Date
- Pre-determined Optimized Background Regimen
- Actual Optimized Background Regimen
- Start Date of the Optimized Background Regimen
- Study Day of the start of Optimized Background Regimen
- Identify whether the Protease Inhibitor (PI) that patient was randomized to discontinued or added (code as: discontinued, or added)
- Name of PI discontinued or added
- Date PI was discontinued or added
- Study day PI was discontinued or added
- Reason PI was discontinued or added
- Identify whether non-PI ARV was discontinued or added (code as: discontinued, or added)
- Name of non-PI ARV discontinued or added
- Date non-PI ARV discontinued or added
- Study day non-PI ARV was discontinued or added
- Reason non-PI ARV was discontinued or added

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/s/

Monica Zeballos
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CSO

Monica Zeballos
2/7/05 10:10:14 AM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 12, 2005
TO: Division File, HFD-530
FROM: Tanima Sinha, Regulatory Project Manager
SUBJECT: **Statistical Information Request Follow Up**
NDA 21-814, tipranavir capsules

The following email was sent to boehringer Ingelheim Pharmaceuticals, Inc. on behalf of Dr. Bhore, the primary statistician for this application.

Good Morning Nancy and Pam,

I hope that both of you are doing well. I am forwarding a message from Dr. Bhore regarding information that was previous requested by her, but we don't seem to have a response to it.

"As requested at one of our teleconferences, please provide us a table showing the database lock dates and length of follow-up of patients corresponding to each of the electronic data submission dates for tipranavir NDA 21-814 that contained efficacy data. The submission dates of efficacy data were 21-Oct-2004, 24-Nov-2004, 05-Dec-2004, 09-Dec-2004, and 29-Dec-2004. During our review we have observed some examples of patient records across these submissions with different lengths of follow-up data. If the requested information has already been provided to us, please give us the reference."

Please let me know when this information will be submitted to the NDA. If you have any questions, please contact me at 301-827-2335. I will be in the office until 11:30 this morning.

Thank you,
Tanima Sinha
Regulatory Project Manager
Division of Antiviral Drug Product
Center for Drug Evaluation and Research
301-827-2335
sinhat@cder.fda.gov

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/s/

Tanima Sinha
2/24/05 11:31:50 AM
CSO
1-11-05 info request

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 07, 2005

TO: Division File, HFD-530

FROM: Tanima Sinha, Regulatory Project Manager

SUBJECT: **Statistical Information Request**
NDA 21-814, tipranavir capsules

On January 07, 2005, the following statistical information request was sent via email to Boehringer Ingelheim, Pharmaceuticals, Inc. on behalf of Dr. Bhore, the primary statistical reviewer for this application.

The following Statistical comments/questions refer to the data for RESIST 1 (Study 1182.12) and RESIST 2 (Study 1182.48).

1. Please refer to your data file SM.XPT called Baseline Antiretrovirals. This file name is a misnomer and unclear to us because this data file does not give the baseline optimized background antiretroviral regimen (ARV) for a patient at Day 0 (start of study). Instead this file provides the names of background drugs taken by the patient prior to baseline and prior to optimizing the background regimen.
2. Please refer to your "raw" data file called RM.XPT (Antiretrovirals on Study) for Studies 1182.12 (RESIST 1) and 1182.48 (RESIST 2).

In particular, consider the data for Patient ID 1182_0012/001001. This patient was randomized to the TPV/RTV treatment group and has received the additional background drugs enfuvirtide (ENF) + lamivudine (3TC) + nevirapine (NVP) + tenofovir (TDF). However, your patient master file shows that the background ARV for this patient was ENF + 3TC + TDF. The dose of nevirapine was apparently tapered. Was nevirapine (NVP) removed from this patient's background at Day 0 or dropped from background later?

With the vertical file structure of RM.XPT file, it is extremely challenging to find out what were the background ARVs for a patient at start of study. How does one identify which drugs form the optimized background antiretroviral (ARV) regimen for a given patient at the start of study (i.e., at baseline)?

3. For each patient, please help us identify which drugs were added/switched to/from a patient's regimen and at what time point during their treatment in the study.

Your raw data file RM.XPT does not clearly identify this, neither does your master patient file submitted on 09-December-2004 specify the switching mechanism for patients. Again, the vertical file structure of your raw data file RM.XPT make it extremely challenging and it may not even be possible to write a statistical program identifying the optimized background ARV regimen of patients, adding and switching of ARV drugs, if any, during the study. Provide us a statistical program for this data file, if you have one.

4. What does the variable VISITNUM taking values 4 and 7 mean in the context of the above questions? Visit numbers 4 and 7 represent Weeks 2 and 16, respectively, in RESIST 1 and RESIST 2 studies.
5. Please give us reference to any other raw data file(s) that address the question of identifying the background ARV drugs and the ARV drugs that were added/switched during the study.

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/s/

Tanima Sinha
2/24/05 12:09:49 PM
CSO
1-7-05 stats request.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 30, 2004
TO: Division File, HFD-530
FROM: Tanima Sinha, Regulatory Project Manager
SUBJECT: **Clinical Information Follow Up.**
NDA 21-814, tipranavir capsules

On December 30, 2004, Boehringer-Ingelheim Pharmaceucials, Inc. was sent via email the following request on behalf of Dr. James, the primary medical reviewer for this application. The contents follow:

Good Morning Nancy and Pam

Happy New Year. Nancy... I hope that you are feeling better. :-)

I am forward more comments from Dr. James regarding your responses... her comments are in 'burgundy' below. If you have problems finding them because the color format didn't forward, please let me know and I can further clarify.

Tanima Sinha

=====

The definition for SMREAS is 'reason'. What exactly does reason stand for? Do you mean what happened with each of the drugs i.e. continued as part of on study treatment versus discontinued.

RESPONSE: Reason is taken from Baseline ARV Medications (All PI and Non-PI) CRF page (page 25 in 1182.12) from the list of values under "Action Taken with ARV Medication". Four choices are provided on the CRF for the investigator to choose from: (1) Drug continued into treatment period, (2) Optimization of background therapy upon randomization, (3) Switch to study PI upon randomization and (4) Other. The "Other" category included any free text comments by the site. The field was to be completed for all ARVs, thus in response to the question of what is meant, it was intended to capture what happened to each of the drugs in the screening regimen with respect to continuation as part of the study regimen. Specifically, (1) captured that the given ARV was continued, (2) captured that the drug was discontinued as part of optimization, (3) specifies switch of the screening PI to the study PI and (4) gave provision for capturing details, i.e. dose modification, however, based on the free text entries provided, some investigators chose to record discontinuation using this code.

FDA Comment: Thanks for the explanation. For future reference, it is most helpful and appreciated if the column definition and the define.pdf file state exactly what it is you are coding. If the column definition said "Action Taken with ARV Medication" and the define.pdf

had numbers 1-4 above spelled out as they are above I would not have had to query you about this.

What does optimization refer to; does it mean the drug was continued as part of the optimized background?

RESPONSE: The optimization code captured that the ARV on the record with a reason of "optimization" was part of the screening regimen but was discontinued for the reason that it was changed and the background regimen was optimized for the study.

If 'cont into treatment' is written under SMREAS can I assume that the drug was continued once the subject was on study?

RESPONSE: We did not utilize this field this way, so, although in almost every case this would most likely be true, to answer this question we would have to do a cross check against the dosing drug records for baseline (SM) and on-study (now RM in response to FDA requests) similar to what you are trying to do (please see response to 6 below).

We did the following on this topic: First we identified the comparator PI (i.e. we did not attempt to address this question for all drugs). Then only for that drug, we cross checked against SM to check for the presence of any drug records for that drug. Because the SM page was intended to only cover the time of the screening period, which is not long, we only checked for the presence of the records and not the dates on the records.

The result of this is provided in the DSRAND datasets in the variable ONAPI (Ongoing Actual PI).

Does SMONGO also mean that the ARV is 'ongoing' while on study

RESPONSE: Unfortunately No. The monitoring manual instructs, in reference to end dates in SM, that "The end date must not be left blank. All ARVs that are continuing into the study treatment must have "cont" entered; otherwise an end date must be entered." The logic used to derive SMONGO was dependent upon this instruction being followed. From your examples below, it is clear that in some cases (e.g. 1182.12, Patient 1736), an end date was written in on the SM page, and the same date was entered as a start date on the AM page (now referred to as the RM dataset in response to FDA requests), without any change in dose. We did not utilize SMONGO in the manner you are attempting to utilize it and did not see this contradiction.

If the two previous bullets are true then why do subjects 4247, 1801, 9318, and 9048 in 1182.48 and subjects 1736, 2161, 2208, 3013, 3042, 3044, 3046, 3049, 3063, 3066, 3081, 3113, 3122, 3196 have 'cont into treatment' under SMREAS but N for no under SMONGO.

RESPONSE: See bullet 4 above. One way this can happen is that CRF shows an end date for the drug on the SM page and the same date (or even the next day) is recorded on the AM page as a start date. Hypothetically, another possible way would be that the reason recorded by the investigator was incorrect, but that does not appear to be the explanation for the cases we have been able to check so far.

FDA comment/question: It appears that with only a couple of exceptions investigators put end dates of 1 day before or after the start of the trial. It is unlikely that these subjects actually had their PI interrupted one day prior or after randomization and then restarted, but please verify. In 2 cases (subject 9048 and 1801) in 1182.48 the end dates are 11 days after and 1,610 days before the start of the trial respectively. Please look into what actually occurred with these subjects.

The comment under SMONGO cannot be correct. Please fix it.

RESPONSE: The current SMONGO does not look at therapy records across the baseline and on-study therapy records to check whether the drug is ongoing in the way Dr. James would like to use it. We have been experimenting with algorithms to do this last evening and this morning. At the moment we can not say for certain if an algorithm will resolve every case Dr. James has highlighted, but along with the algorithm and a new SMONGO flag, we will identify any inconsistencies between the reason stated and results of the algorithm so they can be examined further individually. We estimate that this new flag can be submitted early next week at the latest. In order to avoid delaying Dr. James, as soon as it is finished, we could provide the flag by e-mail slightly earlier if that is desired. At the moment we think we should do this for 1182.12, 1182.48 and possibly 1182.51

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/s/

Tanima Sinha
2/24/05 01:05:23 PM
CSO
12-30-04 clin request.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 28, 2004
TO: Division File, HFD-530
FROM: Tanima Sinha, Regulatory Project Manager
SUBJECT: **Clinical Information Request (2)**
NDA 21-814, tipranavir capsules

On December 28, 2004, another clinical information request was made to Boehringer Ingelheim Pharmaceuticals, Inc. via email on behalf of Dr. James, the primary medical reviewer for this application. The contents follow:

I have another request from Dr. James. Please find the information requested below. Please provide this information by Wednesday morning.

Thank you,
Tanima Sinha
Regulatory Project Manager
Food And Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products
301-827-2335

As I understand it the SM dataset provides the baseline antiretrovirals. In trying to determine which PIs were continued from baseline I have encountered a few problems.

- The definition for SMREAS is 'reason'. What exactly does reason stand for? Do you mean what happened with each of the drugs i.e. continued as part of on study treatment versus discontinued.
- What does optimization refer to; does it mean the drug was continued as part of the optimized background?
- If 'cont into treatment' is written under SMREAS can I assume that the drug was continued once the subject was on study?
- Does SMONGO also mean that the ARV is 'ongoing' while on study
- If the two previous bullets are true then why do subjects 4247, 1801, 9318, and 9048 in 1182.48 and subjects 1736, 2161, 2208, 3013, 3042, 3044, 3046, 3049, 3063, 3066, 3081, 3113, 3122, 3196 have 'cont into treatment' under SMREAS but N for no under SMONGO.

The comment under SMONGO cannot be correct. Please fix it.

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/s/

Tanima Sinha
2/24/05 12:46:09 PM
CSO
12-28-04 info request, (2)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 28, 2004
TO: Division File, HFD-530
FROM: Tanima Sinha, Regulatory Project Manager
SUBJECT: **Clinical Information Request**
NDA 21-814, tipranavir capsules

On December the a clinical information request was made to Boehringer Ingelheim Pharmaceuticals, Inc. via email on behalf of Dr. James, the primary medical review of this application. The contents of that email follow.

Good Morning Nancy,

I hope that you are doing well. I have the following request from Dr. James regarding narratives for various subjects. Please see below for the information request. She would like a response to this by Wednesday morning.

Sincerely yours,
Tanima Sinha
Regulatory Project Manager
Food And Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products
301-827-2335

One of my earlier requests of you was to provide "real narratives". Can you please let us know where you are in meeting that request and let them know that I need to have death narratives separate from SAE narratives, separate from discontinuation narratives? Also I am missing narratives for the following subjects in 1182.12: 1441, 2052, 2280, 2374, 4006, 4073 and the following subjects in 1182.48: 1097, 9328.

I also received a "death narrative" for subject 4184 who was originally enrolled in 1182.48 on the CPI/r arm, discontinued due to an AE and later received TPV through compassionate care. This subject is not listed in any dataset as having died however the CIOMS reports the subject died on [] while on TPV/r. What, if any, study was this subject's death attributed to?

Are there other subjects who died while receiving TPV/r, but are not included in any of the study tallies?

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/s/

Tanima Sinha
2/24/05 12:31:28 PM
CSO
12-28-04 clin request



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

12/21/04

NDA 21-814

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:

We have received your December 20, 2004 correspondence on December 21, 2004 notifying us that you are withdrawing your new drug application (NDA) for tipranavir capsules prior to its filing date.

In accordance with 21 CFR 314.65, this application is withdrawn as of December 21, 2004. If you have paid a user fee, we will refund 75% of your payment.

If you decide to resubmit this application, this withdrawal will not prejudice any future decisions on filing. You may reference information contained in this withdrawn application in any resubmission. Retain the above NDA number for the resubmitted application but obtain a new user fee identification number. The new user fee identification number must be on the check as well as on the User Fee Cover Sheet in the resubmitted application. Submit the check for the appropriate user fee to the following address:

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

For courier delivery, write the NDA number, the FDA Post Office box number (P.O. Box 360909), and the user fee identification number on the check and deliver it to the following address:

Food and drug Administration (360909)
Mellon Client Service Center, Room 670
500 Ross Street
Pittsburgh, PA 15262-0001

If you have any questions, please call Tanima Sinha, Regulatory Project Manager, at 301-827-2335.

Sincerely yours,

{See appended electronic signature page}

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

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/s/

Tony DeCicco
12/21/04 10:54:36 AM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 21, 2004
TO: Division File, HFD-530
FROM: Tanima Sinha, Regulatory Project Manager
SUBJECT: **General request.**
NDA 21-814, tipranavir capsules

On December 20, 2004, the following request was made to Boehringer Ingelheim Pharmaceuticals, Inc via email. The contents of that email follow:

Dear Nancy,

Please reference our telephone conversation this afternoon regarding data submission. The following is from Dr. James, the primary medical reviewer for your applications for tirpranavir.

"When you resubmit your NDA, that you submit one final electronic submission with all of the most current datasets that we are supposed to be using. For example if the most recent death analysis dataset is from 12/5/04, the most recent master dataset is from 12/9/04 and the most recent HIV history dataset is from 10/21/04 then these should all be consolidated on one CD. This is to avoid having different reviewers using different versions of the data."

Sincerely yours,
Tanima Sinha
Regulatory Project Manager
Food And Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products
301-827-2335

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/s/

Tanima Sinha
2/24/05 12:22:55 PM
CSO
general info request 12-20-04



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-814

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┐

12/17/04

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 ┌ ┐ for tipranavir capsules
┌ ┐ 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

DRUG NAME: Tipranavir capsules

| | | |
|-----------------------|-----------------------------|----------------------------|
| 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 the direction of these applications.

B.I. has decided

The Division of Antiviral Drug Products understands their reasoning

ACTION ITEMS:

B.I. will provide

B.I. will

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Debra Birnkrant
12/17/04 01:26:55 PM

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 09, 2004
TO: Division File, HFD-530
FROM: Tanima Sinha
SUBJECT: **Microbiology Information Request**
NDA 21-814, tipranavir capsules

On December 09, 2004, the following email was sent to Boehringer-Ingelheim, Pharmaceuticals, Inc. on behalf of Kimberly Struble, the secondary microbiology reviewer for this application. The contents follow:

Good Morning Nancy,

I have the following comment from Kim Struble regarding the micro responses that were sent on Dec. 3. 2004. Please provide a response as soon as possible.

Thank you,
Tanima Sinha
Regulatory Health Project Manager
Division of Antiviral Drug Products
301-827-2335

Please provide additional information regarding the ARVWK variable, specifically does ARVWK refer to the first activity for a given patient. For example:

PT 3174 - ARVWK = 13.4.
ARVXN1 = 01jul2003 dropped ddi due to AE
ARVXP1 = 27may2003 start date of trial med TPV, 29AUG2003 added APV, 30AUG2003 permanent d/C of trial med TPV.

Therefore, does ARVWK refer to the first activity - meaning dropped DDI or does it refer to the switch from TPV to APV.

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/s/

Tanima Sinha
2/24/05 11:40:04 AM
CSO
12-8-04 micro info request

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 07, 2004
TO: Division File, HFD-530
FROM: Tanima Sinha, Regulatory Project Manager
SUBJECT: **Statistical Information Request**
NDA 21-814, tipranavir capsules

After the initial statistical information request went to Boehringer-Ingelheim, Pharmaceuticals, Inc. via email, the following request was forwarded on behalf of Dr. Zhou, the secondary statistical reviewer for the same application. The contents of that email follow:

Hi,

Please see the following from Dr. Susan Zhou, another statistician reviewer for tipranavir in addition to Dr. Bhore's comments from earlier.

Thanks,
Tanima Sinha

From Dr. Zhou:

We should ask the sponsor to send us a sample SAS program to handle the repeated measurement problems in RN.XPT files. For example, how they compute longitudinal viral load for each patient.

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/s/

Tanima Sinha
2/24/05 12:03:57 PM
CSO
12-06-05 stats request (2)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 07, 2005
TO: Division File, HFD-530
FROM: Tanima Sinha, Regulatory Project Manager
SUBJECT: **Statistical Information Request**
NDA 21-814, tipranavir capsules

On December 6, 2004, the following email was sent to Boehringer Ingelheim, Pharmaceuticals, Inc. on behalf of Dr. Bhore, the primary statistical reviewer for this application. The contents follow:

Good Morning Nancy,

Please see the email below from Dr. Bhore, the statistician for your application for tipranavir. She would like a very prompt response to her query, before our filing meeting.

If you have any questions, please feel free to call me at 301-827-2335

Sincerely,
Tanima Sinha
Regulatory Health Project Manager
Division of Antiviral Drug Products
301-827-2335

The following question concerns your raw data files submitted on November 17, 2004 (FDA receipt date of November 24, 2004) for RESIST 1 and RESIST 2 studies and possibly other studies as well in APTIVUS (tipranavir) NDA 21-814.

Please refer to your RNA (Viral Load) data file called rn.xpt. In this dataset, patients who have viral load measurements at the same visit using both the [] assay and [] assay are vertically stacked. In addition, the date of measurement and the assay description [] is also vertically stacked.

How do we determine which number of the HIV RNA corresponds to which assay in such a vertical file structure? This vertical structure of datasets is difficult to program unless there are appropriate flags to use for transposing the data.

Rafia Bhore, Ph.D.

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/s/

Tanima Sinha
2/24/05 11:45:06 AM
CSO
12-06-04 stats request (1)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 3, 2004
TO: Division File, HFD-530
FROM: Tanima Sinha, Regulatory Project Manager
SUBJECT: **Clinical Pharmacology Information Request**
NDA 21-814, Tipranavir capsules

On December 3, 2004, the following email was sent to Boehringer Ingelheim Pharmaceuticals, Inc., regarding their application for tipranavir

Hi Nancy,

I hope that you are doing well. Please reference an email regarding PK inquiry from Dr. Zhang dated: November 24, 2004, 7:18 am. This is a follow up from that email regarding PK for tipranavir. Dr. Zhang would like an electronic copy of the file for question 2. You can email it to me.

Thank you,
Tanima Sinha
Regulatory Project Manager
Food And Drug Administration
Center for Drug Evaluation and Research
Division of Antiviral Drug Products
301-827-2335

1. []
2. Please provide the control stream (.ctl file) for the population PK study.
3. Are there any updates or changes to the pre-submitted Clin Pharm study reports in the NDA?

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/s/

Tanima Sinha
2/24/05 11:07:30 AM
CSO
clin-pharm info request 12-03-04

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 3, 2004
TO: Division File, HFD-530
FROM: Tanima Sinha, Regulatory Project Manager
SUBJECT: **Clinical Information Request**
NDA 21-814, tipranavir capsules

On December 2, 2004, a clinical information request was sent to Boehringer Ingelheim Pharmaceuticals, Inc., via email on behalf of Dr. James, the primary medical reviewer for this application. The contents of that email are as follows:

1. Please clarify on p 62 vol 1.1 – was the Common Toxicity Criteria used to grade total cholesterol? Was it used to grade anything else?
2. The toxicity tables are referenced, but do they appear in the submission somewhere? If so please tell me where to find them. If not, please send me a copy of all the toxicity tables used.
3. On p. 86 vol 1.1 – Amendment 6 (16 June 2004) reads ‘A note was added concerning serious and life-threatening AEs to the effect that any clinical event considered by the clinician to be serious or life-threatening should be identified as a Grade 4 adverse event’. Does this mean that we can expect to see Grade 3 and Grade 4 events captured separately in the submission of the 48-week data?

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/s/

Tanima Sinha
2/24/05 12:57:24 PM
CSO
12-02-04 info request (2)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 3, 2004

TO: Division File, HFD-530

FROM: Tanima Sinha, M.S., Regulatory Project Manager

SUBJECT: **Clinical Information Request**
NDA 21-814, tipranavir capsules

On December 2, 2004, Dr. Baylor, a secondary clinical reviewer for the above application requested the following information to be sent to the applicant for NDA 21-814 via email. The email was sent to Boehringer Ingelheim, Pharmaceuticals, Inc.

Please use one column that contains information on the treatment period during which the AE occurred (pre, on, or post treatment). We would also like to be able to tell the study day on which the AE occurred. You could have a column with study day of AE and use negative numbers for pretreatment AEs and positive numbers for during treatment. However, this would not allow us to determine the number of days off study drug for those AEs which occurred during the post treatment period. Consider a third column for days off study drug for those AEs which occurred after the treatment period and do not group these study days into cohorts as described in your response.

Dr. James wrote:

11/30/04 query: Treatment period encompasses only the time that the subject is actually on study drug (day 1 = day of first dose through day XX = discontinuation of study drug). The 28-day and 30-day post-treatment time period that you are referring to is specific to AEs, and is a window period that is used to allow AEs that occur during that time to be attributed to study drug. When you give us treatment length or treatment period we expect that time period to **only** include the span of days that the subject was on study drug.

BI Response: In response to your request for treatment periods, we intended to add a column to datasets which labeled pre-treatment data as pre-treatment and on-treatment data as on-treatment. For these two definitions we understand your request. For post-treatment data, these columns could label all post-treatment data with a single post-treatment label; alternatively labels which distinguished between post-treatment up to 3 days, post-treatment from 4 to 28 (or 30 - your choice) days and post-treatment >28 (or 30) days could facilitate various selections for you that could either facilitate reproduction of our displays (allowing the option of combining on treatment and off-

treatment up-to-3-days) or production of your own preferred displays (e.g. perhaps combining AEs on treatment and up to 30 days off treatment).

If this is of no use to you, we will simply label all post-treatment records as post treatment. Unless we hear otherwise, based upon your last response we will not distinguish between various lengths of time off-treatment in labeling records with treatment periods.

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/s/

Tanima Sinha
2/24/05 12:51:16 PM
CSO
12-02-04 info request.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 2, 2004
TO: Division File, HFD-530
FROM: Tanima Sinha, M.S., Regulatory Project Manager
SUBJECT: Microbiology Information Request
NDA 21-814, Tipranavir

On Wednesday, December 1, 2004, a microbiology information request was sent to Boehringer Ingelheim, Pharmaceuticals, Inc. via email regarding their NDA 21-814 for tipranavir. The request was sent on behalf of Dr. L. Naeger, the primary microbiology reviewer for this application and Kim Struble, the secondary microbiology reviewer. Below is the information that was requested. It was also requested that the response be submitted by Friday, December 3, 2004.

For dataset: BASE_RES the following subjects have "other" listed for the treatment outcome column and "introduction of a new ARV to the regimen" for the outcome explanation/reason for DC column. For each subject who started a new ARV during the study, please provide the start date of the medication, visit number and the name of the ARV added to the regimen. For subjects who deleted an ARV or had an in-class substitution for toxicity only and did not start a new ARV please indicate in separate column (comment field) by the subject ID number.

| Study 12 | Start date of medication | Visit Number | Name of ARV | Comment |
|----------|--------------------------|--------------|-------------|---------|
| 1401 | | | | |
| 1412 | | | | |
| 3065 | | | | |
| 3068 | | | | |
| 3110 | | | | |
| 3174 | | | | |
| 3176 | | | | |
| 3186 | | | | |
| 3306 | | | | |
| 4013 | | | | |
| 4021 | | | | |
| 4033 | | | | |
| 4055 | | | | |
| 4103 | | | | |

4178
4221
5052
6131
6137
6170
6209
6224
7014
7016
7144
8049
9025

Study 48

1176
1644
1738
1742
1775
1888
1896
2014
2067
2163
2177
2238
2266
2325
2498
3083

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/s/

Tanima Sinha
12/27/04 10:27:14 AM
CSO
micro request for NDA 21-814.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 2, 2004

TO: Division File, HFD-530

FROM: Tanima Sinha, M.S., Regulatory Project Manager

SUBJECT: Clinical/Statistics Information Request
NDA 21-814, Tipranavir

On Tuesday, November 30, 2004, a clinical/statistical information request was sent to Boehringer Ingelheim, Pharmaceuticals, Inc. via email regarding their NDA 21-814 for tipranavir. The request was sent on behalf of Dr. A. James, the primary clinical reviewer and Dr. R. Bhore, the primary statistical reviewer for this application. Below is the information that was requested.

Comment 1: Based on your second comment, it appears that 'last assessment date' was not captured in the CRF for any of the subjects. Please verify if this is true or false. It also appears that you wish to infer the assessment date from multiple sources within the CRF. Please verify if this is true. If you **did not** capture the 'last assessment date' for any subject in the CRF, we do not want you to infer the 'last assessment date', and therefore no columns pertaining to this subject need to be added to any dataset. If you **did** capture 'last assessment date' for some, but not all subjects please include 'last assessment date' column(s) with the dates for both the primary trial (.12 or .48) and the rollover trial .17. Please label the columns clearly (for example, last assessment date in primary study and last assessment date in rollover study) and populate missing rows with 'unknown' or 'missing'.

Additionally we would like a column that identifies subjects who rolled over from .12 and .48 to .17 in the disposition, demographics, AE, AIDS defining illnesses and death datasets.

Comment 2: We do not want you to infer 'last assessment date', so no, the definition is not acceptable. Please see Comment 1.

FDA Request 1: Please submit a laboratory analysis dataset for each of the Resist trials that includes for each laboratory parameter a baseline value, a last value, a minimum value and a maximum value for each unique subject randomized to study drug. Additional column(s) in this dataset should include randomized treatment arm. See table below for layout example.

| Study | Unique pt. ID | Lab parameter | Units | baseline value | Last value | Minimum value | Maximum value |
|---------|---------------|---------------|-------|----------------|------------|---------------|---------------|
| 1182.12 | 1182.12/1000 | hematocrit | % | 30 | 28 | 23 | 30 |
| 1182.12 | 1182.12/1005 | hematocrit | % | 35 | 35 | 32 | 36 |
| 1182.12 | 1182.12/1000 | glucose | mg/dL | 95 | 165 | 95 | 211 |
| 1182.12 | 1182.12/1005 | glucose | mg/dL | 135 | 150 | 75 | 402 |

Response to 11/30/04 query: Treatment period encompasses only the time that the subject is actually on study drug (day 1 = day of first dose through day XX = discontinuation of study drug). The 28-day and 30-day post-treatment time period that you are referring to is specific to AEs, and is a window period that is used to allow AEs that occur during that time to be attributed to study drug. When you give us treatment length or treatment period we expect that time period to **only** include the span of days that the subject was on study drug.

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Tanima Sinha
12/27/04 10:01:15 AM
CSO
Clin-stats info request for TPV NDA.

10 Page(s) Withheld

11-24-04

✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 24, 2004

TO: Division File, HFD-530

FROM: Tanima Sinha, M.S., Regulatory Project Manager
HFD-530

SUBJECT: Clinical pharmacology information request
NDA 21-814, tipranavir

On Wednesday November 24, 2004, a clinical pharmacology information request was sent to Boehringer Ingelheim, Pharmaceuticals, Inc. via email regarding their NDA 21-814 for tipranavir. The request was sent on behalf of Dr. Derek Zhang, the primary clinical pharmacology reviewer for this application. Below is the information that was requested.

1.
2. Please provide the control stream (.ctl file) for the population PK study.
3. Are there any updates or changes to the pre-submitted Clin Pharm study reports in the NDA?

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/s/

Tanima Sinha
12/27/04 09:44:07 AM
CSO
PK info request to BI re: TPV

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 23, 2004

TO: HFD-530, Division File

FROM: Tanima Sinha, M.S., Regulatory Project Manager

SUBJECT: Clinical Information Request
NDA 21-814, (tipranavir) capsules

On Tuesday, November 23, 2004, a clinical information request was sent to Boehringer Ingelheim, Pharmaceuticals, Inc. via email regarding their NDA 21-814 for tipranavir. This request followed the meeting the Division had with members of Boehringer Ingelheim, Pharmaceuticals, Inc. on Monday, November 22, 2004. The request was sent on behalf of clinical reviewers for this application. Below is the information that was requested.

The following comments were addressed by some reviewers but not all; these comments should be applied to the entire data submission.

1. Please use consistent terms for the different study populations. Provide definitions for each term and include terms that are used in datasets and terms that are used in the text of clinical study reports.
2. Please review all define.pdf files so that all formulas and codes are provided.
3. Please add a column for treatment period and a column for treatment arm to all datasets of all studies.
4. Provide study day for all calendar dates.
5. Provide new datasets for treatment emergent AIDS defining illnesses in RESIST 1 and RESIST 2.
6. Please use collapsed AEs for all AE datasets (one row for an individual AE with a discreet start and stop date).

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/s/

Tanima Sinha
12/23/04 08:55:16 AM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 17, 2004
TO: HFD-530, Division File
FROM: Tanima Sinha, M.S., Regulatory Project Manager
SUBJECT: Statistical Information Request
NDA 21-814, (tipranavir) capsules

On Wednesday, November 17, 2004, a statistical information request was sent to Boehringer Ingelheim, Pharmaceuticals, Inc. via email regarding their NDA 21-814 for tipranavir. The request was sent on behalf of Dr. R. Bhore, the primary statistical reviewer for this application. Below is the information that was requested.

1. The raw datasets in NDA 21-814 have a patient disposition file called DS. How do I identify the following? Specify (or point to) the variable names and datasets.
 - a) Which patients permanently discontinued the study?
 - b) Which patients are in the study and only discontinued treatment?
 - c) What are the reasons for permanent discontinuations?
 - d) What does "NOT Prematurely Discontinued" mean?
 - e) DSTERM variable in the disposition dataset has a category called "Patient Eligible for Randomization". If the patient has no other additional DSTERM classification, are these considered to be study completers? If not, how do we identify the study completers?
2. Why DO NOT the site numbers in the demographics dataset DM, match with the site numbers given in your IND submission 51,979, Serial Number 513 dated July 12, 2004?
3. Please provide us the SAS formats catalog files (or give us the reference to file if already submitted in the NDA) for the following studies
 - a) 1182.12 (RESIST 1)
 - b) 1182.48 (RESIST 2)
 - c) 1182.52
 - d) 1182.51

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/s/

Tanima Sinha
12/23/04 08:42:10 AM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 17, 2004
TO: HFD-530, Division File
FROM: Tanima Sinha, M.S., Regulatory Project Manager
SUBJECT: Clinical Information Request
NDA 21-814, (tipranavir) capsules

On Wednesday, November 17, 2004, a second clinical information request was sent to Boehringer Ingelheim, Pharmaceuticals, Inc. via email regarding their NDA 21-814 for tipranavir. The request was sent on behalf of clinical reviewers for this application. Below is the information that was requested.

Dataset questions for BIPI

For all studies please do the following:

1. Format **ALL** columns in **ALL** datasets so that they appear as they should. For example, dates should appear as dates.
2. Submit new disposition datasets for **ALL** studies (excluding those previously requested in earlier queries). These datasets should contain data on **ALL** randomized subjects with at least the following populated columns:
 - Unique patient identifier
 - Study ID
 - Randomized treatment
 - Randomized VL stratum
 - Randomized T20 stratum
 - Age
 - Sex
 - Race
 - Randomized treatment dose
 - Date of randomization
 - Investigator name
 - Site ID
 - Country

- Study completion (y/n)
 - Study drug prematurely stopped (y/n)
 - Reason for stopping treatment (include a column for general term and a column for specific term e.g. general = other specific = moved away from study site)
 - Days on randomized treatment
 - Days on study
 - Days of exposure based on treatment start and stop date
 - Treatment start date
 - Treatment stop date
 - Study stop date (if subjects were allowed to stop randomized treatment but remain on study)
 - Last date of assessment/contact
 - Individual columns for the individual study populations (namely, FAS, safety, etc) – to include a derived numeric value of whether each subject was included in that population analysis.
3. In all AE datasets include a column for AE grade, namely Grade 1 –4, in lieu of or in addition to categorizing AEs as mild, moderate, or severe.
 4. Provide one dataset for hematology, one for chemistries, one for urinalysis, and one for all other (serology, immunology).
 5. Submit modified demographic datasets that include randomized subjects only.
 6. Provide one dataset for antiretrovirals taken while on the study, a separate dataset with previously used antiretrovirals, and a third dataset for other concomitant medications.

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Tanima Sinha
12/23/04 08:50:45 AM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 17, 2004
TO: HFD-530, Division File
FROM: Tanima Sinha, M.S., Regulatory Project Manager
SUBJECT: Clinical Information Request
NDA 21-814, (tipranavir) capsules

On Wednesday, November 17, 2004, a clinical information request was sent to Boehringer Ingelheim, Pharmaceuticals, Inc. via email regarding their NDA 21-814 for tipranavir. The request was sent on behalf of Dr. A. James, the primary clinical reviewer for this application. Below is the information that was requested.

11_15_04 Study report query

1. In the demographic datasets there appears to be only three study populations the ITT, the Safety and the Completers populations. Please explain 'as treated' as it relates to the different study populations. For example in the study reports all the AE tables state 'FAS (as treated)'. Also clarify if ITT and FAS are used interchangeably throughout the study reports and datasets.

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Tanima Sinha
12/23/04 08:45:33 AM
CSO



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV
Division of Antiviral Drug Products**

FACSIMILE TRANSMITTAL SHEET

DATE: November 12, 2004

| | |
|--|---|
| To: Nancy McKay | From: Tanima Sinha |
| Company: Boehringer Ingelheim Pharmaceuticals, Inc | Title: Regulatory Project Manager, HFD- 530 |
| Fax number: 203-791-6262 | Fax number: 301-827-2471 |
| Phone number: 203-791-6759 | Phone number: 301-827-2335 |
| Subject: Clinical request for NDA 21-814 for Tipranavir | |

Total number of pages including cover:

Comments:

Document to be mailed: YES NO

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MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: 21-814

Drug: Tipranavir

Date: November 12, 2004

To: Nancy McKay

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc

From: Tanima Sinha, M.S. Regulatory Project Manager

Through: Dr. Andrea James Medical Reviewer
Dr. Melisse Baylor Medical Reviewer
Dr. Neville Gibbs Medical Reviewer

Concur: Dr. Rosemary Johann-Liang Medical Team Leader

Subject: Clinical request for NDA 21-814 for Tipranavir

Please reference your upcoming NDA submission for tipranavir, NDA 21-814. The following requests are from the medial reviewers for your application.

The clinical reviewers are finding some of the CRT datasets to be difficult to review and request modification of the CRT datasets to facilitate the review in a timely manner. Please go through each of the queries for different datasets requested by the clinical reviewers and modify the CRT tables. Please submit the modified tables by COB next Wednesday, November 17, 2004.

Dr. Baylor:

1. Study reports for P & U Studies 3 and 4 are not listed in any Table of Contents. Please let us know where in your NDA submission we can find these study reports to review.

Dr. Gibbs:

Study1182.51

2. AE's need to be graded numerically – i.e. Grade 1 , 2 , 3, and 4 as described in narrative , not merely mild, moderate and severe as graded in data set.

3. Please format dates – e.g. in AESTDTM, AESTDTMP columns – the string of numbers provided is not adequate to provide information on the date. The start day for study drug should also be provided.
4. AEACN column. Explain why almost 500 lines are blank. Explain why NA was used for 88 AE's.
5. In AE dataset, clarify the definition of AESDTH, specifically did this capture only deaths resulting from the AE or deaths resulting from that illness, and clarify if there is a time frame within which these deaths had to occur to be reported in this column.
6. Please provide one dataset for antiretrovirals taken while on study, a separate dataset with previously used antiretrovirals, and a third dataset for other concomitant meds.
7. There are more subjects in the demographics dataset than participated in the study. Please indicate which subjects were screening failures and the reason. Please send a modified demographic dataset that includes randomized subjects only.
8. AEENDTM, AEENDMP, AEENDY – Some columns contain a string of numbers. What do these numbers mean? Some columns are blank; does this indicate that the data are missing for the patient?
9. VISITNUM – allegedly refer to “visit numbers”. The numbers in the column are 1, 99 and 98. What do these mean?
10. Laboratory data sets should be divided by lab parameter. For example, provide one dataset for hematology labs, one for chemistries, one for urinalyses, and one for all other (serology, immunology).
11. DISPOSITION DATA SET – please modify with the same specifications as requested by Dr. James.
12. LABS – dates need to be formatted.
13. LBDTMP – Please define and explain why all subjects have result of 60.

Dr. James:

14. Regarding all datasets you need to format all columns that include dates, so that they appear as dates and not as a string of random numbers.
15. Disposition datasets for 1182.12, 1182.48 and 1182.17 are not reviewable. The following columns are either not defined or not defined adequately:
 - a. DSSEQ = sequence number. What are you sequencing? What do 1 and 2 correspond to?
 - b. DSTERM = reported term. Is this an entry term or an exit term or both?

- c. DSSTDTM = Start Date of Disposition Event. There appears to be a formatting problem, none of the numbers in this column correspond to dates e.g. Row 1 = 15791. Please explain if this is a code and if so what the code stands for.
 - c. DSSTDTMP = Precision of DSSTDTM. The numbers '86400' appear in this column. Please explain if this is a code and if so what the code stands for.
 - d. DSREAS = Reason for DSTERM. This column is completely blank. Was it left blank intentionally or is there missing data? According to the define.pdf file this information was not collected in the CRF, please explain why it was not.
 - e. DSROTH = Other reason for DSTERM. Please explain how 'other reason' is captured when the primary 'DSREAS' is not.
16. Please submit a disposition dataset containing data on ALL randomized subjects with at least the following populated columns:
- ◆ Unique patient identifier
 - ◆ Study ID
 - ◆ Randomized treatment
 - ◆ Randomized PI stratum
 - ◆ Randomized T20 stratum
 - ◆ Age
 - ◆ Sex
 - ◆ Race
 - ◆ Randomized treatment dose
 - ◆ Date of randomization
 - ◆ Investigator name
 - ◆ Site ID
 - ◆ Country
 - ◆ Study completion (y/n)
 - ◆ Study drug prematurely stopped (y/n)
 - ◆ Reason for stopping treatment (include a column for general term and a column for specific term e.g. general = other specific = moved away from study site)
 - ◆ Days on randomized treatment
 - ◆ Days on study
 - ◆ Days of exposure based on treatment start and stop date
 - ◆ Treatment start date
 - ◆ Treatment stop date
 - ◆ Study stop date (if subjects were allowed to stop randomized treatment but remain on study)
 - ◆ Last date of assessment/contact
 - ◆ Died (y/n)
 - ◆ Death date

- ◆ Individual columns for the individual study populations (namely, FAS, safety, etc) – to include a derived numeric value of whether each subject was included in that population analysis

AE Dataset

17. Explain the relevance of the column Visit Number if it does not actually correspond to the visit at which the AE occurred.
18. AEs were Graded (namely, Grades 1 – 4) by investigators, a Grade column needs to be included in the dataset, especially since it seems there is no way to discriminate between Grades 3 and 4, which are both described as severe.
19. Please explain whether AESDTH and AESLIFE are subjective terms or if investigators had specific criteria by which to make these determinations. Of note, in 1182.12 AE dataset there are 7 AE events considered life threatening, however, there are 51 AE events that lead to death. Certainly, an AE that resulted in death must have also been life threatening.

Demographics Dataset

20. The demographics dataset should consist only of subjects who were screened AND randomized to study drug.
21. Columns 'COMPLT' and 'SAFETY' have a lot of blank fields. We prefer not to make assumptions regarding data. If subjects are to be included in the completers or safety populations please populate the fields with a 'Y' for yes if not please populate fields with an 'N' for no.
22. We recognize that during the pre NDA meeting DAVDP and BI agreed that BI did not need to provide datasets for 1182.58; however, after reviewing the available datasets we have determined that datasets for 1182.58 will be necessary in order to facilitate our review of the data. Please submit datasets for 1182.58.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-827-2335 if you have any questions regarding the contents of this transmission.

Tanima Sinha, MS
Regulatory Project Manager
Division of Antiviral Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

Tanima Sinha
11/12/04 03:58:29 PM
CSO
clinical dataset request for TPV NDA
please sign off asap. thanks

Rosemary Johann-Liang
11/15/04 11:03:45 AM
MEDICAL OFFICER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 51,979

11-9-04

Boehringer Ingelheim Pharmaceuticals, Inc
Attention: Nancy Steele McKay, P.E.
900 Ridgebury Rd, P.O. Box 368
Ridgefield, CT 06877-0368

Dear Ms. McKay:

Please refer to your Investigational New Drug Application (IND) 51,979 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Tipranavir.

We also refer to the meeting between representatives of your firm and the FDA on June 2, 2004. The purpose of the meeting was to discuss the content and organization of the nonclinical and clinical sections of your proposed New Drug Applications (NDAs) that you plan to submit in Fall 2004.

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

MEETING DATE: June 02, 2004
TIME: 12:00 – 1:30 PM EDT
LOCATION: Corporate Bldg. Room S400
APPLICATION: 51,979
DRUG NAME: Tipranavir (TPV)
TYPE OF MEETING: Type B: Pre-NDA meeting.

FDA ATTENDEES:

| | |
|------------------------|--|
| John Jenkins, M.D. | Director, Office of New Drugs |
| Mark Goldberger, M.D. | Director, ODE IV |
| David Roeder | Associate Director of Regulatory Affairs |
| Antoine El-Hage, Ph.D. | Regulatory Pharmacologist |
| Melissa Truffa, R.Ph. | Safety Evaluator Team Leader |

DAVDP ATTENDEES:

| | |
|-----------------------------|-------------------------------------|
| Debra Birnkrant, M.D. | Director, Antiviral Drug Products |
| Rosemary Johann-Liang, M.D. | Medical Team Leader |
| Andrea James, M.D. | Medical Reviewer |
| Melisse Baylor, M.D. | Medical Reviewer |
| Neville A. Gibbs, M.D. | Medical Reviewer |
| Ko-Yu Lo, Ph.D. | Chemistry Reviewer |
| James Farrelly, Ph.D. | Pharmacology/Toxicology Team Leader |
| Anita Bigger, Ph.D. | Pharmacology/Toxicology Reviewer |
| Jules O'Rear, Ph.D. | Microbiology Team Leader |
| Lisa Naeger, Ph.D. | Microbiology Reviewer |
| Kellie Reynolds, Pharm.D. | Clinical Pharmacology Team Leader |
| Derek Zhang, Ph.D. | Clinical Pharmacology Reviewer |
| Greg Soon, Ph.D. | Biostatistics Team Leader |
| Kendall Marcus, M.D. | Medical Team Leader |
| Kimberly Struble, Pharm.D. | Medical Reviewer |
| Lincy Thomas, Pharm.D. | Clinical Pharmacology Fellow |
| Olive Ayime | Pharm.D. Student Fellow |
| Virginia Behr | Chief, Project Management Staff |
| Kenny Shade, J.D., B.S.N. | Regulatory Project Manager |
| Tanima Sinha, M.S. | Regulatory Project Manager |

Boehringer Ingelheim Pharmaceuticals, Inc (BI) ATTENDEES:

| | |
|--------------------|--|
| Dr. Burkhard Blank | Senior VP, BI Medical and DRA |
| Dr. Paul Carter | International Project Management Virology /CNS and International Project Leader, Tipranavir |

| | |
|--------------------------|--|
| Dr. Chris Corsico | Drug Safety |
| Ms. Holly Nursemaid | Toxicology |
| Dr. David Hall | Director, Biometrics and Data Management |
| Dr. David Jones | International Core Team Member, DRA |
| Dr. Martin Kaplan | VP, BI DRA |
| Dr. Veronika Kolhbrenner | BI Medical |
| Dr. Tom MacGregor | Drug Metabolism and Pharmacokinetics |
| Dr. Douglas Mayer | Therapeutic Area Head, Virology |
| Mr. Charlie Mazzarella | Associate Director, Drug Regulatory Affairs |
| Dr. Scott McCallister | International Core Team Member, Medicine |
| Ms. Nancy McKay | BI DRA |
| Mr. Dietmar Neubacher | Project Statistician |
| Dr. Ken Rakowski | VP, BI Medical |
| Mr. Paul Roszko | BI Medical |
| Mr. John Sabo | Senior Scientist, Drug Metabolism and Pharmacokinetics |
| Dr. Veit Schmelmer | International Core Team Member, R&D |
| Ms. Pam Strode | Group Leader, DRA |
| Dr. Mike Tsianco | Head, BDM |
| Mr. Jim Webb | BI Tech DRA |

BACKGROUND:

Boehringer Ingelheim Pharmaceutical Inc.(BI) is planning to submit their NDA for Tipranavir in Fall of 2004.

MEETING OBJECTIVES:

The purpose of the meeting was to discuss the content and organization of the nonclinical and clinical sections and obtain FDA feedback of BI's proposed New Drug Applications (NDAs) that they plan to submit in Fall 2004.

BI presented a summary of the RESIST protocol and amendments, along with the impact of each amendment on the statistical analysis plan.

DISCUSSION POINTS:

Procedural/Data-Driven Issues

Procedural

Question 1.1

BI plans to submit — NDA' Ƨ in late 2004. NDA will cover the capsule dosage form, Ƨ Ƨ

BI plans to include all available clinical data in the capsule NDA. Ƨ Ƨ

Does the Division agree with this proposal?

DAVDP concurred and had no further comments to convey at this time.

Question 1.2

BI plans to request a priority review for TPV. Does the Division agree that TPV will meet the criteria for a priority review?

If a priority review is foreseen, please comment on the timing of a safety update following NDA submission – 2 months vs. 4 months.

If a 2- month safety update is expected, would the division agree to accept the safety update in lieu of an IND annual report? The IND annual report for TPV would be due in the same timeframe as a 2-month safety update.

DAVDP determines whether an NDA gets a priority or standard review at the 45-day filing meeting.

If DAVDP grants a priority review, we will need a 2 month safety update. The purpose of the early safety update is to provide additional data to the Antiviral Advisory Committee during the Advisory Committee meeting 4 months following the NDA submission.

The 2 month safety update cannot be submitted in lieu of the IND annual report; however, information that is pertinent to both may be duplicated and sent to both the IND and NDA.

Clinical/Labeling

Question 1.3

BI proposes the following indication for the TPV package insert based on the clinical trial program. While BI appreciates that labeling content is a review issues, does FDA agree, in principle, that the proposed wording would be appropriate?

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This indication is based on analyses of plasma HIV-1 RNA levels in two controlled studies of TPV of 24 weeks duration. Both studies were conducted in treatment experienced adults with evidence of HIV-1 viral replication despite ongoing antiretroviral therapy. A study in treatment naïve adult patients and one in pediatric patients over 2 years of age are currently ongoing; consequently, the risk-benefit ratio for these populations has yet to be determined.

There are no study results demonstrating the effect of TPV on clinical progression of HIV-1.”

While DAVDP was pleased that BI presented package inserts and specifically the indication at this time, DAVDP will need to review the data prior to commenting on a possible indication, as this is a review issue. Additionally, DAVDP stated that it is taking

the "Indication and Usage" section seriously, focusing more on providing usage information as part of the indication.

Question 1.4

Because TPV is not a fixed-does combination product, the PI will not adopt sections of the RTV label. Rather the TPV label will include information based on the TPV/RTV development program. Where appropriate, the TPV/RTV labeling will refer to the RTV PI. Does the Division concur with this labeling plan?

DAVDP agreed with this and had no further comments to convey at this time.

Question 1.4a

Because of the difficulty with patient enrollment, we do not expect to be in a position to provide substantial data on Child Pugh B subjects at the time of the initial NDA submission. Rather we propose the following wording in the TPV/r labeling:

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()

Does the Division agree with this approach?

From the Clinical Pharmacology perspective the approach is acceptable at this time. However, these data will need to be reviewed before labeling is finalized.

Non-Clinical

Question 1.5

At the TPV EOP2 meeting in December 2002, the Division agreed that the nonclinical package was adequate to support NDA submission. This item was not reflected in the formal meeting minutes issued by the Division on January 14, 2003. Please confirm concurrence with the adequacy of the nonclinical package in support of NDA submission.

DAVDP suggested that BI refer to the Immunotoxicology Guidance on-line, paying particular attention to the section on HIV, to ensure that Tipranavir is meeting immunotoxicology needs.

DAVDP requested that BI conduct *in vitro* combination antiviral activity studies of Tipranavir with all approved anti-retroviral (ARV) drugs to rule out unanticipated antagonism between drugs.

Statistical Analysis

Question 1.6

The analysis plan for the tipranavir NDA is described in the background document. Does the Division agree with the analysis plan, as written?

This question was initially discussed during the May 10, 2004 teleconference, at which time DAVDP deferred discussion of it until the face-to-face meeting due to the extensive discussion on the topic of non-inferiority versus superiority. As presented by Dr. McCallister during today's meeting, BI agreed with DAVDP that a superiority analysis is appropriate.

Submission Format Issues

Summaries

Question 2.1

BI plans a clinical summary in the CTD structure to be included in 2.7.4. Associated appendices will be included in Module 5. Does the Division concur with this format? Does the Division agree with the suggested division of data and intended groupings as outline in Module 2.7.4, Section 1.1.2?

The information contained within the SCS comes from multiples tables, figures and listing. Supporting tables, figures and listings that are noted within the summary document are planned as appendices to be located in Module 5. It is anticipated that these supporting documents will range from 500-1000 pages. Module 5 will also contain clinical trial reports (CRTs). Does the FDA agree that placement of the supportive tables, figures and listing referred to in Module 2.7.4. are best place in Module 5 (specifically 5.3.5.3: Reports of Analyses of Data from more than one Study)?

This question was initially discussed during the May 10, 2004 teleconference. At that time, DAVDP agreed with the format of 2.7.4 Summary of Clinical Safety (SCS) as described in the background document. At that time, DAVDP requested a clear description of the source data including the volume and page number in the text of 2.7.4 SCS and cross reference with the associated Module 5 appendix.

BI agreed to meet DAVDP's request for clear cross-referencing. However, the details of how BI will meet this request will need to be clarified, and BI will submit their proposal to DAVDP by the end of June.

Question 2.2

The Open Label Safety Study (OLSS) safety data will not be formally integrated into the SCS/2.7.4) analyses but will be described in narrative form in these documents. NO EAP safety data are expected in the initial NDA, since the EAP will begin after the date of the safety data

cut-off for the initial NDA submission. An EAP update would be generated for the post-submission safety update. Are these proposals generally acceptable to the FDA?

This question was initially discussed during the May 10, 2004 teleconference. During that teleconference, the Division requested that the OLSS data be integrated in the Summary of Clinical Safety (SCS). DAVDP would like to see all data integrated in the SCS, including HIV (-) subjects. DAVDP understands the value of separating out different patient populations like pediatrics, etc. but the data should be integrated initially.

DAVDP added that all HIV (+) patients including those in the OLSS should also be integrated; the studies could then be separated out into individual sections as appropriate.

DAVDP and BI agreed to have further discussions regarding this matter at the future time.

Question 2.3:

Does the Division agree with the format of the Summary Sections including tabular presentation?

This question was initially discussed during the May 10, 2004 teleconference. However, only the Clinical and Statistical sections were discussed due to the representation at that teleconference. The Division asked the that following be provided in the NDA submission:

- Intensity be broken down by Grades 1-4, 2-4 and 3-4
- Provide narratives for deaths, SAE's and discontinued due to AE for key trials (RESIST 1 & RESIST 2)
- Provide analysis by gender, race and age
- Provide efficacy endpoints based on strata, including T20 and comparator PIs
- Provide a table on results for the secondary endpoint for change from baseline (VL and CD4)

BI agreed to all of the above.

Non-Clinical

Question 2.4

Based on the draft table of contents (TOC) provided for Module 4, does the Division agree with the general organization of the nonclinical data for the NDA?

DAVDP from the Pharmacology/Toxicology perspective agrees with the general organization of the non-clinical data for the NDA.

DAVDP from the Microbiology perspective would like non-clinical and clinical pre-data placed in Module 5, section 5.3.5.4.

BI added that resistance data will also be linked in Summary of Clinical Efficacy (SCE).

Question 2.5

Does the Division agree with the proposed organization of the nonclinical summaries and tabulations?

DAVPD agreed with the proposed organization of the nonclinical summaries and tabulations.

Submission Format Issues

Clinical

Question 2.6

Based on the draft TOC provided for Module 5, does the Division agree with the general organization for the clinical data for the NDA?

DAVDP agrees with the general organization for the clinical data for the NDA.

Question 2.7

In accordance with ICH guidance, BI will include investigator lists in each clinical trial report. A separate investigator list is not planned. Does the Division concur with the approach?

DAVDP concurred with this approach. BI noted that non- US studies are not conducted under the IND, but are conducted under local regulations and under Good Clinical Practices.

Electron Submission Plan

Question 2.8:

BI plans to submit some sections of the TPV NDA electronically, as described in the background document. Does the Division concur with the proposed electronic submission plan?

This question was initially discussed during the May 10, 2004 teleconference. At which time, DAVDP asked for the following in addition to datasets in electronic format:

- **An Output folder, which will house data sets,**
- **Outputs for relevant files, source data and figures**
- **Programs generating output for the datasets and decodes for coded variables (including SAS catalogs – for formatted variables)**

BI agreed to all of the above.

Furthermore, regarding CRT's for each data set, DAVPD requested lead columns with patient number, trial number, gender, age, treatment regimen and strata and asked if such additions to the data sets are possible and whether data will be provided using CDISC

format. BI confirmed that this is technically possible and plans to provide data in CDISC format.

BI further clarified that efficacy data will be provided as BI analysis data sets and usable programs are available and will be provided.

DAVDP and BI agreed to have further discussions on CDISC.

Question 2.9

Analysis datasets for the ECG data will be included in the CRT section. A copy of the ECG report is not part of the CRF as it is maintained at the site and therefore will not be included in the NDA CRFs of deaths and dropouts due to AEs. BI will provide these ECG reports only upon FDA request. Does the Division agree with this proposal?

DAVDP concurred with this proposal and had no comments to convey at this time.

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BI added that the NDA submission will include a number of pediatric patients at 4 weeks; including PK, safety and efficacy data through the data cut-off of 11 June. All SAEs will also be included in the report since the data cut-off for the pediatric trial coincides with the project data cut-off for SAEs.

ACTION ITEMS:

In regards to question 2.1, BI and DAVDP will have further discussions regarding clear cross-referencing and BIPI will submit their proposal to the division by the end of June.

In regards to question 2.2, BI and DAVDP will have further discussion regarding the integration of data in the Summary of Clinical Safety.

BI and DAVDP will further discuss BI's electronic submission plans.

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

/s/

Debra Birnkrant
11/9/04 02:03:06 PM
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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 05, 2004
TO: HFD-530 Division File
FROM: Tanima Sinha, M.S., Regulatory Project Manager
SUBJECT: Clinical information request
NDA 21-814

On Friday, November 5, 2004, a clinical information request was sent to Boehringer Ingelheim, Pharmaceuticals, Inc. via email regarding their NDA 21-814 for tipranavir. The request was sent on behalf of Dr. A. James, the primary clinical reviewer for this application. Below is the information that was requested.

1. The narratives do not appear to be narratives, but instead appear to be excerpts from the SAE medwatch reports. Please submit narratives that tell a concise and relevant story of what happened to the patient using all of the available information medwatch reports, CRFs, etc.
2. Many of the columns in the Tabular presentations of deaths are blank although the information is contained in the narrative, fax or CRF. Please use all available resources to fill in the blanks in the tables. If after exhausting all sources the information cannot be found please put "unknown" in that field. It is particularly important to have the ATRSTDT, ATRSSPDT, TRT DUR, ENDTODTH fields filled in.
3. The number of fatal outcomes still do not add up. Please see table below for our assessment:

| Trial | Subject ID | Regimen | BI & FDA agree on outcome | Unresolved issues |
|---------|------------|---------|----------------------------|--|
| 1182.12 | 1029 | TPV/r | died on study | |
| 1182.12 | 1050 | TPV/r | died after database closed | |
| 1182.12 | 1308 | TPV/r | | ◆ ? wrong DOD – in submission 001 = 5/14/01; Fax to FDA 12/03 ◆ based on provided |

| Trial | Subject ID | Regimen | BI & FDA agree on outcome | Unresolved issues |
|---------|------------|---------|---------------------------|--|
| | | | | FDA believes this subject died on study |
| 1182.12 | 1341 | TPV/r | died on study | |
| 1182.12 | 1550 | TPV/r | died on study | |
| 1182.12 | 1568 | TPV/r | died on study | |
| 1182.12 | 1647 | TPV/r | died on study | |
| 1182.12 | 1878 | TPV/r | died post study | |
| 1182.12 | 1917 | TPV/r | died on study | |
| 1182.12 | 2052 | TPV/r | | <ul style="list-style-type: none"> ◆ not listed in NDA presubmission; listed in NDA SN 001 ◆ based on provided data FDA believes this subject died on study. |
| 1182.12 | 2280 | TPV/r | died post study | |
| 1182.12 | 2374 | TPV/r | died on study | |
| | | | | |
| 1182.12 | 1950 | N/A | died in screening phase | |
| 1182.12 | 1970 | N/A | died in screening phase | |
| 1182.12 | 2060 | N/A | died in screening phase | |
| 1182.12 | 2370 | N/A | died in screening phase | |
| 1182.12 | 3087 | N/A | died in screening phase | |
| 1182.12 | 3185 | N/A | died in screening phase | |
| 1182.12 | 3212 | N/A | died in screening phase | |
| | | | | |
| 1182.12 | 1199 | CPI/r | died on study | |
| 1182.12 | 1219 | CPI/r | died on study | |
| 1182.12 | 2087 | CPI/r | died on study | |
| 1182.12 | 2090 | CPI/r | died on study | |
| 1182.12 | 2091 | CPI/r | died on study | |
| 1182.12 | 4006 | CPI/r | | <ul style="list-style-type: none"> ◆ not listed in NDA presubmission; listed in NDA SN |

| Trial | Subject ID | Regimen | BI & FDA agree on outcome | Unresolved issues |
|---------|------------|---------|--|---|
| | | | | 001 ◆ based on provided data FDA believes that this subject died on study. |
| 1182.12 | 4073 | CPI/r | died on study | |
| 1182.48 | 1097 | TPV/r | died post cutoff date | |
| 1182.48 | 3305 | TPV/r | died on study | |
| 1182.48 | 4168 | TPV/r | died on study | ◆ died 8 days after treatment d/c; considered post study death by BI |
| 1182.48 | 5061 | TPV/r | died on study ◆ died 9 days after treatment considered on study death by BI and FDA | |
| 1182.48 | 9137 | TPV/r | | |
| 1182.48 | 1431 | Pre-tx | died in screening phase | According to NDA presubmission only 2 subjects died in pretreatment phase, which 2 not specified. |
| 1182.48 | 1808 | Pre-tx | died in screening phase | |
| 1182.48 | 3234 | Pre-tx | died in screening phase | |
| 1182.48 | 9155 | Pre-tx | died in screening phase | |
| 1182.48 | 2211 | CPI/r | | ◆ BI considers death post treatment ◆ based on provided data FDA believes that this subject died on study. |
| 1182.48 | 3033 | CPI/r | died on study | |
| 1182.48 | 3150 | CPI/r | died on study | |
| 1182.48 | 3270 | CPI/r | | ◆ not listed in NDA presubmission; |

| Trial | Subject ID | Regimen | BI & FDA agree on outcome | Unresolved issues |
|---------|------------|---------|---------------------------|---|
| | | | | <p>listed in NDA SN 001</p> <ul style="list-style-type: none"> ◆ based on provided data FDA believes that this subject died on study. |
| 1182.48 | 7135 | CPI/r | died on study | |
| 1182.48 | 8032 | CPI/r | died on study | |
| 1182.48 | 9328 | CPI/r | | <ul style="list-style-type: none"> ◆ not listed in NDA presubmission; listed in NDA SN 001 ◆ based on provided data FDA believes that this subject died on study. ◆ per medwatch report subject on TPV/r, BUT per BI narrative and tabular presentation subject on CPI/r |

Please provide concurrence on the column titled "BI & FDA agree on outcome". Please provide evidence to reconcile each of the issues for each of the subjects with a comment under "Unresolved Issues".

4. The CRFs for the following subjects who had a fatal outcome while on study (as assessed by the FDA based on the information provided) are missing: subjects 1308, 2052, 3270, 4006, 9328. Please provide these CRFs ASAP.

Please send a response to the above query by COB November 12, 2004.

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this page is the manifestation of the electronic signature.**

/s/

Tanima Sinha
12/23/04 08:48:02 AM
CSO

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

| | | |
|--|--|-------------------------------|
| DATE RECEIVED: October 27, 2004 | DESIRED COMPLETION DATE: December 27, 2004 PDUFA DATE: June 22, 2005 | ODS CONSULT #: 04-0279 |
| TO: Debra Birnkrant, MD Director, Division of Anti-Viral Drug Products HFD-530 | | |
| THROUGH: Tanima Sinha Project Manager HFD-530 | | |
| PRODUCT NAME: Aptivus® (Tipranavir) 250 mg Capsules (NDA# 21-814) L | NDA SPONSOR: Boehringer-Ingelheim Pharmaceuticals, Inc. | |
| NDA# 21-814 | | |
| SAFETY EVALUATOR: Linda M. Wisniewski, RN | | |
| RECOMMENDATIONS: | | |
| <ol style="list-style-type: none">1. DMETS has no objections to the use of the proprietary name, Aptivus. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.2. DMETS recommends implementation of the labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.3. DMETS suggests submitting the Proposed Patient's Instructions to the Division of Surveillance, Research, and Communication Support for review and comment.4. DDMAC finds the proprietary name Aptivus acceptable from a promotional perspective. | | |
| Denise Toyer, PharmD Deputy Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242 | Carol Holquist, RPh Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242 | Fax: (301) 443-9664 |

**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 9, 2004

NDA# 21-814 ㄸ ㄿ

NAME OF DRUG: Aptivus (Tipranavir Capsules 250 mg : ㄸ ㄿ

NDA HOLDER: Boehringer-Ingelheim Pharmaceuticals, Inc.

*****NOTE:** This review contains proprietary and confidential information that should not be released to the public.***

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Viral Drug Products (HFD-530), for assessment of the proprietary name "Aptivus", regarding potential name confusion with other proprietary or established drug names. Draft container label and carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Aptivus is the brand name for tipranavir, a non-peptidic protease inhibitor (NPPI) of HIV. It is co-administered with low-dose ritonavir, and is indicated for combination antiretroviral treatment of HIV-1 infected patients who are protease inhibitor treatment-experienced. It is supplied as a 250 mg capsule ㄸ ㄿ The recommended dose of Aptivus is 500 mg (two 250 mg capsules ㄸ ㄿ), twice daily. Tipranavir is co-administered with 200 mg ritonavir (low-dose ritonavir). Aptivus capsules ㄸ ㄿ should be stored at 25° C (77°F); excursions permitted to 15-30° C (59-86°F). Aptivus is packaged in HDPE unit-of-use bottles that contain 120 capsules with a child resistant closure ㄸ ㄿ

ㄿ Tipranavir must be used within 60 days after first opening of the bottle.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Aptivus to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and

¹ MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, Drugs@fda, and the electronic online version of the FDA Orange Book.

Trademark Office's Text and Image Database was also conducted⁴. The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Aptivus. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Aptivus acceptable from a promotional perspective.
2. The Expert Panel identified eight names as having potential for confusion with Aptivus. These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel and Prescription Study Analysis

| Product Name | Dosage form(s), Established name | Usual adult dose* | Other** |
|---|--|--|---------|
| Aptivus | Elipranavir Capsules 250 mg | Two 250 mg tablets twice a day | N/A |
| Optivar | Azelastine Hydrochloride, 0.05 % Ophthalmic Drops | One drop into each affected eye twice a day. | LA/SA |
| Optivite | Vitamins (OTC). | Once daily. | LA/SA |
| Optison | Human Albumin Injection 5 to 8 × 10 ⁸ human albumin microspheres, 10 mg albumin human, 0.22 ± 0.11 mg/mL octafluoropropane in 0.9% aqueous sodium chloride. | Individualized, 1 mL to 8.7 mL per study. | LA/SA |
| Antabuse | Disulfiram 250 mg tablet | 125 mg to 500 mg per day. Maximum of 500 mg per day. | SA |
| Capoten | Captopril Tablet 12.5 mg, 25 mg, 37.5 mg, 50 mg, 75 mg, 100 mg, 150 mg | 6.25 mg to 450 mg. Maximum of 450 mg per day. | LA |
| Ultiva | Remifentanyl Hydrochloride Injection: 1 mg, 2 mg, 5 mg | 0.025 mcg/kg/min-4 mcg/kg/min intravenously as an adjunct to anesthesia. | LA |
| Raptiva*** | Efalizumab 125 mg/vial Injection | 0.7 mg/kg to 1 mg/kg. Subcutaneous once, and weekly. | SA |
|  | | | |
| <p>*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike) ***Identified through verbal prescription study. ****NOT FOI Releasable.</p> | | | |

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁵ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

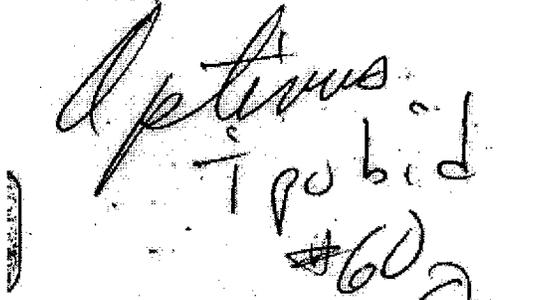
B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. The POCA did not identify any other names which were considered to have significant orthographic similarities to Aptivus.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Aptivus with currently marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 122 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient and outpatient prescription were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Aptivus (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, one inpatient order was recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

| HANDWRITTEN PRESCRIPTION | VERBAL PRESCRIPTION |
|--|--------------------------------|
| <p>Inpatient RX#1:</p>  | <p>Aptivus</p> |
| <p>Outpatient RX:</p>  | <p>Take one PO BID #60</p> |

2. Results:

One of the respondents in the verbal study interpreted the proposed name as Aptiva, which sounds similar to the currently marketed U.S. product, Raptiva. See Appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Aptivus, the primary concerns related to look-alike and sound-alike confusion with Optivar, Optivite, Optison, Antabuse, Capoten, Ultiva, Raptiva, and

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. One respondent from the verbal study misinterpreted the proposed name as Aptiva which sounds similar to the name Raptiva. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Aptivus.

1. Optivar may look and sound similar to Aptivus when written or spoken. Optivar is a prescription ophthalmic antihistamine used for the treatment of allergic conjunctivitis. The orthographic similarities stem from the fact that both names begin and end with letters that may look similar when scripted (O vs. A and ar vs. us). The similarity in appearance of the first letter of each name (O vs. A) is most likely to occur when the name is written in cursive handwriting as opposed to a printed presentation using block letters (see below). Sixteen of the participants in the written prescription study misinterpreted the spelling of the study name as a drug name beginning with the letter 'O'. Both names also contain the same four letters in the same placement (ptiv) which may look similar in either cursive or block letters. Although the beginnings of each name sound similar (apti vs. opti), the endings (var vs. vus) are phonetically different. Although both products are dosed twice daily, there are some product characteristics that may help to differentiate them, such as dose (500 mg, 2 capsules vs. one drop), dosage forms (capsules vs. ophthalmic drops), strength (250 mg vs. 0.05%), route of administration (oral vs. ophthalmic), indication of use (HIV vs. allergic conjunctivitis), and storage location (oral solids vs. ophthalmic products). Although there are similarities between the orthographic presentations of the two names, the accompanying information will help to differentiate the correct drug ordered (500 mg BID, 2 capsules BID, or one drop vs. one drop BID). Additionally, the dosage form for an inpatient order for Aptivus will need to be identified (capsules). Moreover, because Aptivus is supplied in more than one dosage form, the dosing amount for each form is very specific (2 capsules). An order for Optivar would most likely include information such as '1 drop' or 'as directed', both of which would be inappropriate for an order for either dosage form of Aptivus. Even if a prescription written for Aptivus 2 BID is misinterpreted as Optivar 2 (gtts) BID, the quantity to be dispensed will help to differentiate it. Although Aptivus is packaged in a unit-of-use container, orders are likely to say '#120' or 'XX month' or 'XX days supply.' Prescribers may not be aware that this is a unit-of-use container and will generally order the amount required to last the patient 30 days. In contrast, if Optivar 2 BID is misinterpreted as Aptivus 2 BID where #1 is interpreted to represent a bottle of Aptivus, the dose would help to differentiate the product. Additionally, since Aptivus is supplied the identification of the dosage form would help to identify the correct product. Thus, confusion will be mitigated by the differentiating dose and dosage forms.

aptivus APTIVUS
optivar OPTIVAR

2. Optivite may look and sound similar to Aptivus when written or spoken. Optivite is an over-the-counter vitamin used as a nutritional supplement. The similar spelling and beginnings of each name (O vs. A and ptiv) contribute to the look-alike and sound-alike similarities of the names. Sixteen of the participants in the written prescription study misinterpreted the spelling of the study name as a drug name beginning with the letter 'O'. However, the upstroke and crossbar required for the second 't' in Optivite may help to distinguish the name when written (see below). The endings of each name are also phonetically different. There are differentiating product characteristics such as dose (500 mg, 2 capsules, [] vs. one tablet), strength (250 mg [] vs. no strength), frequency of administration (twice daily vs. once daily), and indication of use (HIV infection vs. nutritional supplement). Although both products are supplied as oral solids (capsules vs. tablets), [] Therefore, an order [] will include the number of [] to be administered, which will help to distinguish the correct product ordered. Additionally, an order for Aptivus capsules would need to include the number of capsules to be administered 'take two capsules twice daily'. An Aptivus BID prescription is unlikely to be confused as Optivite BID, because this is an uncommon frequency of administration for this nutritional supplement. The orthographic and phonetic differences along with the differentiating product characteristics will help to minimize confusion involving this name pair.

Optivite
Aptivus

3. Optison may look and sound similar to Aptivus when scripted or spoken. Optison is used as a radiological cardiac imaging agent. The look-alike similarities stem from the fact that both names contain letters that look similar when scripted (O vs. A, pti, and son vs. vus) (see below). Sixteen of the participants in the written prescription study misinterpreted the spelling of the study name as a drug name beginning with the letter 'O'. The similar letters at the beginning of each name contribute to the phonetic similarities, however, the endings are phonetically different. Despite some similarities in the product name, there are differentiating product characteristics such as dose (500 mg vs. 1 mL to 8.7 mL), dosage form (capsule [] vs. injection), strength (250 mg [] vs. 5 to 8 x 10⁸ human albumin microspheres, 10 mg albumin human, 0.22 ± 0.11 mg/mL octafluoropropane in 0.9% aqueous sodium chloride), frequency (twice daily vs. once), route of administration (oral vs. intravenous), indication of use (HIV vs. cardiac imaging), and storage location (oral solids [] vs. injectable contrast agents). Although a 5 mL dose of Optison could be potentially confused [] the dosing intervals would help differentiate the products. The product differences will help to differentiate this name pair and minimize confusion.

Optison
Aptivus

4. Antabuse may sound similar to Aptivus when spoken. Antabuse is indicated as an alcohol deterrent. The endings of each name may be pronounced with a long 'u', and as a result may sound similar (buse vs. vus). However, the beginnings of each name (apti and anta) are phonetically different. Although both drugs are supplied in the same strength (250 mg),
- Thus, an order for Aptivus will most likely include further information such as 'take two capsules twice daily', whereas an order for Antabuse would have a specific dose because it's dose ranges from 125 mg to 500 mg and is dosed on a once daily basis. The dose may overlap at 500 mg, however, the frequency of administration is different (once daily vs. twice daily). Although the frequency of administration is not a significant differentiating product characteristic, an Aptivus BID prescription is less likely to be confused as Antabuse BID, because this is an uncommon frequency of administration for Antabuse. Additionally, the maximum dosage of Antabuse is 500 mg. Therefore, a BID Aptivus order misinterpreted as 500 mg Antabuse BID would result in an Antabuse overdose. Therefore, the phonetic differences between the beginnings of each name and product differences (dose and frequency) will help to differentiate the two products and help to minimize confusion.
5. Capoten may look similar to Aptivus when scripted. Capoten is indicated in the treatment of heart failure and hypertension. Both names contain letters that look similar when scripted (Apt and Capot) (see below). However, the endings of each name are orthographically different (ivus vs. oten). Although there are some similar product characteristics such as frequency of administration (twice daily), and route of administration (oral), there are product characteristics that will help to differentiate the two when ordered. They include the dose (500 mg vs. 6.25 mg to 450 mg per day), dosage form (capsule vs. tablet), and strength (250 mg vs. 12.5 mg, 25 mg, 37.5 mg, 50 mg, 75 mg, 100 mg, and 150 mg). An order for Aptivus 500 mg BID misinterpreted as Capoten 500 mg BID would result in a daily dose that is two times the recommended maximum daily dose. This would serve as a potential warning that the prescriber should be contacted for clarification. The orthographic differences and the product characteristics will help to differentiate between these two products and minimize error.

Capoten Aptivus

6. Ultiva may look similar to Aptivus when scripted. Ultiva is indicated as an adjunct to anesthesia. Both names contain letters that may look similar when scripted (apti vs. ulti) (see below) which contribute to the look-alike similarities of the name pair. Despite this similarity, there are differentiating product characteristics, such as dose (500 mg vs. 0.025 mcg/kg/min to 4 mcg/kg/min), dosage form (capsule vs. injection), strength (250 mg vs. 1 mg, 2 mg, and 5 mg), frequency of administration (twice daily vs. continuously), route of administration (oral vs. intravenous), indication of use (HIV vs. adjunct to anesthesia), and storage location (oral solids vs. injectable narcotics). Although, there are orthographic similarities, the product characteristics will help to minimize confusion.

Ultiva
Aptivus

7. One respondent from the verbal prescription study interpreted the proposed name as Aptiva, which sounds similar to Raptiva. Thus, we will evaluate the sound-alike similarity to Aptivus. Raptiva is indicated in the treatment of psoriasis. Both names contain five of the same letters (aptiv) which contributes to the sound-alike similarities of this name pair. The last 'a' in Raptiva may sound similar to 'us' particularly if a short 'u' is utilized such as in 'bus' and the letter 's' is not clearly enunciated. Despite the phonetic similarities, there are differentiating product characteristics, such as dose (500 mg vs. 0.7 mg/kg to 1 mg/kg up to a maximum dose of 200 mg), dosage form (capsule [] vs. injection), strength (250 mg [] vs. 125 mg), frequency of administration (twice daily vs. once and weekly), route of administration (oral vs. subcutaneous), indication of use (HIV vs. psoriasis), and storage location (oral solids [] vs. injection) that will help to minimize confusion involving Raptiva and Aptivus.

8.

E. INDEPENDENT NAME ANALYSIS []

On the 27th of February, 2002, Boehringer Ingelheim commissioned [] to conduct a name validation study using its proprietary [] for tipranavir, a new non-peptidic protease inhibitor. Although the scope of the tipranavir name validation study was global, for the purpose of this report, the specific findings and conclusions will be limited to the candidate 'Aptivus' and the U.S. market. The assessment, dated August 10, 2004 is based on the dispensing-specific data of the []

NOTE: This review contains proprietary and confidential information that should not be released to the public.

The study included 100 primary research respondents of which included 50 U.S. physicians, comprising of HIV specialists (40), and Primary Care physicians (10), and 50 U.S. pharmacists comprising of hospital pharmacists (25) and retail pharmacists (25).

1. Verbal Assessment – U. S. Pharmacists

25 Hospital-based pharmacists and 25 Retail-based pharmacists were asked to rate the ability (*unaided*) of the candidate to be communicated clearly when spoken as well as when written, to identify (*unaided*) first their immediate associations then specific pharmaceutical associations with existing pharmaceutical brand (trade/invented) as well as generic names. Respondents were finally asked to provide an overall assessment (*aided by product description/context*) of the candidate as a pharmaceutical brand name, potentially including a determination as unsuitable due to the risk of mis-prescription with presently marketed brand names, to rate their level of personal consideration, and vote for their most preferred/least preferred candidates. There were no exact matches to currently marketed U.S. drug products

DMETS Response:

Although [] included pharmacists in the verbal interpretations, nurses were not included as participants in this study. Quite often, nurses are called upon to receive and interpret verbal orders. This leaves open the possibility of additional information concerning the interpretation of the pronunciation of the proposed name being omitted in the evaluation process. DMETS notes that several respondents provided spelling variations that begin with the letter 'O'. These include Octivus, Optavos, Optivious, Optivos, and Optivus. DMETS notes that these responses confirm the possibility that the candidate drug name may be mispronounced and subsequently misinterpreted using the vowel "O" rather than 'A'. Additionally, after a verbal order were transcribed, it may be written as a name beginning with the letter 'O'. However, despite this finding DMETS agrees with [] in that this name does not pose a significant safety risk.

2. Written Assessment – U. S. Pharmacists

25 Hospital-based pharmacists and 25 Retail-based pharmacists were asked to identify [spell] (*unaided*) the candidate when written by a prescriber using a representative set of sample written orders communicated by fax. Due to the wide variations present in prescriber handwriting, a sampling of four written orders was provided. The representative set of sample written orders provide a reasonable facsimile of what a dispenser is likely to encounter during the first week of availability post-launch. There were no exact spelling matches with the candidate name.

DMETS Response:

DMETS acknowledges the results and agree that the none of the misspelling variations identified in this study are orthographically or phonetically similar to currently marketed drug products.

3. Verbal Assessment – U. S. Physicians

The following research findings were identified related to the interpretation of a simulated verbal order using 50 physicians in the U.S., comprising of 40 HIV specialists and 10 Primary Care physicians. As noted by the listing of spelling variations, there were no citations for presently marketed brand or generic names as well as known investigational drugs.

DMETS Response:

DMETS acknowledges the results and agree that the none of the misspelling variations identified in this study are orthographically or phonetically similar to currently marketed drug products.

4. Error Index Dispensing Assessment –Aptivus

Potential conflicts identified during the fieldwork are included for further assessment and a side-by-side comparison of dispensing factors is conducted with the anticipated dispensing profile for tipranavir. No citations were derived from the Error Index Verbal Assessment or Error Index Visual Assessment.

DMETS Response:

Table 1 refers to the “unaided immediate associations assessment” and to the ‘aided overall assessment’. However, these sections (e.g. methodology) are not included in the report. Thus, DMETS did not have the opportunity to evaluate and comment on the summary analysis.

Additionally, Table 1 listed three citations with error index ratings and respondent type. The three products are Activella, Actifed, and Optivar. Of note is that one respondent who misinterpreted the name as Optivar, an ophthalmic drug, is an HIV specialist. This is interesting since an HIV specialist would be the same type of practitioner who would prescribe Aptivus. However, without the methodology, DMETS is unable to determine how the name Aptivus was misinterpreted as Optivar. In particular, DMETS questions what “aided overall assessment” refers to (e.g. scripted order for Aptivus, information as to the class of drug, indication of use, dosage and administration information, etc.). Without the actual methodology, DMETS is unable to evaluate and comment further.

However, despite this finding, DMETS evaluated Optivar in section II-D above and found the potential for confusion to be minimal. Additionally, after evaluation of the additional two products, Activella and Actifed, DMETS agrees with Table 1 that due to differentiating product characteristics, they do not pose a significant safety risk.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Aptivus, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

1. DMETS notes that the draft container label for the capsules was submitted in black and white. [] It appears that the fonts, graphics, etc of these two samples are similar. Therefore, DMETS will make comments relating to the capsules with the assumption that the color, fonts, graphics, etc. []
2. The proprietary and established names should be the most prominent information on the primary display panel. In the current presentation, the [] are most prominent. Increase the font on the proprietary and established names so that they are more prominent than the [] We refer you to 21 CFR201.1(a)(1).
3. In the current presentation, the dosage form ([] capsules), strength, and the proprietary name have equal prominence. The proprietary and established names should be the most prominent information on the label. Increase the font size of the proprietary name so that it is more prominent than the dosage form and strength.

B. CONTAINER LABEL Capsules (120 count)

1. See GENERAL COMMENTS A1 through A3.
2. Relocate the net quantity so that it does not appear in close proximity to the strength.
3. Include a usual dose statement such as "Usual dose is 500 mg BID".
4. Increase the size and prominence of the statement "Must be used within 60 days after first opening".

C. CONTAINER LABEL []

1. []
2. []

D. CARTON LABELING

1. []

2. DMETS notes :

[

]

E. INSERT LABELING

1. DOSAGE AND ADMINISTRATION section:

This section states that "Aptivus Capsules, co-administered with low-dose ritonavir, should be administered with food". However, the patient instructions sheet states "Take Aptivus with food at all times to improve tolerability". Revise to provide consistency between these two documents.

2. HOW SUPPLIED SECTION:

This section states that '*They are packaged in HDPE unit-of-use bottles with a child resistant closure and 120 capsules*'. The wording is confusing and DMETS questions whether there are two different packaging configuration for this product, one with a child resistant closure and one with 120 capsules. DMETS suggest revising this section to state something similar to "[

]

F. PATIENT INSTRUCTIONS FOR USE

1. The use of trailing zeros, such as — has historically been associated with a ten-fold overdose of some medications. Therefore, delete all references to trailing zeros.
2. The statement 'Patients receiving estrogen-based hormonal contraceptives should be instructed that additional or alternative contraceptive measures should be used during therapy with Aptivus' is found in the precautions section of the insert labeling. However, this information is not included in the Patient Instructions for Use. Revise to provide consistency between these two documents.
3. PRECAUTIONS section, Information for Patients subsection:

[

]

[]

Revise to provide consistent wording between these two documents. Additionally, this wording seems complex and difficult to follow. DMETS recommends that the Division of Surveillance, Research, and Communication Support be consulted for review and comment.

III. RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name, Aptivus. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.
3. DMETS suggests submitting the Proposed Patient's Instructions to the Division of Surveillance, Research, and Communication Support for review and comment.
4. DDMAC finds the proprietary name Aptivus acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

|S|

Linda M. Wisniewski, RN
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A:

| Verbal | Written Inpatient | Written Outpatient |
|---------------|------------------------------|-------------------------------|
| Activist | Aptimus | Aptivus |
| Activis | Aptimus | Aptivus |
| Activis | Aptimus | Optivus |
| Activis | Aptinus | Optivus |
| Activis | Aptinus | Optivus |
| Activis | Aptinus | Optivus |
| Activist | Aptinus | Optivus |
| Activos | Aptinus | Optivus |
| Activus | Aptinus | Optivus |
| Activus | Aptisucs | Optivus |
| Activus | Aptisurs | Optivus |
| Activus | Aptivus | Optivus |
| Aptiva | Ceptirius | Optivus |
| | Optimis | Optivus |
| | Optimus | Optivus |
| | Optinus | |

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

/s/

Linda Wisniewski
4/19/05 08:04:22 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
4/19/05 12:36:06 PM
DRUG SAFETY OFFICE REVIEWER
Signing for Carol Holquist, R.Ph., Director of DMETS



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation IV
Division of Antiviral Drug Products

FACSIMILE TRANSMITTAL SHEET

DATE: October 20, 2004

| | |
|---|--|
| To: Nancy McKay | From: Tanim Sinha |
| Company: Boehringer Ingelheim Pharmaceuticals, Inc | Title: Regulatory Project Manager, HFD- 530 |
| Fax number: 203-791-6262 | Fax number: 301-827-2471 |
| Phone number: 203-791-6759 | Phone number: 301-827-2335 |

Subject: Clinical request for NDA 21-814 for Tipranavir

Total number of pages including cover: 3

Comments:

Document to be mailed: • YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-2330. Thank you.



MEMORANDUM OF FACSIMILE CORRESPONDENCE

IND: 21-814

Drug: Tipranavir

Date: October 20, 2004

To: Nancy McKay

Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc

From: Tanima Sinha, M.S. Regulatory Project Manager

Through: Dr. Andrea James Medical Reviewer

Concur: Dr. Rosemary Johann-Liang Medical Team Leader

Subject: Clinical request for NDA 21-814 for Tipranavir

Please reference your upcoming NDA submission for tipranavir, NDA 21-814. The following request is from Dr. James, the primary medical reviewer for your application.

In reviewing your pre-submission data and comparing those data to previously submitted data, we noted that the number of deaths were inconsistent. In order to reconcile these numbers we need you to provide the following information to the NDA. We would appreciate a 7 day turn-around time.

Please provide four desk copies and one archival copy of a TPV death summary. The summary should be divided into sections by study and EACH section should include the following:

- A tabular presentation of deaths for an individual study (similar to the table constructed for the January 16, 2004 face-to-face meeting (SN280)). Each table should contain the following fields (columns): Trial number, mfr report no, pt no., age gender, country, screen date, randomization date, treatment status, treatment start date, treatment end date, duration of treatment (days/weeks), date of death, date reported to BI, date reported to FDA, baseline CD4, last available CD4, baseline VL, last available VL, treatment, cause of death
- A copy of all 7-day death faxes that correspond to the individual study
- A narrative for EACH death associated with the individual study

IND 51,979
October 20, 2004

Please order the narratives and faxes to match the order of the tabular presentation (for example if subject xyz is the first subject in the table, please make sure subject xyz is the first subject in the fax section and the first subject in the narrative section).

Please provide the above information for at least the following studies: 1182.12, 1182.48, 1182.17, 1182.58.

We are providing this above information via telephone facsimile for your convenience. **THIS MATERIAL SHOULD BE VIEWED AS UNOFFICIAL CORRESPONDENCE.** Please feel free to contact me at 301-827-2335 if you have any questions regarding the contents of this transmission.

Tanima Sinha, MS
Regulatory Project Manager
Division of Antiviral Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration

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this page is the manifestation of the electronic signature.**

/s/

Tanima Sinha

10/20/04 04:05:04 PM

CSO

Death report request fax for tpv, upcoming NDA 21-814
please sign of by COB 10-20-04.

Rosemary Johann-Liang

10/20/04 04:39:16 PM

MEDICAL OFFICER

| | | | | |
|---|-------------------|--|---|---|
| DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION | | | REQUEST FOR CONSULTATION | |
| (Division/Office): Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 PKLN Rm. 6-34 | | | FROM: Tanima Sinha, Regulatory Project Manager, Division of Antiviral Drug Products, HFD-530 | |
| DATE October 15, 2004 | IND NO. 51,979 | NDA NO. 21-814 | TYPE OF DOCUMENT: Paper | DATE OF DOCUMENT: September 30, 2004 |
| NAME OF DRUG: Established name: tipranavir | | PRIORITY CONSIDERATION: Priority Review | CLASSIFICATION OF DRUG: Anti-HIV | DESIRED COMPLETION DATE: December 15, 2004 |
| NAME OF FIRM: Boehringer-Ingelheim Pharmaceuticals, Inc. | | | | |
| REASON FOR REQUEST | | | | |
| I. GENERAL | | | | |
| <input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY | | | | |
| <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT | | | | |
| <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review | | | | |
| II. BIOMETRICS | | | | |
| STATISTICAL EVALUATION BRANCH | | | STATISTICAL APPLICATION BRANCH | |
| <input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW): | | | <input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW): | |
| III. BIOPHARMACEUTICS | | | | |
| <input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES | | | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST | |
| IV. DRUG EXPERIENCE | | | | |
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | | | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS | |
| V. SCIENTIFIC INVESTIGATIONS | | | | |
| <input type="checkbox"/> CLINICAL | | | <input type="checkbox"/> PRECLINICAL | |
| COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: Initially BI submitted an 'evaluation of tradename' for τ JDMETS found it acceptable, however, BI has decided that they would like to use APTIVUS instead. I am forwarding the relevant document via interoffice mail for your review and consideration. PDUFA DATE: end of April 2005. ATTACHMENTS: Draft Package Insert, Container and Carton Labels CC: Archival IND/NDA HFD-530/RPM | | | | |
| SIGNATURE OF REQUESTER | | | METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND | |
| SIGNATURE OF RECEIVER | | | SIGNATURE OF DELIVERER | |

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this page is the manifestation of the electronic signature.**

/s/

Rosemary Johann-Liang
10/26/04 01:21:25 PM

10/8/04

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

PRESCRIPTION DRUG USER FEE COVER SHEET

Form Approved: OMB No. 0910-0297
Expiration Date: December 31, 2006.

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

| | |
|---|---|
| 1. APPLICANT'S NAME AND ADDRESS Boehringer Ingelheim Pharmaceu4809ticals, Inc. 900 Ridgebury Road Ridgefield, CT 06877 | 4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER NDA 21-814 |
| 2. TELEPHONE NUMBER (Include Area Code) (203) 791-6759 | 5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO: _____ (APPLICATION NO. CONTAINING THE DATA). |
| 3. PRODUCT NAME APTIVUS (tipranavir) 250mg Capsules | 6. USER FEE I.D. NUMBER 4809 |

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

| | |
|--|---|
| <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) | <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.) |
| <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.) | <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory) |

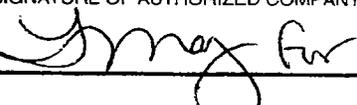
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FORTHIS APPLICATION?

YES NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

| | | | |
|--|-----|--|--|
| Department of Health and Human Services Food and Drug Administration CDER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448 | and | Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852 | An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. |
|--|-----|--|--|

| | | |
|--|---|-------------------|
| SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE  | TITLE Nancy McKay, Senior Associate Director | DATE 10/8/2004 |
|--|---|-------------------|

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

| Application Information | | |
|---|------------------------------|--|
| NDA 21-814 | Efficacy Supplement Type SE- | Supplement Number |
| Drug: APTIVUS (Tipranavir) Capsules | | Applicant: Boehringer Ingelheim Pharmaceuticals, Inc |
| RPM: Tanima Sinha | HFD- 530 | Phone # 301-827-2368 |
| <p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p> | | Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): |
| ❖ Application Classifications: | | |
| • Review priority | | <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority |
| • Chem class (NDAs only) | | 1 |
| • Other (e.g., orphan, OTC) | | AA |
| ❖ User Fee Goal Dates | | June 22, 2005 |
| ❖ Special programs (indicate all that apply) | | <input type="checkbox"/> None Subpart H <input checked="" type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 |
| ❖ User Fee Information | | |
| • User Fee | | <input checked="" type="checkbox"/> Paid UF ID number 4809 |
| • User Fee waiver | | <input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify) |
| • User Fee exception | | <input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify) |
| ❖ Application Integrity Policy (AIP) | | |
| • Applicant is on the AIP | | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| • This application is on the AIP | | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |

| | |
|--|--|
| <ul style="list-style-type: none"> • Exception for review (Center Director's memo) | n/a |
| <ul style="list-style-type: none"> • OC clearance for approval | n/a |
| <ul style="list-style-type: none"> ❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent. | (X) Verified |
| <ul style="list-style-type: none"> ❖ Patent | |
| <ul style="list-style-type: none"> • Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. | (X) Verified |
| <ul style="list-style-type: none"> • Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. | 21 CFR 314.50(i)(1)(i)(A) () Verified 21 CFR 314.50(i)(1) () (ii) () (iii) |
| <ul style="list-style-type: none"> • [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). | |
| <ul style="list-style-type: none"> • [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i> • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? () Yes () No</p> <p>(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).</p> <p><i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i></p> <p>(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? () Yes () No</p> <p><i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i></p> <p><i>If "No," continue with question (3).</i></p> <p>(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? () Yes () No</p> | (X) N/A (no paragraph IV certification) () Verified |

| | |
|--|---|
| <p>(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).</p> <p><i>If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.</i></p> <p>(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?</p> <p><i>If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i></p> <p><i>If "No," continue with question (5).</i></p> <p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p> | <p>() Yes () No</p> <p>() Yes () No</p> |
| <p>❖ Exclusivity (approvals only)</p> | <p style="background-color: #cccccc;"></p> |
| <ul style="list-style-type: none"> • Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) | <p>See exclusivity summary in pkg</p> |
| <ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. | <p>() Yes, Application # _____</p> <p>(X) No</p> |
| <p>❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)</p> | <p>NDA Filing Review</p> |

| General Information | |
|--|---|
| ❖ Actions | |
| • Proposed action | (X) AP () TA () AE () NA |
| • Previous actions (specify type and date for each action taken) | n/a |
| • Status of advertising (approvals only) | () Materials requested in AP letter (X) Reviewed for Subpart H |
| ❖ Public communications | |
| • Press Office notified of action (approval only) | (X) Yes () Not applicable |
| • Indicate what types (if any) of information dissemination are anticipated | () None (X) Press Release (X) Talk Paper () Dear Health Care Professional Letter |
| ❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)) | |
| • Division's proposed labeling (only if generated after latest applicant submission of labeling) | n/a |
| • Most recent applicant-proposed labeling | June 20, 2005 |
| • Original applicant-proposed labeling | December 22, 2004 |
| • Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings) | See consults section of action pkg |
| • Other relevant labeling (e.g., most recent 3 in class, class labeling) | n/a |
| ❖ Labels (immediate container & carton labels) | |
| • Division proposed (only if generated after latest applicant submission) | n/a |
| • Applicant proposed | June 20, 2005 |
| • Reviews | See chemistry review |
| ❖ Post-marketing commitments | See action letter |
| • Agency request for post-marketing commitments | n/a |
| • Documentation of discussions and/or agreements relating to post-marketing commitments | June 07, 2005; June 22, 2005 |
| ❖ Outgoing correspondence (i.e., letters, E-mails, faxes) | See action package |
| ❖ Memoranda and Telecons | See action package |
| ❖ Minutes of Meetings | |
| • EOP2 meeting (indicate date) | December 17, 2002 |
| • Pre-NDA meeting (indicate date) | June 02, 2004 |
| • Pre-Approval Safety Conference (indicate date; approvals only) | n/a |
| • Other | n/a |
| ❖ Advisory Committee Meeting | |
| • Date of Meeting | May 19, 2005 |
| • 48-hour alert | May 23, 2005 |
| ❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable) | n/a |

| Summary Application Review | |
|---|---|
| ❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i> | June 22, 2005 |
| Clinical Information | |
| ❖ Clinical review(s) <i>(indicate date for each review)</i> | June 22, 2005 |
| ❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i> | June 22, 2005 |
| ❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i> | Incorporated in clinical review |
| ❖ Risk Management Plan review(s) <i>(indicate date/location if incorporated in another rev)</i> | ???? |
| ❖ Pediatric Page(separate page for each indication addressing status of all age groups) | June 21, 2005 |
| ❖ Demographic Worksheet <i>(NME approvals only)</i> | See clinical and stats reviews |
| ❖ Statistical review(s) <i>(indicate date for each review)</i> | June 22, 2005 |
| ❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i> | June 22, 2005 |
| ❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i> | n/a |
| ❖ Clinical Inspection Review Summary (DSI) | |
| • Clinical studies | May 16, 2005 |
| • Bioequivalence studies | n/a |
| CMC Information | |
| ❖ CMC review(s) <i>(indicate date for each review)</i> | June 22, 2005 |
| ❖ Environmental Assessment | |
| • Categorical Exclusion <i>(indicate review date)</i> | See chemistry review |
| • Review & FONSI <i>(indicate date of review)</i> | See chemistry review |
| • Review & Environmental Impact Statement <i>(indicate date of each review)</i> | See chemistry review |
| ❖ Microbiology (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i> | n/a |
| ❖ Facilities inspection (provide EER report) | Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation |
| ❖ Methods validation | <input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested |
| Nonclinical Pharm/Tox Information | |
| ❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i> | June 22, 2005 |
| ❖ Nonclinical inspection review summary | n/a |
| ❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i> | n/a |
| ❖ CAC/ECAC report | See pharm/tox review |

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

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/s/

Virginia Behr

6/29/05 12:25:02 PM

not sure that methods validation was completed; see approval
letter.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 13, 2004

TO: Debra Birnkrant, M.D., Director
Division of Antiviral Drug Products
HFD-530

VIA: Tanima Sinha, Regulatory Health Project Manager
Division of Antiviral Drug Products
HFD-530

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication
Support (DSRCS), HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication
Support (DSRCS), HFD-410

SUBJECT: DSRCS Review of Patient Labeling for Aptivus
(tipranavir) Capsules ☐ ☐ NDA 21-814

Background and Summary

The following is the revised patient labeling for Aptivus (tipranavir) Capsules ☐ ☐ NDA 21-814. We have simplified the wording, made it consistent with the PI, and removed unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications). We have put this PPI in the patient-friendly format that we are recommending for all patient information, although, this format is not required for voluntary PPIs. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

These revisions are based on draft labeling submitted by the sponsor, dated June 3, 2005. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

Comments and Recommendations

1. The sponsor's proposed PPI was submitted with a Flesch-Kincaid reading level of 9.3 and a Flesch reading ease of 54%. For optimal comprehension among a broad range of patients, including those with lower literacy levels, patient materials should be

written at a 6th to 8th grade reading level and have a reading ease of at least 60%.

2. The PI, PRECAUTIONS section, Information for Patients subsection, states: “The Patient Package Insert provides written information for the patients, and should be dispensed with each new prescription and refill.” The sponsor should state their planned mechanism for accomplishing the distribution of the PPI with new prescription and refills of APTIVUS for the following reasons:
 - A PPI for Aptivus is voluntary patient labeling. There is no regulation requiring its printing or distribution.
 - Rarely, do pharmacies copy, store, or distribute voluntary PPIs. A patient is unlikely to receive an approved FDA PPI unless it is packaged with and distributed in a sealed unit-of-use package.

Comments to the review division are bolded, underlined and italicized. We can provide revised documents (marked and clean) in Word if requested by the review division. Please call us if you have any questions.

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_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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this page is the manifestation of the electronic signature.**

/s/

Jeanine Best
6/13/05 11:53:13 AM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
6/14/05 03:25:49 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

5 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 51,979

1-14-03

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 the meeting between representatives of your firm and FDA on December 17, 2002. The purpose of the Clinical End of Phase 2 meeting was to discuss clinical and nonclinical issues in support of the Phase 3 tipranavir program.

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

If you have any questions, call Nitin Patel, Regulatory Project Manager, at 301-827-2335.

Sincerely,

{See appended electronic signature page}

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

Enclosure



RECORD OF FDA/INDUSTRY MEETING

Date of Meeting: December 17, 2002
IND: 51,979
Drug: Tipranavir (PNU-140690)
Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc. (BI)
Indication: Treatment of HIV-1 infection
Type of Meeting: End of Phase 2 Clinical Meeting

FDA Participants:

Mark J. Goldberger, M.D., M.P.H., Office Director, ODEIV
Debra B. Birnkrant, M.D., Division Director, DAVDP
Jeffrey S. Murray, M.D., M.P.H., Deputy Division Director, DAVDP
Russell Fleischer, PA-C, M.P.H., Senior Clinical Analyst, DAVDP
Andrea James, M.D., Medical Officer, DAVDP
Anita H. Bigger, Ph.D., Pharmacologist, DAVDP
Kellie S. Reynolds, Pharm.D., Pharmacokinetics Team Leader, DAVDP
Derek Zhang, Ph.D., Pharmacokinetics Reviewer, DAVDP
Julian J. O'Rear, Ph.D., Microbiology Team Leader, DAVDP
Rafia Bhore, Ph.D., Mathematical Statistician, DAVDP
David L. Roeder, Associate Director, Regulatory Affairs, ODEIV
Harry W. Haverkos, M.D., Medical Officer, DAVDP
Virginia L. Yoerg, Regulatory Project Manager, DAVDP
Nitin Patel, R.Ph., Regulatory Project Manager, DAVDP

BI Participants:

Dr. Burkhard Blank (Senior VP, BIPI Medical and DRA)
Dr. Ulrich Drees (Head, International Project Management Virology / Immunology and
International Project Leader, Tipranavir)
Ms. Holly Dursema (Senior Research Associate, Toxicology)
Dr. Manfred Haehl (Head, International DRA / Medical)
Dr. Barry Hafkin (Medical Director, Virology / Immunology)
Dr. David Hall (Director, Biometrics and Data Management)
Dr. David Jones (Corporate DRA; International Core Team Member, DRA, Tipranavir)
Dr. Martin Kaplan (VP, BIPI DRA)
Dr. Veronika Kohlbrenner (Clinical Program Director, Clinical Monitor, Tipranavir Studies
1182.52/ 1182.12)

Dr. Elena Koundourakis (Associate Director, International Project Management Virology)
Dr. Tom MacGregor (Highly Distinguished Scientist, Drug Metabolism and Pharmacokinetics)
Dr. Douglas Mayers (Therapeutic Area Head, Virology)
Dr. Scott McCallister (Sr. Associate Director, Virology, International Core Team Member,
Medicine, Tipranavir)
Ms. Nancy McKay (Senior Associate Director, BIPI DRA and DRA-US, Tipranavir)
Mr. Dietmar Neubacher (Sr. Statistician, Project Statistician, Tipranavir)
Mr. John Sabo (Senior Scientist, Drug Metabolism and Pharmacokinetics)
Dr. Veit Schmelmer (Associate Director, R & D Project Management, International Core Team
Member, R&D, Tipranavir)
Ms. Pam Strode (Therapeutic Head Virology/Oncology/Immunology, DRA)

BACKGROUND:

This End of Phase 2 (EOP2) clinical meeting was held at the request of the Sponsor, Boehringer Ingelheim Pharmaceuticals, Inc. (BI), to discuss clinical and nonclinical issues in support of the Phase 3 tipranavir program. The objectives of this EOP2 meeting were (1) to reach consensus on the dose selection for the Phase 3 program, (2) to agree on an appropriate drug interaction management plan, (3) to agree on a plan for pediatric development, and (4) to gain concurrence on the completeness of the planned Phase 3 clinical program and the nonclinical program and their suitability to support an NDA submission for tipranavir.

The Sponsor submitted an EOP2 meeting request on October 11, 2002 (SN176), and a briefing package to the Division on November 15, 2002 (SN186).

DISCUSSION:

The Sponsor presented a brief overview of the rationale for the dose that was selected for the two Phase 3 trials. The meeting then pertained to the questions provided in the briefing package. Please note, the Sponsor's questions and proposals are shown in regular font, followed by the Division's response in bold font.

List of questions and proposals:

Question 1.1 Based on the provided information in the EOP2 meeting package, BI has identified a single TPV/RTV dose of 500 mg/200 mg BID which BI intends to carry into the Phase 3 pivotal trials, 1182.12 and 1182.48. FDA concurrence with the dose selection for the pivotal trials is sought

The Division agreed that the TPV/RTV dose of 500 mg/200 mg BID is a reasonable dose for use in the Phase 3 trials. However, the Division considered it important for the Sponsor to evaluate the following questions:

- (a) Are there better ways of meeting the needs of different patient populations and providing clinicians with dosing recommendations for those patients?**
- (b) Are there any dose-reduction or dose-escalation schemes that could be evaluated?**
- (c) Is there a role for therapeutic drug monitoring?**

Question 1.2 Trials 1182.12 and 1182.48 will represent the Phase 3 pivotal trials in the TPV clinical development program. As we understand from previous meetings with the Division in April and October 2001, the Division recommends that BI conduct two adequate and well-controlled studies in support of accelerated and traditional approval. FDA concurrence is sought

that these trials, as designed, can serve as the pivotal basis for submission of an NDA in support of accelerated approval and for subsequent traditional approval. It is clearly understood that a decision on approvability of such applications would first require review of the data.

We would like to ask for specific feedback on the following points addressed in the Special Protocol Assessment for protocol 1182.12:

- (a) Access to TPV/RTV in the long-term safety and efficacy extension trial (1182.57) for patients randomized to the comparator arm who fail virologically.
- (b) Sequential testing (non-inferiority and superiority) and use of comparator drugs

The Division concurred that in general, the trials as designed, can serve as the pivotal basis for submission of an NDA in support of accelerated approval and for subsequent traditional approval, and that a decision on approvability will be a review issue. Additionally, the Division agreed to provide specific comments on protocol 1182.12 by December 31, 2002.

Question 1.3 BI also intends to use the same TPV/RTV dose of 500 mg/200 mg BID for the Phase 1/2 pharmacokinetic/safety Trial 1182.51. FDA agreement with the dose selection for this boosted dual protease inhibitor trial is sought.

The Division agreed with the dose selection for this trial and requested the Sponsor to submit the final protocol for review.

Question 1.4 Does FDA concur with BI's proposal for the scope of studies to be provided at the time of accelerated and traditional approval?

The Division concurred with the proposal for the scope of studies to be provided at the time the accelerated and traditional approval applications are submitted.

Question 2.1 In the End of Phase 2 package, BI provided a drug interaction management plan for the Phase 3 program. FDA concurrence is sought on this plan in support of proceeding with the Phase 3 program

The Division indicated that the drug interaction management plan is acceptable. Specific comments and questions about the drug interaction management program were conveyed to the Sponsor prior to the EOP2 meeting, by telephone facsimile on December 10, 2002; the Sponsor responded on December 13, 2002 (SN196). The Division concurred with the Sponsor's responses. Since levels of zidovudine decrease when co-administered with TPV, the Division asked the Sponsor to assess the potential for zidovudine failure (resistance) in the Phase 3 trials.

Question 2.2 All TPV PK studies to date have monitored RTV levels. Based on the available data, BI has concluded that the drug monitoring of RTV plasma concentrations is no longer warranted, with the exception of trial 1182.51 (boosted dual protease inhibitor PK study) and the pediatric program. Does the FDA concur with this conclusion?

The Division concurred with this conclusion. However, in the event of unexpected drug-drug interactions, the Division indicated that available RTV levels could provide help to identify causes. The Division also recommended the inclusion of the hepatic impairment study to the list of studies for the drug monitoring of RTV plasma concentrations.

Question 2.3 At a dose of TPV/RTV 500/200 mg, ritonavir is the dominant chemical entity that influences all drug interactions. The erythromycin breath test has shown ritonavir to inhibit the CYP3A4 pathway with a single dose. Therefore, we propose to perform all future healthy-volunteer drug interaction studies using a single-dose, 3-way crossover design consistent with the guidance "*In Vivo* Drug Metabolism/Drug Interaction Studies - Study Design, Data Analysis, and Recommendations for Dosing and Labeling". This single-dose design would be: (A) substrate drug, (B) TPV/RTV 500/200 mg, and (C) substrate + TPV/RTV. Does the FDA concur?

The Division stated that multiple dose drug interaction studies are necessary with TPV/RTV because of the combination of CYP3A4 induction and inhibition. The Division indicated that multiple dose studies are desirable so that TPV/RTV can be assessed at steady-state.

Question 2.4 BI plans to provide data on single dose TPV/RTV pharmacokinetics in individuals with mild and moderate hepatic impairment at the time of submission for accelerated approval. Does FDA agree with this proposal?

The Division indicated the need for multiple dose data, since there is no evidence that single-dose TPV/RTV pharmacokinetic data can accurately predict multiple dose pharmacokinetics in subjects with hepatic impairment.

Question 3.1 BI has proposed a pediatric program for TPV. FDA concurrence is sought on this proposed program with regard to content and timing.

The Division suggested that the Sponsor's pediatric proposal could be simplified. The Division indicated that it will issue a Pediatric Written Request letter which will provide information on the type of studies that will be needed. [

]

Question 4.1 BI has presented listings of studies for the tipranavir nonclinical program in Section 4.0. Does FDA concur that the scope and timing of nonclinical studies is adequate for start of Phase 3 and for NDA submission?

The Division indicated that it is waiting for the submission of a protocol for a 26-week oral safety study in beagle dogs that was agreed to in the teleconference of December 13, 2002.

ACTION ITEMS:

1. The Division will provide specific comments regarding protocol 1182.12 by December 31, 2002.
2. The Sponsor will provide a final protocol of the Phase 1/2 pharmacokinetic/safety trial 1182.51.
3. The Division will plan to issue a Pediatric Written Request letter by December 31, 2002, but may be delayed by a few days.
4. The Sponsor will submit a protocol for a 26-week oral safety study in beagle dogs by December 31, 2002.

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/s/

Tony DeCicco
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