CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-814

Administrative/Correspondence Reviews
1.3.5.1 PATENT INFORMATION

Annexed hereto is a FORM FDA 3542a for each of the following patents:

1) U.S. Patent 5,852,195
2) U.S. Patent 6,147,095
3) U.S. Patent 6,169,181
4) U.S. Patent 6,231,887
**DEPARTMENT OF HEALTH AND HUMAN SERVICES**
**Food and Drug Administration**

**PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

**TRADE NAME (OR PROPOSED TRADE NAME)**

**APTIVUS**

**ACTIVE INGREDIENT(S)**

Tipranavir

**STRENGTH(S)**

250 mg

**DOSAGE FORM**

Capsules

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

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<th></th>
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<tbody>
<tr>
<td>5,852,195</td>
<td>12/22/1998</td>
<td>12/22/2015</td>
</tr>
</tbody>
</table>

d. Name of Patent Owner
Pharmacia & Upjohn Company LLC
c/o General Patent Counsel
Pfizer Inc.

Address (of Patent Owner)
235 East 42nd Street

City/State
New York, NY

ZIP Code
10017

Telephone Number
(212) 733-2323

FAX Number (if available)

E-Mail Address (if available)

f. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (ij)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

Telephone Number

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f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?  
   - [ ] Yes  
   - [x] No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?  
   - [ ] Yes  
   - [ ] No
### 2. Drug Product (Composition/Formula)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  
- Yes [ ]  
- No [X]

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  
- Yes [ ]  
- No [X]

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  
- Yes [ ]  
- No [ ]

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.  
- Not applicable

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement?  
- Completes the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.

2.6 Does the patent claim only an intermediate?  
- Yes [ ]  
- No [X]

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  
- Yes [ ]  
- No [X]

### 3. Method of Use

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  
- Yes [ ]  
- No [X]

3.2 Does the patent claim only an intermediate?  
- Yes [ ]  
- No [X]

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  
- Yes [ ]  
- No [X]

### 4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  
- Yes [ ]  
- No [X]

4.2 Claim Number (as listed in the patent)  
- Not applicable

| Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? | Yes [ ]  
| No [X] |

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.  
- Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

### 5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  
- Yes [ ]
6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provider information below)

[Signature]

Date Signed
09/14/2004

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- [x] NDA Applicant's/Holder's Attorney, Agent (Representative) or Other Authorized Official
- [ ] Patent Owner
- [ ] Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name
Alan Stempel

Address
900 Ridgebury Road, PO Box 368

City/State
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ZIP Code
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Telephone Number
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| DOSAGE FORM | Capsules |

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<tbody>
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<td>a. United States Patent Number 6,147,095</td>
</tr>
<tr>
<td>b. Issue Date of Patent 11/14/2000</td>
</tr>
<tr>
<td>c. Expiration Date of Patent 10/23/2019</td>
</tr>
<tr>
<td>d. Name of Patent Owner Pfizer Inc.</td>
</tr>
<tr>
<td>d. Address (of Patent Owner) 235 East 42nd Street</td>
</tr>
<tr>
<td>d. City/State New York, NY</td>
</tr>
<tr>
<td>d. ZIP Code 10017</td>
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f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?  
[ ] Yes  
[ ] No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?  
[ ] Yes  
[ ] No
For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

### Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  
☐ Yes  ☑ No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  
☐ Yes  ☑ No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  
☐ Yes  ☑ No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.  
Not applicable

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement?  
(Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  
☐ Yes  ☑ No

2.6 Does the patent claim only an intermediate?  
☐ Yes  ☑ No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  
☐ Yes  ☑ No

### Drug Product (Composition/formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  
☐ Yes  ☑ No

3.2 Does the patent claim only an intermediate?  
☐ Yes  ☑ No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  
☐ Yes  ☑ No

### Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  
 ☑ Yes  ☐ No

4.2 Claim Number (as listed in the patent)  
1-6, 8-13  
Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  
☑ Yes  ☐ No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.  
Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

### No Relevant Patents

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- No

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- No

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### Method of Use

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4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?
- Yes
- No

4.2 Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
- Yes
- No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)

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c/o General Patent Counsel

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Address (of Patent Owner)

235 East 42nd Street

City/State

New York, NY

ZIP Code

10017

FAX Number (if available)

Telephone Number

(212) 733-2323

E-Mail Address (if available)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>e. Name of agent or representative who resides or maintains a place of business within the United States</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Authorized to receive notices of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

☐ Yes ☐ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

☐ Yes ☐ No

FORM FDA 3542a (7/03)
For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

### Patent Substance

<table>
<thead>
<tr>
<th>2.1</th>
<th>Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?</th>
<th>☑ Yes</th>
<th>☐ No</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2</td>
<td>Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?</td>
<td>☑ Yes</td>
<td>☐ No</td>
</tr>
<tr>
<td>2.3</td>
<td>If the answer to question 2.2 is &quot;Yes,&quot; do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).</td>
<td>☑ Yes</td>
<td>☐ No</td>
</tr>
<tr>
<td>2.4</td>
<td>Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3. Not applicable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Drug Product (Composition/Formulation)

<table>
<thead>
<tr>
<th>3.1</th>
<th>Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)</th>
<th>☑ Yes</th>
<th>☐ No</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2</td>
<td>Does the patent claim only an intermediate?</td>
<td>☑ Yes</td>
<td>☐ No</td>
</tr>
<tr>
<td>3.3</td>
<td>If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)</td>
<td>☑ Yes</td>
<td>☐ No</td>
</tr>
</tbody>
</table>

### Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

<table>
<thead>
<tr>
<th>4.1</th>
<th>Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?</th>
<th>☑ Yes</th>
<th>☐ No</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.2</td>
<td>Claim Number (as listed in the patent)</td>
<td>☑ Yes</td>
<td>☐ No</td>
</tr>
<tr>
<td>4.2a</td>
<td>Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. | ☑ Yes |
6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

<table>
<thead>
<tr>
<th>NDA Applicant/Holder</th>
<th>NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patent Owner</td>
<td>Patent Owner's Attorney, Agent (Representative) or Other Authorized Official</td>
</tr>
</tbody>
</table>

Note: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

Name: Alan Stempel
Address: 900 Ridgebury Road, PO Box 368
City/State: Ridgefield, CT
ZIP Code: 06877
Telephone Number: (203) 798-4868
Fax Number (if available): (203) 837-4868
E-Mail Address (if available): arstempel@rdg.boehringer-ingelheim.com

The public reporting burden for this collection of information has been estimated to average 9 hours 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:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

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.
EXCLUSIVITY SUMMARY

NDA # 21-814             SUPPL #                HFD # 530

Trade Name  APTIVUS

Generic Name  tipranavir (capsules) 250 mg

Applicant Name  Boehringer Ingelheim Pharmaceuticals, Inc

Approval Date, If Known  June 22, 2005

PART I  IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?  YES ☑  NO ☐

   If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

   505(b)(1)

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")  YES ☑  NO ☐

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simplify a bioavailability study.

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:
d) Did the applicant request exclusivity?  

YES ☒  NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐  NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐  NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II  FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES  
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐  NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(#s).
2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #.(s).

NDA#
NDA#
NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of
summary for that investigation.  

YES ☐  NO ☐ 

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?  

YES ☐  NO ☐ 

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?  

YES ☐  NO ☐ 

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.  

YES ☐  NO ☐ 

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?  

YES ☐  NO ☐ 

If yes, explain:
(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

   a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

<table>
<thead>
<tr>
<th>Investigation #1</th>
<th>YES □ NO □</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigation #2</td>
<td>YES □ NO □</td>
</tr>
</tbody>
</table>

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

   b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

<table>
<thead>
<tr>
<th>Investigation #1</th>
<th>YES □ NO □</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigation #2</td>
<td>YES □ NO □</td>
</tr>
</tbody>
</table>

If you have answered "yes" for one or more investigation, identify the NDA in which a
similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"): 

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1  

IND #  YES ☐ ! NO ☐ ! Explain:

Investigation #2  

IND #  YES ☐ ! NO ☐ ! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  

YES ☐ ! NO ☐
(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

Name of person completing form:
Title:
Date:

Name of Office/Division Director signing form:
Title:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05
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
7/1/05 03:15:10 PM
PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-814 Supplement Type (e.g. SE5): _______ Supplement Number: _______

Stamp Date: December 22, 2004 Action Date: June 22, 2005

HFD-530 Trade and generic names/dosage form: APTIVUS (tipranavir) capsules, 250 mg

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc. Therapeutic Class: 7030020

Indication(s) previously approved: none, new NDA

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: This new drug application provides for the use of Aptivus® (tipranavir) capsules, 250 mg, co-administered with 200mg of ritonavir, for combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors.

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

☒ No: Please check all that apply: Partial Waiver ☒ Deferred ☐ Completed
 NOTE: More than one may apply
 Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other: ____________________________

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min ______ kg ______ mo. ______ yr. ______ Tanner Stage ______
Max ______ kg ______ mo. ______ yr. ______ Tanner Stage ______

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
Section C: Deferred Studies:

There are two deferrals for this application

Age/weight range being deferred:

Pediatric PMC # 03 on Approval Letter

<table>
<thead>
<tr>
<th>Min</th>
<th>kg</th>
<th>mo.</th>
<th>yr. 02</th>
<th>Tanner Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max</td>
<td>kg</td>
<td>mo.</td>
<td>yr. 18</td>
<td>Tanner Stage</td>
</tr>
</tbody>
</table>

Reason(s) for deferral:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☒ Adult studies ready for approval
☐ Formulation needed
Other: ________________________________

Date studies are due (mm/dd/yy): 06/30/06

Pediatric PMC # 04 on Approval Letter

<table>
<thead>
<tr>
<th>Min</th>
<th>kg</th>
<th>mo. 2 weeks</th>
<th>yr.</th>
<th>Tanner Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max</td>
<td>kg</td>
<td>mo. 2 weeks</td>
<td>yr.</td>
<td>Tanner Stage</td>
</tr>
</tbody>
</table>

Reason(s) for deferral:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☒ Adult studies ready for approval
☐ Formulation needed
Other: ________________________________

Date studies are due (mm/dd/yy): 01/31/09

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:
NDA 21-814
Page 3

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:
If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

Tanima Sinha, HFD-530

[See appended electronic signature page]

________________________________
Regulatory Project Manager

cc: NDA 21-814
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)
Attachment A
(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: ________________________________

Is there a full waiver for this indication (check one)?

☐ Yes: Please proceed to Section A.

☐ No: Please check all that apply: ___ Partial Waiver ___ Deferred ___ Completed

NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Other: ____________________________

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other: ____________________________

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.
Section C: Deferred Studies

Age/weight range being deferred:

<table>
<thead>
<tr>
<th>Min</th>
<th>kg</th>
<th>mo.</th>
<th>yr.</th>
<th>Tanner Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max</td>
<td>kg</td>
<td>mo.</td>
<td>yr.</td>
<td>Tanner Stage</td>
</tr>
</tbody>
</table>

Reason(s) for deferral:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other:

Date studies are due (mm/dd/yy): __________

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

<table>
<thead>
<tr>
<th>Min</th>
<th>kg</th>
<th>mo.</th>
<th>yr.</th>
<th>Tanner Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Max</td>
<td>kg</td>
<td>mo.</td>
<td>yr.</td>
<td>Tanner Stage</td>
</tr>
</tbody>
</table>

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

(See appended electronic signature page)

Regulatory Project Manager

cc: NDA
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Virginia Behr
6/29/05 01:00:11 PM
Boehringer Ingelheim  
NDA 21-814  
(tipranavir) 250mg Capsules

1.3.3 DEBARMENT CERTIFICATION

Certification Requirement Section 306(k)(l) of the Act 21 U.S.C. 355a(k)(1)

The undersigned certifies that Boehringer Ingelheim Pharmaceuticals, Inc. did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [Section 306(a) or (b)] of the Federal Food, Drug and Cosmetic Act in connection with tipranavir 250 mg Capsules.

Signature: [Signature]

Name of Applicant: Martin M. Kaplan, M.D., J.D.  
Vice President, Drug Regulatory Affairs  
Boehringer Ingelheim Pharmaceuticals, Inc.

Date: Oct. 11, 2004

Mailing Address: Boehringer Ingelheim Pharmaceuticals Inc.  
900 Ridgebury Road  
P.O. Box 368  
Ridgefield, CT 06877-0368
406 PAGES REMOVED. SEE THE ADVISORY COMMITTEE MEETING INFORMATION LOCATED ON THE FDA WEBSITE BELOW:

http://www.fda.gov/ohrms/dockets/ac/

[transcript]
Deputy Office Director Memo

Applicant: Boehringer Ingelheim Pharmaceuticals, Inc.

NDA #s: NDA 21-814 Aptivus® (tipranavir) 250 mg capsules

Drug: tipranavir

Trade Name: Aptivus®

Indication: APTIVUS® (tipranavir), co-administered with 200 mg of ritonavir, is indicated for combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors

Date of submission: December 22, 2004

PDUFA goal date: June 22, 2005

Recommended Regulatory Action:

- NDA 21-814 Aptivus® (tipranavir) 250 mg capsules Approval under 21 CFR 314.510 Subpart H, accelerated approval for NDA 21-814

The pre-clinical and clinical reviewers have reviewed the issues in their disciplines in detail with regards to the safety and efficacy of Aptivus® (tipranavir). For a detailed review of the individual disciplines the reader is referred to these individual reviews. The reader is also referred to Dr. Johann-Liang's Medical Team Leader Memos and Dr. Birnkrant's Division Director's Memo. This review will focus on selected findings and issues from the application.

The Chemistry for Aptivus® (tipranavir) capsules is discussed in Dr. Lo's review and she has recommended approval for NDAs 21-814 (capsule). Pre-approval inspections of the manufacturing and testing facilities were found to be acceptable.
The Pharmacology/Toxicology studies for tipranavir are reviewed in detail in Dr. Anita Bigger's review. The target organs in repeat dose studies were primarily the liver and gastrointestinal tract (with GI effects of emesis, soft stool, diarrhea, or excessive salivation). Liver-related findings in animal studies included histopathologic changes consistent with tipranavir's induction of microsomal enzymes, increases in liver analytes (alkaline phosphatase, AST, and ALT), and histopathologic effects on the biliary system that were more commonly noted in tipranavir-treated dogs. Liver-related findings in mice included AST and ALT elevations at high doses that was correlated with hepatocellular necrosis.

Tipranavir demonstrated inhibition in a HERG assay, but did not demonstrate an effect on action potential in guinea pig papillary muscle at concentrations up to 10 μM. In beagle dogs at doses up to 160 mg/kg, tipranavir did not demonstrate effects on the QT interval. Tipranavir is labeled as Pregnancy Category C. Carcinogenicity studies are currently ongoing.

The Clinical Pharmacology of tipranavir is described in Dr. Derek Zhang's Review. Tipranavir 500 mg administered in combination with ritonavir 200 mg twice daily is a net inhibitor of CYP3A. In vitro studies indicate that CYP3A is the predominant cytochrome isofrom involved in the metabolism of tipranavir. Tipranavir is also a P-gp substrate. Tipranavir co-administered with ritonavir should be taken with food; the bioavailability of tipranavir is increased in the setting of a high fat meal. Tipranavir is highly protein bound in human plasma (>99.9%).

The Aptivus (tipranavir) product label provides a listing of drug interactions for tipranavir co-administered with ritonavir (TPV/r). TPV/r should not be co-administered with the following drugs: the antiarrhythmics, amiodarone, bepridil, flecanide, propafenone, or quinidine; rifampin; the ergot derivatives dihydroergotamine, ergonovine, ergotamine, or methylergonovine; cisapride; St. John's wort; the HMG CoA reductase inhibitors lovastatin or simvastatin; pimozide; or the sedative hypnotics midazolam or triazolam. The label also provides a listing of other drugs with which there are established or potential drug interactions with TPV/r. Additional drug interaction studies are planned, many of which are postmarketing commitments.

The dose for the phase 3 studies was selected largely based upon data from study 1182.52 which examined doses of TPV/r of 500/100 mg; 500/200 mg; and 750/200 mg. The selection of the 500/200 mg dose for the phase 3 studies was based upon virologic response and tolerability of 500/200 mg dose.

Exposure-response data from the clinical studies were analyzed. The data demonstrated that response was related to the Inhibitory Quotient (IQ) defined as the $C_{\text{min}}/IC_{50}$, corrected for protein binding. As noted in the Aptivus label “Among the 206 patients receiving APTIVUS/ritonavir without enfuvirtide, the response rate was 23% in those with an IQ value < 75 and 55% in those with an IQ value ≥ 75. Among the 95 patients receiving APTIVUS/ritonavir with enfuvirtide, the response rates in patients with an IQ value < 75 versus those with an IQ value ≥ 75 were 43% and 84%, respectively.
These IQ groups are derived from a select population and are not meant to represent clinical breakpoints." Also noted was an exposure-response relationship with grade 3/4 ALT elevations. Boehringer Ingelheim will continue to work with the agency to develop a protocol for a pilot study to investigate therapeutic drug monitoring in HIV-infected patients receiving TPV/r.

Tipranavir solution 100mg/mL was not found to be bioequivalent to tipranavir capsules. The solution was found to be approximately 30% more bioavailable than the capsule when administered under fasted conditions. This may relate to the differences in the excipients for the two formulations and possibly their effects on CYP3A and P-gp. In addition, because of the effects on enzymes/transporters, the relative bioavailability should be evaluated at steady state.

The microbiology of tipranavir is described in Dr. Lisa Naeger’s microbiologist’s review for NDAs 21-814, Tipranavir is an HIV protease inhibitor. Ninety percent (94/105) of HIV-1 isolates resistant to amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, and ritonavir had a ≤ 3-fold decrease in tipranavir susceptibility. Mutations in the HIV-1 protease associated with reduced susceptibility to tipranavir were characterized by genotypic evaluation of resistant isolates and additional in vitro studies utilizing site-directed mutagenesis.

The detailed results of the clinical trials are discussed in Dr. Andrea James’ Medical Officer’s review and Dr. Bhore and Dr. Zhou Statistical reviews and Dr. Johann-Liang’s Medical Team Leader memo. For a detailed review of the findings, the reader is referred to their reviews.

For the indication of combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors, the applicant provided data from two phase 3 studies in highly treatment experienced patients. The studies evaluated tipranavir 500 mg co-administered with ritonavir 200 mg twice daily in highly treatment experienced patients. On average patients had received treatment with 4 protease inhibitors prior to enrollment. The studies included an escape clause at Week 8 that provided a means for patients with virologic failure at Week 8 to be classified as failures and receive tipranavir in a rollover study. The primary endpoint was confirmed ≥ 1 log reduction in viral load from baseline at 24 weeks. In both studies the tipranavir treatment arm of the study was superior to the comparator arm which included a ritonavir boosted protease inhibitor. The observed outcomes by treatment arm through week 24 for the primary endpoint of virologic response was 40% for the TPV/r arm and 18% for the comparator arm. The secondary endpoints corroborated the findings for the primary endpoint.

The results of the studies support the efficacy of tipranavir for the treatment of HIV-1 adults patients with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors.
The clinical safety data for tipranavir is derived from approximately 3200 subjects who received at least one dose of tipranavir. Approximately 1400 patients received doses of tipranavir 500 mg with ritonavir 200 mg with 761 patients receiving this regimen for a duration of at least 24 weeks.

Review of patients with changes in liver-associated enzymes in phase 2 studies shows that the incidence of grade 3/4 ALT elevations were related to tipranavir exposure. In the phase 3 trials 6% (45/732) of patients on the tipranavir arm experienced grade 3 or 4 elevations in ALT/AST compared to 2% (18/723) of patients in the comparator arm. The risk for elevations in transaminases was greater in patients with underlying chronic hepatitis B or C. The Aptivus label provides a boxed warning about clinical hepatitis and hepatic decompensation including some fatalities and the increased risk in patients who are co-infected with hepatitis B or C. Monitoring of liver function tests should be performed prior to initiating therapy and during therapy with TPV/r.

Rashes of mild to moderately severe have been observed in patients receiving ritonavir. In phase 2 and 3 trials rash was reported in 14% of female patients and 8 to 10% of males. In a drug interaction study of ethinyl estradiol 33% (17/51) of female patients experienced rash. The product label describes the rash adverse events from the clinical program.

Elevations in plasma triglycerides and cholesterol occurred in patients receiving TPV/r. Grade 3 or 4 treatment emergent laboratory abnormalities in cholesterol or triglycerides were reported more frequently in patients receiving TPV/r than comparator in the phase 3 studies. Monitoring of triglycerides and cholesterol should be performed prior to and during therapy with TPV/r.

The drug-drug interactions profile of tipranavir co-administered with ritonavir is detailed in the product label. TPV/r is metabolized predominantly by CYP3A and is a net CYP3A inhibitor and hence there are interactions with a number of other therapeutic agents. Additional drug interactions studies will be conducted as phase 4 studies.

The effect of tipranavir on cardiac repolarization was evaluated in vitro and in vivo. Tipranavir had an effect on the hERG-associated potassium channel. No effect was noted on action potential in the guinea pig papillary muscle in vitro. In a dog study no effect was noted on electrocardiograms. From analysis of ECGs performed in 5 phase 1 studies no findings regarding cardiac repolarization safety issues were noted. The company has agreed to conduct a formal QT study as a postmarketing commitment.

The tipranavir application was discussed before the Antiviral Drug Products Advisory Committee on May 19, 2005. With regards to the question as to whether safety and efficacy had been demonstrated the votes were 11 Yes and 3 No that safety and efficacy had been demonstrated. The committee discussions also included discussion of hepatic adverse effects, rash, drug interactions, longer term data and a discussion of therapeutic drug monitoring.
Aptivus (tipranavir) 500 mg co-administered with ritonavir 200 mg twice daily provides a therapeutic option for patients with limited or no therapeutic options for HIV-1 infected adult patients with evidence of viral replication, who are highly treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors. In this patient population where there are limited treatment options, the risk benefit for tipranavir co-administered with ritonavir as part of a regimen for treatment of HIV-1 infection is satisfactory. The product label provides a description of the safety profile of tipranavir.

The applicant has agreed to perform a number of studies as phase 4 commitments including studies to further characterize drug interactions, perform a formal QT study, and perform a pilot study that investigates therapeutic drug monitoring. As part of the accelerated approval of Aptivus the applicant will provide 48-week data to confirm the findings from the 24-week data from the phase 3 trials.

**Summary Recommendations**

- NDA 21-814 Aptivus® (tipranavir) 250 mg capsules

  **Approval** under 21 CFR 314.510 Subpart H, accelerated approval for NDA 21-814
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/s/
Edward Cox
6/22/05 04:50:24 PM
MEDICAL OFFICER
DATE: 6-21-05

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

TO: Division File

SUBJECT: Division Director's Memorandum for NDA 21-814 for tipranavir 250 mg capsules co-administered with ritonavir for combination antiretroviral treatment of HIV-1 infected adult patients with evidence of viral replication who are heavily treatment experienced or have HIV-1 strains resistant to multiple protease inhibitors

1.0 Background

To date, there are 20 antiretroviral drug products on the market. They fall into four classes: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and fusion inhibitors. In the last category, there is only one drug product, enfuvirtide, also known as T-20. This is an injectable product with a significant adverse event profile that is labeled for use in combination with other antiretrovirals in treatment experienced patients with evidence of HIV-1 replication despite ongoing antiretroviral therapy. Thus, the armamentarium for treatment of advanced patients is quite limited, not only because of the challenges related to T-20, but many drugs within the same class, such as NNRTIs can show substantial levels of cross resistance.

On December 22, 2004, Boehringer Ingelheim (BI) submitted a New Drug Application (NDA) for tipranavir (TPV) capsules in combination with boosted ritonavir for treatment of HIV-1 infected adults who are heavily treatment experienced or have HIV-1 strains resistant to multiple protease inhibitors. The application received a priority review because it was determined that the drug product would be a significant improvement compared to marketed drugs for the same indication. The NDA for tipranavir was presented to an Antiviral Drugs Advisory Committee on May 19, 2005. Following discussion of the safety and efficacy data contained in the NDA, the advisory committee voted 11-3 in favor of approving tipranavir in combination with ritonavir, for patients with limited treatment options, based on its risk/benefit profile.

This memorandum summarizes the findings in the NDA and is written in support of approval of this application.

2.0 Summary of Efficacy

Dosage selection for the phase 3 studies was rational and based on phase 2 study 1182.52. The 500 mg/200 mg dose was selected because the lower dose
was inferior with regard to efficacy and the higher dose, although effective, showed greater toxicity, especially hepatotoxicity.

The efficacy of TPV was demonstrated in two phase 3 clinical trials, 1182.12 (RESIST 1) and 1182.48 (RESIST 2). Both studies were of similar design and had the following common features:

- Open-label, multicenter, controlled
- Optimized comparator arm consisted of one of the choice of 4 boosted PIs – lopinavir, amprenavir, indinavir and saquinavir; the protocols were later amended to allow patients who were resistant to the protease inhibitors to still receive them
- Week 8 escape clause whereby patients in the comparator arm who experienced virologic failure could leave the study and receive tipranavir in a roll over study
- Entry viral load ≥ 1000 copies/mL
- 3 ARV class experienced and dual PI experienced
- Genotype resistance testing performed at baseline with at least 1 primary PI mutation at codons 30N, 46I/L, 48V, 50V, 82 A/F/L/T, 84V or 90M
- ≤ 2 mutations at codons 33,82, 84 or 90

For both trials, the primary efficacy endpoint was confirmed > 1 log reduction in viral load from baseline at 24 weeks; secondary endpoints included proportion of patients with viral load < 50 and < 400 copies/mL and changes from baseline in CD4 counts.

The patient population was highly treatment experienced with limited treatment options. On average they had received 4 protease inhibitors (range 1-7) prior to entry. At baseline 97% of isolates were resistant to at least one PI, 95% of the isolates were resistant to at least 1 NRTI and > 75% of the isolates were resistant to at least 1 NNRTI. Forty percent of the population had a baseline HIV RNA > 100,000, 61% had a CD4 count < 200 cells/mL and 57% had experienced an AIDS-defining illness. Twelve percent of subjects had used enfuvirtide (T-20), a fusion inhibitor prior to entry.

In the primary efficacy analysis in both pivotal studies, TPV was shown to be statistically superior to the comparator arm. TPV was also superior to the comparator for multiple secondary endpoints. These findings are outlined in the medical officer review by Dr. Andrea James and in the statistical review by Dr. Rafia Bhoore and summarized below. Sensitivity analyses underscored the robust treatment findings.

Briefly, for Resist 1 and 2, a total of 1,159 patients received either TPV with low-dose ritonavir(r) plus an optimized background regimen(OBR) or just the OBR
containing a boosted protease inhibitor that will be referred to as control PI
boosted with low-dose ritonavir or CPI/r. Virologic responders were 40% in the
TPV/r arm compared to 18% in the CPI/r arm. The proportion of patients in the
TPV/r arm compared to the CPI/r arm with HIV-1 RNA < 400 copies/mL was 34%
and 16%, respectively. Similarly, a greater proportion of subjects in the TPV/r
arm compared to the CPI/r arm achieved < 50 copies/mL of HIV RNA, 23% versus 9%,
respectively. The activity of TPV/r also translated into a more
favorable immunologic outcome. The median change from baseline in CD4 cell
count was +34 cells/mm3 in the TPV arm compared to +4 cells/mm3 in the CPI/r
arm.

Subjects who received TPV/r had a better virologic outcome if they were also
receiving T-20. Specifically, among patients also receiving T-20, treatment
response was seen in 48% of subjects compared to 19% of subjects on the
TPV/r and CPI/r arms, respectively. Not only were TPV and T-20 synergistic in
vitro, but if TPV/r is used with a second new agent, such as T-20, then there is a
greater likelihood that the treatment effect will be greater and functional
monotherapy avoided. A more favorable outcome was also seen in the T-20
trials if T-20 was used with another new antiretroviral agent.

Outcome was also affected by baseline mutations, both number and type. This
is detailed in the microbiology reviews by Drs. Lisa Naeger and Kim Struble.

3.0 Summary of Safety

The safety of TPV was demonstrated in studies comprising 3,195 subjects who
received TPV as follows:

- 2,430 HIV positive subjects and 765 HIV negative subjects have been
  exposed to at least 1 dose of TPV in 39 studies as of June 11, 2004
- 1,397 HIV positive patients have received TPV/r at the to-be-marketed
dose of 500 mg TPV/200 mg ritonavir
- 761/1,397 HIV positive patients have been exposed to TPV/r at a dose of
  500 mg/200 mg for ≥ 24 weeks

Hepatotoxicity was seen in 19% of healthy volunteers receiving TPV in phase 1
studies. Dose-dependent hepatotoxicity was seen in a dose-finding phase 2
trial, 1182.52. In that trial it was determined that increasing doses of TPV were
associated with greater TPV concentrations and the TPV concentrations, not the
ritonavir concentrations were responsible for the dose-dependent hepatotoxicity.

In the RESIST trials, through 24 weeks, 6% of subjects on the TPV/r arm (n=45)
compared to 2% (n=18) on the CPI/r arm experienced grade 3 or 4 ALT/AST
elevations. Among subjects with baseline ALT/AST > grade 1, 1/21 developed a
grade 3 or 4 ALT/AST compared to 4/23 on the CPI/r arm. Hepatotoxicity among
subjects with baseline hepatitis B or C was 12% (9/76) in the TPV/r arm compared to a rate of 5% (6/113) in the control arm. Most of the elevated AST/ALT levels were asymptomatic and treatment often continued despite elevated levels. Management of this finding can be accomplished by obtaining baseline AST/ALT determinations with cautious and frequent monitoring during treatment.

Concerns about hepatotoxicity will be placed in the labeling for TPV. A box warning will state that reports of clinical hepatitis and hepatic decompensation including fatalities have been reported in patients receiving TPV/r. Further, extra vigilance is warranted in patients with chronic hepatitis B or C co-infection, as these patients have an increased risk of hepatotoxicity. In the warnings section of the label, health care providers are advised to obtain tests of liver function at baseline and frequently throughout treatment. The combination of TPV with low-dose ritonavir is contraindicated in patients with moderate-to-severe hepatic insufficiency (Child-Pugh Class B and C).

The second safety issue of rash is worthy of comment. A discussion of rash can be found in the review by Dr. Melissa Baylor, appended to Dr. Andrea James’ extensive safety review. In a drug interaction study, 1182.22, healthy female volunteers received a single dose of ethinyl estradiol followed by TPV/r. Thirty-three percent (n=17) developed a rash. An additional 18% of subjects had musculoskeletal symptoms or symptoms consistent with hypersensitivity. The study was prematurely stopped due to these findings. Apparently subjects in trial 1182.22 were not allergic to sulfia drugs; this is important as TPV contains a sulfia moiety. In the RESIST trials, 11% of subjects with a sulfia allergy developed a rash compared to the same percentage in those without a sulfia allergy history who also developed a rash. Looking at rash by gender in the RESIST trials, the percentage of females who developed a rash was greater on the TPV/r arm compared to the control arm, 17/118 versus 8/90. It is unclear if rash is associated with a better immune status, female gender or sulfia allergy. It is clear that women receiving TPV/r experience rash more frequently than men. Examination of rash will be further evaluated in a post-marketing study in women and in a treatment study in naïve patients, 1182.33.

A third important safety issue was related to lipid elevations. Increased cholesterol and triglycerides were seen more commonly in TPV/r-containing regimens as compared to control. Hypertryglyceridemia was observed in 1.9% of subjects receiving TPV/r in the RESIST trials compared to 0.8% in the control group. Cholesterol > 400 mg/dL was seen in 3.3% of subjects receiving TPV/r compared to a rate of 0.3% in the control arm. Triglycerides > 750 mg/dL were observed at a greater rate in the TPV/r group than the CPI/r group, 20.8% versus 11.2%. The label contains wording in the precautions section that triglyceride and cholesterol testing should be performed prior to and during therapy with ritonavir-boosted TPV and should be managed as clinically appropriate, noting drug interactions with some of the statins.
A total of 102 deaths occurred in the TPV development program as of June 11, 2004, the date when the clinical database was locked for analysis purposes. This figure included deaths from expanded access studies. In the RESIST clinical trials, the death rates were comparable at a rate of 1%. This rate is not unexpected because this was a heavily treatment experienced population. It is also not surprising that the death rates were comparable given the greater activity of TPV/r. These trials were not long enough to see the treatment effect of viral load reduction translate into improved mortality. Perhaps when these trials are submitted with longer term data, then a mortality difference may be seen. Also, the 8-week escape clause in the RESIST trials allowed for advanced subjects to leave the CPI/r arm and receive TPV/r. If patients stayed on the CPI/r arm longer then mortality rates may have been higher in control subjects.

5.0 Summary of Clinical Pharmacology Issues

TPV must be administered with 200 mg of ritonavir to help to ensure its therapeutic effect. TPV/r is both a CYP3A inhibitor and a P-gp inducer. Consequently, drug interactions are of concern. Contraindicated drug classes include certain antiarrhythmics, antihistamines, antimycobacterials such as rifampin, ergot derivatives, GI motility agents such as cisapride, herbal products, HMG CoA reductase inhibitors, neuroleptics and sedative/hypnotics; not all drugs in these classes are contraindicated and it is recommended that health care providers consult product labeling. Please see an extensive clinical biopharmaceutics review by Dr. Derek Zhang.

Exposure response data were reviewed. Based on review of data from the RESIST trials, the Inhibitory Quotient (IQ), defined as Cmin/IC50 (corrected for protein binding) was determined for a subset of patients (n=301). Ninety-five of these patients received T-20 along with tipranavir/ritonavir (TPV/r). There was a relationship between the probability of a ≥1 log10 reduction of viral load from baseline at week 24 and the IQ. For an IQ < about 75, the response rate was 23% and 43% for patients who did not receive T-20 and who did receive T-20, respectively. For an IQ greater than or equal to approximately 75 the response rate was 55% and 84% for patients who did not receive T-20 and who did receive T-20, respectively. Of note, the IQ values are not meant to represent clinical breakpoints. Conclusions regarding the relevance of the IQ data are subject to change pending additional data.

Although this metric appears to be promising, an assay for therapeutic drug monitoring (TDM) is unavailable at present. Thus, dose adjustments for both efficacy and toxicity have not been confirmed in a clinical trial. The division has asked and BI has agreed to conduct a pilot study examining TDM. In addition BI has agreed to incorporate TDM in a trial examining TPV/r in subjects who are HIV and hepatitis B or C co-infected.
6.0 Summary of Regulatory Issues

The following phase 4 commitments will be requested of the applicant:

**Drug-Drug Interaction Trials**

1. Conduct a human drug-drug interaction study of TPV/r twice daily and atazanavir.
   
   Protocol Submission: Study completed
   Final report Submission: Submitted by December 31, 2005
2. Conduct a human drug-drug interaction study of TPV/r twice daily and buprenorphine/naloxone.
   
   Protocol Submission: July 15, 2005
   Final report Submission: Submitted by June 30, 2006
3. Conduct a human drug-drug interaction study of TPV/r twice daily and carbamazepine.
   
   Protocol Submission: July 15, 2005
   Final report Submission: Submitted by September 30, 2006
   
   Protocol Submission: August 31, 2005
   Final report Submission: Submitted by December 31, 2006
   
   Protocol Submission: August 31, 2005
   Final report Submission: Submitted by June 30, 2007
6. Conduct a human drug-drug interaction study of TPV/r twice daily and methadone.
   
   Protocol Submission: Study completed.
   Final report Submission: Submitted by September 30, 2005
Pharmacology/Toxicology

7. Complete ongoing carcinogenicity study in mice and submit final report.
   Protocol Submission: Completed
   Final report Submission: December 31, 2006

8. Complete ongoing carcinogenicity study in rats and submit final report.
   Protocol Submission: Completed
   Final Report submission: December 31, 2005

Special Populations

9. Assess the long term (48 week) antiviral efficacy and safety of TPV/r in ARV treatment naïve patients through the conduct of study 1182.33.
   Protocol Submission: Completed
   Final report Submission: 

10. Evaluate drug resistance in viruses from patients with virologic rebound on initial ART (in 1182.33).
    Final report Submission: 

11. Assess metabolic changes being studied in sub-study of 1182.33.
    Final report Submission: September 30, 2006

12. Assess two alternative doses of either TPV/r liquid formulation or capsules in ARV naïve and experienced children and adolescents between 2 and 18 years of age.
    Protocol Submission: Completed
    Final report Submission: June 30, 2006

13. Evaluate dose requirements in pediatric patients age 2 weeks to 2 years with HIV-1 infection (after review of 48 week data from the 2 to 18 year old children in trial 1182.14 with the FDA).
    Protocol Submission: September 30, 2006
    Final report Submission: January 31, 2009

14. Conduct a 48-week prospective observational diversity cohort study with TPV/r twice daily stratified by race and gender in HIV-positive patients to
assess efficacy and safety, including potential risk parameters such as CD4+ cell count.

Protocol Submission: March 30, 2006
Final report Submission: September 1, 2008

15. Conduct a 48-week prospective observational cohort study with TPV/r twice daily in patients co-infected with HIV and HBV or HCV to assess efficacy and safety. BI will discuss potential therapeutic drug monitoring substudy for this protocol with the FDA.

Protocol Submission: March 30, 2006
Final report Submission: July 1, 2008

16. Assess TPV/r pharmacokinetics in HIV-negative subjects with Child-Pugh B liver disease.

Protocol Submission: December 31, 2006
Final report Submission: December 31, 2007

Pharmacokinetics

17. Conduct a CYP/P-gp mechanistic study to determine effect of TPV/r on individual CYPs.

Protocol Submission: September 30, 2005
Final report Submission: December 31, 2006

Clinical

18. Conduct a formal QT prolongation study.

Protocol Submission: Special Protocol Assessment Complete
Final report Submission: June 30, 2006
Furthermore, BI intends to conduct the following studies, but not as post-marketing commitments:

Drug-Drug Interaction Trials

1. Conduct a human drug-drug interaction study of TPV/r twice daily and bupropion.

2. Conduct a human drug-drug interaction study of TPV/r twice daily and the investigational antiviral drug [ ]

3. Conduct a human drug-drug interaction study of TPV/r twice daily and the investigational antiviral drug [ ]

4. Conduct a human drug-drug interaction study of TPV/r twice daily and the investigational antiviral drug [ ]

5. Conduct a human drug-drug interaction study of TPV/r twice daily and the investigational antiviral drug [ ]

6. Conduct a human drug-drug interaction study of TPV/r twice daily and the investigational antiviral drug [ ]

Pharmacokinetics

7. Conduct a study to assess intracellular triphosphate levels of zidovudine and abacavir when co-administered with TPV/r twice daily.

Clinical

8. Conduct a long-term cardiovascular safety of PI/r (including TPV) from epidemiologic databases.

Microbiology

9. Evaluate cleavage site mutations in rebound samples on TPV.

Therapeutic Drug Monitoring

10. Work with the DAVDP to develop a pilot study of the utility of therapeutic drug monitoring in HIV-infected patients receiving TPV/r twice daily. BI commits to work with outside investigators to conduct a larger trial if the initial data show evidence of a clinical benefit with therapeutic drug monitoring.
7.0 Recommendation

I concur with the findings of the multidisciplinary review team that the New Drug Application for TPV 250 mg capsules to be used in combination with ritonavir given as a bid regimen of TPV 500 mg/ritonavir 200 mg in combination with other antiretrovirals should be approved under subpart H, accelerated approval regulations for serious or life-threatening illnesses (314.500). Approval under this section is subject to the requirement that the applicant study the drug further to verify and describe its clinical benefit; long term data of greater than 48 weeks from RESIST 1 AND 2 will be used as confirmatory clinical trials.

My recommendation is based on a review of the safety and efficacy data contained in this application and the expert opinions of our advisory panel. TPV/r will provide another treatment option in the armamentarium of therapies for highly treatment-experienced patients. The risk/benefit profile of TPV/r applies to the group of subjects with limited treatment options that can benefit from use of TPV/r to be able to construct a viable treatment regimen. The risk/benefit profile will be different for naïve patient populations and those with less advanced HIV disease. Thus, TPV will receive an indication that is limited to HIV-1 infected adult patients with evidence of viral replication who are heavily treatment-experienced or have HIV-1 strains resistant to multiple protease inhibitors.
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/s/

Debra Birnkrant
6/22/05 02:26:38 PM
MEDICAL OFFICER
DD memo for TPV capsules

Edward Cox
6/22/05 04:31:22 PM
MEDICAL OFFICER
MEMORANDUM

Date: June 15, 2005

From: Markham C. Luke, M.D., Ph.D., Dermatology Team Leader

Through: Stanka Kukich, M.D., Deputy Division Director, DDDDP

To: Andrea James, M.D., Medical Officer, DAVDP
Rosemary Johann-Liang, M.D., Clinical Team Leader, DAVDP
Debra Birnkrandt, M.D., Division Director, DAVDP

Cc: Tania Sinha, Project Manager, DAVDP
Florence Houn, M.D., Office Director, ODE 3
Julie Bietz, M.D., Deputy Office Director, ODE 3
Browyn Collier, ADRA, ODE 3
M.J. Kozmaformaro, R.N., Sup. P.M., DDDDP

Re: NDA 21-814 DDDDP Consult received April 1, 2005. Text of consult request: “The NDAs for tipranavir had been submitted for review on December 22, 2004. On 09-Feb. 2005, we received photos of healthy HIV(-) women with rashes from the applicant. These photos are available on the EDR under the NDA 21-814. The clinical reviewers are wondering if there is an increased risk of rash in women receiving oral contraceptives and what your experience with rash in healthy volunteers in drug interaction studies has been. Our clinical reviewers are available for discussion regarding these rashes seen in HIV(-) healthy women volunteers if needed. PDUFA date is June 22, 2005. Advisory Committee Meeting is scheduled for May 19, 2005.”

Material Reviewed: Photographs of rash.

Review: As was previously verbally discussed with the Primary Clinical Reviewer and Team Leader, the rashes observed in this study were difficult to assess from the photographs. No biopsy reports or dermatology office notes were available to me. The
photographs did not have anatomical landmarks available for perspective. They appeared to be close-up photographs. Greater detail was requested, but not provided.

It is apparent that no further information was going to be forthcoming on this issue at this time, so this written consult reply reiterates the previous clinical discussion regarding the rash observed in the clinical trials.

Other drugs have reported rashes with increased predominance in the female population (e.g. gemifloxacin). The exact mechanism for this gender inequality is not clear. In addition, certain types of rashes (e.g. the rash associated with lupus or rashes associated with pregnancy) have a predisposition for the female gender and may be related to estrogen or progesterone action.

It is recommended that labeling adequately reflect this potential concern and that this be included in the risk-benefit assessment. This was discussed with Dr. James. Rash was not a barrier to approval previously for gemifloxacin, however, discussion for gemifloxacin included concern about crossover of the rash effect (e.g. a rash to one drug in a class potentially affect the use of other drugs in the same class by the same patients who get the rash). Clearly, if there is a need for this drug, the benefits would potentially outweigh any risk associated with a rash such as seen in the photographs.

Thank you for allowing us to participate in your evaluation of this drug product. Please do not hesitate to contact the Division of Dermatologic and Dental Drug Products with any further questions or comments.
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/s/

Markham Luke
6/15/05 12:11:41 PM
MEDICAL OFFICER

Stanka Kukich
6/15/05 06:56:37 PM
MEDICAL OFFICER
On June 03, 2005, an email was sent to Boehringer Ingelheim, Pharmaceuticals, Inc. on behalf of Dr. Lisa Naeger, the primary Microbiology reviewer for this application. Contained in that email, was the microbiology section proposed by Dr. Naeger for the applicant’s consideration. Please see below for the proposed wording.

Microbiology

[Note to Applicant: Please put in a statement about the antiviral activity of TPV against different clades of HIV-1 and activity against HIV-2.]
3 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓  § 552(b)(5) Draft Labeling
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tania Sinha
6/3/05 12:05:11 PM
CSO
Micro label to BIPI, 6-3-05.
REQUEST FOR CONSULTATION

FROM: Tanima Sinha, HFD-530 (Division of Antiviral Drug Products)


NAME OF DRUG: Tipranavir (Aprivus®)  PRIORITY CONSIDERATION: Priority Review of NDA  CLASSIFICATION OF DRUG: Anti-HIV  DESIRED COMPLETION DATE: June 17, 2005

NAME OF FIRM: Boehringer Ingelheim Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- NEW PROTOCOL
- PROGRESS REPORT
- NEW CORRESPONDENCE
- DRUG ADVERTISING
- ADVERSE REACTION REPORT
- MANUFACTURING CHANGE/ADDITION
- MEETING PLANNED BY
- PRE-NDA MEETING
- END OF PHASE II MEETING
- RESUBMISSION
- SAFETY/EFFICACY
- PAPER NDA
- CONTROL SUPPLEMENT
- RESPONSE TO DEFICIENCY LETTER
- FINAL PRINTED LABELING
- ORIGINAL REVISION
- ORIGINAL NEW CORRESPONDENCE
- FORMULATIVE REVIEW
- OTHER (SPECIFY BELOW):

II. BIOMETRICS

- STATISTICAL EVALUATION BRANCH
  - TYPE A OR B NDA REVIEW
  - END OF PHASE II MEETING
  - CONTROLLED STUDIES
  - PROTOCOL REVIEW
  - OTHER (SPECIFY BELOW):

- STATISTICAL APPLICATION BRANCH
  - CHEMISTRY REVIEW
  - PHARMACOLOGY
  - BIOPHARMACEUTICS
  - OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
- BIOAVAILABILITY STUDIES
- PHASE IV STUDIES
- DEFICIENCY LETTER RESPONSE
- PROTOCOL-BIOPHARMACEUTICS
- IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- CASE REPORTS OF SPECIFIC REACTIONS (List below)
- COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- SUMMARY OF ADVERSE EXPERIENCE
- POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- CLINICAL
- PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

We have an NDA (21-814) in the Division of Antiviral Drug Products with a PDUFA date of June 22, 2005 for Tipranavir capsules (Aprivus®). We were recommended by DMETS to consult DSRCS regarding the label. I have forwarded the latest PI and PPI via email to Jeanine Best and Tara Turner.

Thanks,
Tania Sinha

*SIGNATURE OF REQUESTER  METHOD OF DELIVERY (Check one)  X MAIL  HAND

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

/s/

Rosemary Johann-Liang
6/6/05 10:03:50 AM
## REQUEST FOR CONSULTATION

### (Office/Division): Division of Dermatologic and Dental

**HFD-540, Mary Jean Kozma-Fornaro**

### FROM (Name, Office/Division, and Phone Number of Requestor): Tanima Sinha, Division of Antiviral Drug Products, HFD-530

**301-827-2368**

### DATE

**March 22, 2005**

### IND NO.

**51,979**

### NDA NO.

**21-814 (caps)**

### TYPE OF DOCUMENT

**Electronic (EDR)**

### DATE OF DOCUMENT

**09-Feb. 2005**

### NAME OF DRUG

**tipranavir**

### PRIORITY CONSIDERATION

**Priority Review**

### CLASSIFICATION OF DRUG

**Anti-HIV-1**

### DESIRED COMPLETION DATE

**April 30, 2005**

### NAME OF FIRM: Boehringer-Ingelheim Pharmaceuticals, Inc.

### REASON FOR REQUEST

#### I. GENERAL

- [ ] NEW PROTOCOL
- [ ] PROGRESS REPORT
- [ ] NEW CORRESPONDENCE
- [ ] DRUG ADVERTISING
- [ ] ADVERSE REACTION REPORT
- [ ] MANUFACTURING CHANGE / ADDITION
- [ ] MEETING PLANNED BY
- [ ] PRE-ND A MEETING
- [ ] END-OF-PHASE 2a MEETING
- [ ] END-OF-PHASE 2 MEETING
- [ ] RESUBMISSION
- [ ] SAFETY / EFFICACY
- [ ] PAPER NDA
- [ ] CONTROL SUPPLEMENT
- [ ] RESPONSE TO DEFICIENCY LETTER
- [ ] FINAL PRINTED LABELING
- [ ] LABELING REVISION
- [ ] ORIGINAL NEW CORRESPONDENCE
- [ ] FORMULATIVE REVIEW
- [ ] OTHER (SPECIFY BELOW):

#### II. BIOMETRICS

- [ ] PRIORITY P NDA REVIEW
- [ ] END-OF-PHASE 2 MEETING
- [ ] CONTROLLED STUDIES
- [ ] PROTOCOL REVIEW
- [ ] OTHER (SPECIFY BELOW):

- [ ] CHEMISTRY REVIEW
- [ ] PHARMACOLOGY
- [ ] BIOPHARMACEUTICS
- [ ] OTHER (SPECIFY BELOW):

#### III. BIOPHARMACEUTICS

- [ ] DISSOLUTION
- [ ] BIOAVAILABILITY STUDIES
- [ ] PHASE 4 STUDIES
- [ ] DEFICIENCY LETTER RESPONSE
- [ ] PROTOCOL - BIOPHARMACEUTICS
- [ ] IN-VIVO WAIVER REQUEST

#### IV. DRUG SAFETY

- [ ] PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- [ ] DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- [ ] CASE REPORTS OF SPECIFIC REACTIONS (List below)
- [ ] COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- [ ] REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- [ ] SUMMARY OF ADVERSE EXPERIENCE
- [ ] POISON RISK ANALYSIS

#### V. SCIENTIFIC INVESTIGATIONS

- [ ] CLINICAL
- [ ] NONCLINICAL

### COMMENTS / SPECIAL INSTRUCTIONS: The NDA for tipranavir had been submitted for review on December 22, 2004. On 09-Feb. 2005, we received photos of healthy HIV(-) women with rashes from the applicant. These photos are available on the EDR under the NDA 21-814. The clinical reviewers are wondering if there is an increased risk of rash in women receiving oral contraceptives and what your experience with rash in healthy volunteers in drug interaction studies has been. Our clinical reviewers are available for discussion regarding these rashes seen in HIV(-) healthy women volunteers if needed. PDUA date is June 22, 2005. Advisory Committee Meeting is scheduled for May 19, 2005

### SIGNATURE OF REQUESTOR

### METHOD OF DELIVERY (Check one)

- [ ] DFS
- [ ] EMAIL
- [ ] MAIL
- [ ] HAND

### PRINTED NAME AND SIGNATURE OF RECEIVER

### PRINTED NAME AND SIGNATURE OF DELIVERER
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/s/

Rosemary Johann-Liang
3/23/05 11:14:24 AM
MEMORANDUM

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

DATE: March 16, 2005

TO: HFD-530; Division File

FROM: Tania Sinha, Project Manager: HFD-530

SUBJECT: Statistical comments/query to sponsor.
NDA 21-814, Tipranavir capsules

On March 16, 2005, an email was sent to Boehringer Ingelheim Pharmaceuticals, Inc on behalf of Dr. Zhou, the secondary statistical reviewer for this application. The contents of that email are below.

Please explain the data coding problems identified below and revise the data in the labo.xpt, labc.xpt and labh.xpt, if necessary. As mentioned at the teleconference on Wednesday, 16, 2005, during our evaluations of TPV/r toxicity grades of ten laboratory parameters of interests, HGB, WBC, PLTCT, SGPT, SGOT, GGT, TBILI, CRE, CHOL and TRIGL (CDISC names) for Studies _0004, _0012, _0048, _0051 and _0052, we found data coding problems as follows.

1) Multiple (1-22) upper limit normal (ULN) values for these ten laboratory parameters of interest;
2) Overlapping of data ranges for toxicity grades; and
3) Duplicated records per subject per visit date per lab parameter.

These data files were the most recent versions submitted on December, 29, 2004.

We hereby include two tables for your references. Table 1 lists the upper limit normal (ULN) values in the Studies 1182_0004, _0012, _0048, _0051 and _0052 datasets by ten laboratory parameters of interests. Since six enzyme parameters (SGPT, SGOT, GGT, TBILI, CHOL and CRE) use ULN to quantify the toxicity grades, different ULN values may have impact on the results if one creates toxicity grade values according to the DAIDS definitions (Table 7.1.5:1 Toxicity grades for laboratory tests of special interest (Page 226 of 318, U04-0174)).

In addition, the toxicity grade values such as D_SGPT, D_SGOT, D_GGT, D_TBILI, in these databases may not necessarily correspond to the definitions provided in Table 7.1.5:1. Table 2 shows the data range by toxicity grades for the four liver enzyme parameters GGT, TBILI, SGPT and SGOT. It is evident that some of the toxicity grades in D_SGPT, D_SGOT, D_GGT, D_TBILI, etc, would not be reliable for analyses.

- Please explain why there are multiple values in ULN for the laboratory parameters and whether these values are valid to use for the transformation of the original measurements to obtain the toxicity grades.
• Please explain why the toxicity grading values do not correspond to those by DAIDS definitions as mentioned in the submission.

• Please provide revised datasets so one can perform adequate statistical analyses such as obtaining percentages of subjects who had developed a Grade 3 or 4 toxicity for a given laboratory parameter of interest.

Table 1: Upper Limit Normal (ULN) Value in Studies 1182_0004, 0012, 0048, 0051 and 0052 Databases

<table>
<thead>
<tr>
<th></th>
<th>0004</th>
<th>0012</th>
<th>0048</th>
<th>0051</th>
<th>0052</th>
</tr>
</thead>
<tbody>
<tr>
<td>HGB</td>
<td>15.6,17.2</td>
<td>15.8,16.4,17.18.1</td>
<td>15.8,16.4,17.18.1</td>
<td>15.8,16.4,17.0,18.1</td>
<td>14.99,15.17</td>
</tr>
<tr>
<td>WBC</td>
<td>10.8</td>
<td>10.7</td>
<td>10.7,13.2</td>
<td>10.7</td>
<td>10.5</td>
</tr>
<tr>
<td>PLTCT</td>
<td>400</td>
<td>394,400</td>
<td>394,400</td>
<td>394,400</td>
<td>415</td>
</tr>
<tr>
<td>SGPT</td>
<td>48,52</td>
<td>32,34,35,43</td>
<td>34,35,43</td>
<td>34,35,43</td>
<td>40</td>
</tr>
<tr>
<td>SGOT</td>
<td>36,42,59</td>
<td>34,36</td>
<td>34,36,40</td>
<td>34,36</td>
<td>40</td>
</tr>
<tr>
<td>GGT</td>
<td>45,65,73</td>
<td>49,50,61</td>
<td>49,50,51,61</td>
<td>49,50,61</td>
<td>60,65</td>
</tr>
<tr>
<td>TBILI</td>
<td>1.29,1.30</td>
<td>1.2,1.23</td>
<td>1.2,1.23</td>
<td>1.2,1.23</td>
<td>1.2,1.23</td>
</tr>
<tr>
<td>CHOL</td>
<td>199,199.15,200</td>
<td>218-352, n=17</td>
<td>218-352, n=17</td>
<td>235-320, n=16</td>
<td>199,199.15</td>
</tr>
<tr>
<td>TRIGL</td>
<td>198.4,199.99,200</td>
<td>144-327, n=16</td>
<td>124-327, n=22</td>
<td>176-327, n=16</td>
<td>149,149.20</td>
</tr>
<tr>
<td>CRE</td>
<td>1.2,1.4,1.5</td>
<td>1.1-1.6, n=8</td>
<td>1.1-1.6, n=7</td>
<td>1.1-1.55, n=7</td>
<td>1.5,1.504</td>
</tr>
</tbody>
</table>

N - number of distinct ULN values.

Table 2: Data Ranges for the Upper Limit Normal (ULN) Values in Selected Liver Enzyme Parameters by TPV/r Studies

<table>
<thead>
<tr>
<th>Grade</th>
<th>4</th>
<th>12</th>
<th>48</th>
<th>51</th>
<th>52</th>
</tr>
</thead>
<tbody>
<tr>
<td>GGT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>&lt;1.25 ULN</td>
<td>7-90</td>
<td>6-76</td>
<td>6-76</td>
<td>8-76</td>
</tr>
<tr>
<td>1</td>
<td>_1.25-2.5</td>
<td>59-182</td>
<td>54-152</td>
<td>31-152</td>
<td>50-152</td>
</tr>
<tr>
<td>2</td>
<td>&gt;2.5-5.0</td>
<td>103-364</td>
<td>69-305</td>
<td>103-305</td>
<td>47-305</td>
</tr>
<tr>
<td>3</td>
<td>&gt;5.0-10.0</td>
<td>195-716</td>
<td>109-609</td>
<td>112-610</td>
<td>64-603</td>
</tr>
<tr>
<td>4</td>
<td>&gt;10.0</td>
<td>756-1265</td>
<td>250-3248</td>
<td>403-2921</td>
<td>33-2620</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGPT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>&lt;1.25 ULN</td>
<td>7-90</td>
<td>6-53</td>
<td>5-53</td>
<td>7-53</td>
</tr>
<tr>
<td>1</td>
<td>1.25-2.5</td>
<td>41-179</td>
<td>20-107</td>
<td>20-107</td>
<td>35-107</td>
</tr>
<tr>
<td>2</td>
<td>&gt;2.5-5.0</td>
<td>128-347</td>
<td>20-208</td>
<td>66-213</td>
<td>29-208</td>
</tr>
<tr>
<td>3</td>
<td>&gt;5.0-10.0</td>
<td>76-511</td>
<td>15-424</td>
<td>27-405</td>
<td>70-424</td>
</tr>
<tr>
<td>4</td>
<td>&gt;10.0</td>
<td>79-939</td>
<td>80-1582</td>
<td>11-1579</td>
<td>39-1096</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGOT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.25-2.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>&gt;2.5-5.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&gt;5.0-10.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>&gt;10.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level</td>
<td>ULN</td>
<td>0-30</td>
<td>31-90</td>
<td>91-240</td>
<td>241-744</td>
</tr>
<tr>
<td>-------</td>
<td>-----</td>
<td>------</td>
<td>-------</td>
<td>--------</td>
<td>---------</td>
</tr>
<tr>
<td>0</td>
<td>&lt;1.25 ULN</td>
<td>10-73</td>
<td>9-44</td>
<td>7-44</td>
<td>11-44</td>
</tr>
<tr>
<td>1</td>
<td>1.25-2.5</td>
<td>41-140</td>
<td>24-90</td>
<td>19-90</td>
<td>22-90</td>
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<tr>
<td>2</td>
<td>&gt;2.5-5.0</td>
<td>36-255</td>
<td>21-175</td>
<td>27-179</td>
<td>34-178</td>
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<tr>
<td>3</td>
<td>&gt;5.0-10.0</td>
<td>28-365</td>
<td>22-341</td>
<td>18-360</td>
<td>58-317</td>
</tr>
<tr>
<td>4</td>
<td>&gt;10.0</td>
<td>25-423</td>
<td>65-604</td>
<td>377-737</td>
<td>25-663</td>
</tr>
</tbody>
</table>

**Total Bilirubin**

<table>
<thead>
<tr>
<th>Level</th>
<th>ULN</th>
<th>0-30</th>
<th>31-90</th>
<th>91-240</th>
<th>241-744</th>
<th>745-11,44</th>
<th>&gt;11,44</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>≤1.0 ULN</td>
<td>0.2-1.3</td>
<td>0.08-1.23</td>
<td>0.18-1.23</td>
<td>0.18-1.23</td>
<td>0.06-1.23</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>&gt;1.0-1.5</td>
<td>1.0-1.8</td>
<td>0.6-1.7</td>
<td>0.47-1.81</td>
<td>1.29-1.81</td>
<td>1.23-1.81</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>&gt;1.5-2.5</td>
<td>2.2-2.8</td>
<td>0.9-3.0</td>
<td>1.5-2.9</td>
<td>1.80-2.80</td>
<td>0.4-2.51</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>&gt;2.5-5.0</td>
<td>3.3-6.1</td>
<td>3.2-4.7</td>
<td>3.1-6.1</td>
<td>3.20-5.20</td>
<td>1.29-5.03</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>&gt;5.0</td>
<td>12.1</td>
<td>na</td>
<td>6.4-19.7</td>
<td>2.50-6.20</td>
<td>1.2-8.9</td>
<td></td>
</tr>
</tbody>
</table>
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/s/

Tania Sinha
3/17/05 03:44:32 PM
CSO
stats. info reg. 3-16-05
MEMORANDUM

DATE: March 10, 2005

TO: HFD-530; Division File

FROM: Tanim Sinha, Project Manager: HFD-530

SUBJECT: Clinical comments/query to sponsor.
NDA 21-814, Tipranavir capsules

On March 10, 2005, an email was sent to Boehringer Ingelheim Pharmaceuticals, Inc on behalf of Dr. Baylor, the secondary medical reviewer for this application. The contents of that email are below.

Good afternoon Nancy and Pam,

I have the following comments from Dr. Baylor as discussed in yesterday's telecon. Please respond as soon as possible.

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

1. Please provide the Division with additional data on adverse events for study 1182.33 (the treatment naive study) at the earliest possible date. At a minimum, this should include line listings of demographic data; laboratory values for ALT, bilirubin, and serum creatinine; line listings of adverse events in the following super classes - renal, hepatobiliary, skin, and general; and finally line listings of all possible allergic events or hypersensitivity reactions.

2. Please provide an updated copy of your proposed label. We understand that you will need much more time for the Clinical Pharmacology section, but we need to begin our review of other sections of the product labeling.

Melisse
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/s/

Tanimo Sinha
3/17/05 03:32:28 PM
CSO
clin info request (2) 3-10-05
On March 10, 2005, an email was sent to Boehringer Ingelheim Pharmaceuticals, Inc on behalf of Dr. James, the primary medical reviewer for this application. The contents of that email are below.

1. Tables 10.2.1 on p. 115 of the CSR for Resist 1 and p. 131-132 of the CSR for Resist 2 lists "relevant protocol deviations" as defined by you. Below please find Table 1 that combines your relevant protocol deviation numbers for Resist 1 and 2 and in the case of immunomodulatory and investigational drugs protocol deviation, categories are combined. Our analysis of your BASCO, lbc and Resistance datasets have revealed the following discrepancies thus far (your numbers appear in black, FDAs in red):

<table>
<thead>
<tr>
<th>Treatment group/No. (%) of patients</th>
<th>TPV/r</th>
<th>CPI/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total treated</td>
<td>582 (100%)</td>
<td>577 (100%)</td>
</tr>
<tr>
<td>Total with relevant protocol deviations</td>
<td>211 (36%)</td>
<td>217 (38%)</td>
</tr>
<tr>
<td>Protocol Deviations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 18</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>No protease gene mutations at codons 30N, 46L/L, 48V, 50V, 82A/F/L/T, 84V or 90M</td>
<td>6 9</td>
<td>3 4</td>
</tr>
<tr>
<td>More than two protease gene mutations at codons 33, 82, 84, 90</td>
<td>17 20</td>
<td>16 21</td>
</tr>
<tr>
<td>Less than 2 PIs or less than 3 months of treatment on historical HIV-1 therapy page</td>
<td>4 5</td>
<td>6 10</td>
</tr>
<tr>
<td>No NRTI with &gt; 1 month duration or no NNRTI with &gt; 1 month duration</td>
<td>5 4</td>
<td>7 8</td>
</tr>
<tr>
<td>Screening viral load &lt; 1000</td>
<td>7 4</td>
<td>1 1</td>
</tr>
<tr>
<td>AIDS Defining Event not resolved and treatment less than 2 months</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Treatment group/No. (%) of patients</td>
<td>TPV/r</td>
<td>CPI/r</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Total treated</td>
<td>582 (100%)</td>
<td>577 (100%)</td>
</tr>
<tr>
<td>Total with relevant protocol deviations</td>
<td>211 (36%)</td>
<td>217 (38%)</td>
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<tr>
<td><strong>Protocol Deviations</strong></td>
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<td>OBR of less than 2 non PI ARV drugs</td>
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a. For the protocol deviation of no new or recycled ARV it seems per the numbers that you only captured subjects from Resist 2 and not Resist 1. Please clarify why this was done in this way.

b. For the remainder of the protocol deviations please see the attached list of subjects from your datasets that meet the criteria of the protocol deviation. Please compare this list with your data analysis and line listings and explain for each subject with a discrepancy why that discrepancy occurs.

2. Analysis using the PIARVCHG and BARVCHG datasets submitted on 2/16/05 have revealed the following discrepancies:
   a. In Resist 1 subject 1225 is listed as ‘yes’ for actual Enfuvirtide Use Decode however the subjects’ actual optimized background regimen consists of 3TC + ddf only. Please clarify whether the Actual Enf use or the Actual OBR is correct.
   b. In Resist 1 subjects 4071 and 3209 have their Actual OBR listed as ‘none+EFV+ENF’. Please explain what, if anything, this means.

3. In Resist 2, subjects 2017, 2018, and 2019 from site NLDE0030 appear to be missing all chemistry, hematology and most ‘other’ labs including CD4 counts. Please provide
CRFs for these subjects. If it is true that these subjects had no labs taken during their time on study, please inform us of what, if any, disciplinary steps have been taken at site NLDE0030, since based on the disposition dataset 2 of the 3 subjects are still on study.

**No protease gene mutations at codons 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V or 90M**

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**More than two protease gene mutations at codons 33, 82, 84, 90**

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Less than 2 PIs or less than 3 months of treatment on historical HIV-1 therapy page

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**Screening viral load < 1000**

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**ALT or AST > DAIDS grade 1**

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/s/

Tania Sinha
3/17/05 03:26:37 PM
CSO
Clinical info request to sponsor 3-10-05
MEMORANDUM

DATE: March 10, 2005

TO: HFD-530; Division File

FROM: Tania Sinha, Project Manager: HFD-530

SUBJECT: Statistical comments/query to sponsor.
NDA 21-814, Tipranavir capsules

On March 10, 2005, an email was sent to Boehringer Ingelheim Pharmaceuticals, Inc on behalf of Dr. Bshore the primary statistical reviewer for this application. The contents of that email are below.

Good morning Nancy and Pam,

I am forwarding the following comments/queries from Dr. Bshore, the primary statistical reviewer for your application. Please see below for message.

Thank you,
Tania 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: Bshore, Rafia
Sent: Wednesday, March 09, 2005 5:17 PM
To: Sinha, Tania
Cc: James, Andrea; Johann-Liang, Rosemary; Soon, Guoxing
Subject: #5 STAT Queries on Tipranavir NDA 21-814, N000
Importance: High

Hi Tania.

Please forward the following request to BIPI regarding tipranavir? Please ask them to respond earliest by Tuesday, 3/15/2005 COB and latest by Friday, 3/17/2005 COB?

Thanks
-Rafia

The following request is regarding the RESIST clinical trials (Studies 1182.12 and 1182.48)
1) Provide us a listing of patients whose pre-determined optimized background regimen was different from their actual background antiretroviral regimen at start of study. Also submit the corresponding electronic dataset for these patients similar to the one provided on 16-February-2005 on Background ARV switches (merge barvchg.xpt and pichg.xpt dataset by subject id and date of adding/switching drug).

2) Summarize the total number and proportion of patients (whose pre-determined OBR did not match their actual background regimen) by treatment group for RESIST 1, RESIST 2, and Overall (RESIST 1 and RESIST 2 combined) in a tabular form.

3) Provide a table (in order of frequency) of the pre-determined and actual background regimen (that is using names of drugs) by treatment group and by trial.

---

Rafia Bhore, Ph.D.
Statistician

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On Original
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/s/

Tania Sinha
3/17/05 02:15:27 PM
CS0
Stats. Info. request sent to BIPI 3-10-05
MEMORANDUM

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

DATE: March 10, 2005

TO: HFD-530, Division File

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

SUBJECT: Microbiology query regarding Tipranavir NDAs.
NDA 21-814
Tipranavir Capsules.

On March 9, 2005, an email was sent to Boehringer Ingelheim, Pharmaceuticals, Inc on behalf of Dr. Lisa Naeger and Ms. Kimberly Struble, the primary and secondary microbiology reviewers for these NDAs. The contents of the email are below.

1. In the TPV Resistance report, please clarify the following:
   • On Page 52, is the Ki for V82A 3 μM or 0.3 μM
   • On Page 54, Table 4.3: 1 is the TPV concentration nM or μM

2. Please provide detailed information as to how the GST (GSS) score was determined.

3. For your information, we are providing the following details of the microbiology review of the TPV application. The review team is conducting analyses for baseline genotype and phenotype and outcome. For these analyses outcome is defined as confirmed one log decrease in HIV RNA (primary endpoint) and DAVG_{24}. As referenced in the Draft Guidance for Industry on the Role of HIV Drug Resistance Testing in Antiretroviral Drug Development and consistent with our evaluation of other antiretroviral agents, we censored subjects for our resistance analyses. The rules for censoring subjects for the primary endpoint and DAVG_{24} analyses are summarized below.

   In addition, we are conducting the following analyses.
   • Presence and absence of baseline protease inhibitor mutations and outcome
   • Number of baseline protease inhibitor mutations and outcome
   • Number and type of baseline protease inhibitor mutations and outcome
   • Number of key mutations (33, 82, 84, 90) and outcome
   • Number of baseline protease inhibitor mutations including key mutations and outcome
   • Baseline genotypic sensitivity score and outcome
   • Baseline genotypic sensitivity score and number of baseline protease inhibitor mutations and outcome
   • Baseline TPV susceptibility and outcome
We analyzed the data for the overall treatment group and with or without concomitant T20 use. For the genotypic analyses, we included the following positions in the number of PI mutations: 30, 32, 36, 46, 47, 48, 50, 53, 54, 82, 84, 88, and 90

Censoring Rules for primary endpoint

TRESPDC and TEXPDL columns were used for identification

**Included** the following in the analyses (did NOT censor) -
- Responder
- Virologic Failure
- D/C Before Achieve Viral Suppression
  - Subjects with HIV RNA data through week 16 and/or 24
  - Subjects with HIV RNA data only through week 8 and did not achieve at least 0.5 log decrease in HIV RNA. The 0.5 log criteria used was based on the rollover criteria for study 1182.17 where subjects were allowed to enroll if they did not achieve at least 0.5 log decline in HIV RNA)
- Other
  - Add new ARV: (also see chart below)
    - nRTI in class substitution regardless of time (see chart below)
  - TEXPDL categories - No VR prior to: or Unconfirmed VR prior to:
    - Subjects with HIV RNA data only through week 8 and did not achieve at least a 0.5 log decrease in HIV RNA.
    - Subjects with HIV RNA data through week 16 and/or 24
  - "Blank" - n=7 subjects from RESIST 2 with week 24 data - included the following subjects
    - pt ID 1601 (responder), 5096, 6279, 7140 (responder), 9039, 9149, 9151

**Censored:**
- "BLANK" (no info in either TRESPDC and TEXPDL - these subjects are from RESIST 2 who did not reach week 24 - only week 16 data available)
- Other –
  - Add new ARV: subjects were censored for the following reasons
    - Added new ARV
    - Change in PI, including change to TPV
    - Added therapeutic dose of RTV
  - TEXPDL categories: No VR prior to: or Unconfirmed VR prior to
    - Subjects with no week 8-24 data (D/C between Week 0-4)
    - Subjects with HIV RNA data only through week 8 (no week 16 or 24 data) censored if achieve at least 0.5 log decrease
- D/C While Suppressed
- D/C Before Achieve Viral Suppression:
  - Subjects with no week 8-24 HIV RNA data (D/C between Week 0-4)
  - Subjects with HIV RNA data only through week 8 (no week 16 or 24 data) censored if achieve at least 0.5 log decrease

<table>
<thead>
<tr>
<th>Overall number of subjects in Resistance dataset from BIPI</th>
<th>1482</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td>349</td>
</tr>
<tr>
<td>Failures</td>
<td>152</td>
</tr>
<tr>
<td>D/C While Suppressed</td>
<td>61</td>
</tr>
<tr>
<td>D/C Before achieve viral suppression</td>
<td>279</td>
</tr>
<tr>
<td>Other</td>
<td>317</td>
</tr>
<tr>
<td>&quot;Blank:</td>
<td>324</td>
</tr>
</tbody>
</table>
FDA dataset and reasons for censoring/
Differences from BiP1 dataset

<table>
<thead>
<tr>
<th>Overall Number in BiP1 dataset</th>
<th>1482</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall number of subjects in Resistance dataset from FDA</td>
<td>1015</td>
</tr>
<tr>
<td>FDA Censored</td>
<td>467</td>
</tr>
</tbody>
</table>

**Reasons for Censoring**

- **D/C While Suppressed Category**
  - Subjects with HIV RNA data only through week 8 (no wk 16-24) and achieved 0.5 log decrease at week 8
  - Subjects with no week 8-24 HIV RNA data (D/C between weeks 0-4)

- **Other Category**
  - Added new ARV or changed PI
  - Subjects with HIV RNA data only through week 8 (no wk 16-24) and achieved 0.5 log decrease at week 8

- **"BLANK" Category (RESIST 2 subjects censored because did not have week 24 data)**

<table>
<thead>
<tr>
<th>FDA Included the following</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
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<td>Failures</td>
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<td>D/C Before achieve viral suppression</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>&quot;Blank&quot;</td>
</tr>
</tbody>
</table>

RESIST 2 subjects – included 7 in this category because they had HIV RNA data at week 24

**Censoring Rules for DAVG analyses**

- The TRESPDC and TEXPL columns for identification

  Included the following categories in the analyses (did NOT censor) -
  - Responder
  - Virologic Failure
  - "BLANK" (note: no info no info in either TRESPDC and TEXPL - these subjects are from resist 2 who did not reach week 24 - only week 16 data available)
  - D/C While Suppressed
  - D/C Before Achieve Viral Suppression (censored subjects if week 8, 16 and 24 values were missing; otherwise these subjects were included in the analyses – 234/279 subjects in this category were included)

  - Other - included the following categories
    - unconfirmed VR prior to: ...
    - No VR prior to:...
    - Add new ARV:
      - nRTI class substitution regardless of time (see chart below)

  **Censored:**

  - D/C Before Achieve Viral Suppression (censored subjects if week 8, 16 and 24 values were missing; otherwise these subjects were included in the analyses – 45 subjects in this category were censored)
  - Other – Add new ARV: subjects were censored for the following reasons
- Added new ARV
- Change in PI, including change to TPV
- Added therapeutic dose of RTV

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<tr>
<td>&quot;Blank:&quot;</td>
<td>324</td>
</tr>
</tbody>
</table>

**FDA dataset and reasons for censoring/
Differences from BIPI dataset**

<table>
<thead>
<tr>
<th>Overall number of subjects in BIPI dataset</th>
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</thead>
<tbody>
<tr>
<td>Overall number of subjects in FDA resistance dataset</td>
<td>1409</td>
</tr>
<tr>
<td>FDA censored</td>
<td>73</td>
</tr>
<tr>
<td>Reasons for Censoring</td>
<td></td>
</tr>
<tr>
<td>D/C before achieve viral suppression category</td>
<td></td>
</tr>
<tr>
<td>- Subjects with no week 8-24 HIV RNA data (D/C between weeks 0-4)</td>
<td>45</td>
</tr>
<tr>
<td>Other Category</td>
<td></td>
</tr>
<tr>
<td>- Added new ARV or changed PI</td>
<td>28</td>
</tr>
</tbody>
</table>

**FDA Included the following**

<table>
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<th>Overall number of subjects in Resistance dataset from FDA</th>
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<td>D/C While Suppressed</td>
<td>61</td>
</tr>
<tr>
<td>D/C Before achieve viral suppression</td>
<td></td>
</tr>
<tr>
<td>- 45 had no week 8-24 HIV RNA data</td>
<td>234</td>
</tr>
<tr>
<td>- censored 28/43 who added new ARV or changed PI; remaining 15 subjects had nRTI in class substitution</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>289</td>
</tr>
<tr>
<td>&quot;Blank:&quot;</td>
<td>324</td>
</tr>
</tbody>
</table>
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tanim Sinha
3/17/05 01:29:13 PM
CSO
Microbiology information request to application (3-9-05)
On Friday, February 25, 2005, a statistical information request was sent via email to Boehringer Ingelheim Pharmaceuticals, Inc. on behalf of Dr. Rafia Bhore. Dr. Bhore requested that the information be provided to her by COB February 28, 2005. The information that was requested follows:

The following question refers to the RESIST clinical trials (Studies 1182.12 and 1182.48).

- In your raw datasets, which variable(s) in which dataset(s) refers to the intent-to-treat (ITT) population used in the 24 week analyses for each RESIST study?

  For RESIST 1, the variables POPU and POPUNY given in the DSRAND dataset gives 620 patients using indicator value Yes for POPUNY. This is the ITT population (or FAS population according to your reference) for RESIST 1 given in the NDA.

  For RESIST 2, the variables POPU and POPUNY given in the DSRAND dataset gives 863 patients using indicator value Yes for POPUNY. What criteria did you use to obtain a total of 539 ITT patients (i.e., FAS24 in master file) in the 24 week analysis of RESIST 2?
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Tamina Sinha
2/25/05 08:22:17 AM
CSO
Stats info request 2-25-05.