

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

Appears This Way
On Original

**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**

NDA NUMBER

21-814

NAME OF APPLICANT / NDA HOLDER

Boehringer Ingelheim Pharmaceuticals, Inc.

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.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

5,852,195

b. Issue Date of Patent

12/22/1998

c. Expiration Date of Patent

12/22/2015

d. Name of Patent Owner

Pharmacia & Upjohn Company LLC

Address (of Patent Owner)

235 East 42nd Street

c/o General Patent Counsel

City/State

New York, NY

Pfizer Inc.

ZIP Code

10017

FAX Number (if available)

Telephone Number

(212) 733-2323

E-Mail Address (if available)

e. 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 (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)

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

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

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.

2. 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

3. 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

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

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

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

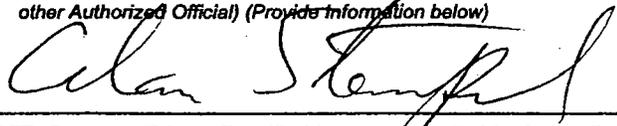
Declaration Certification

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)

Date Signed



09/14/2004

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Check applicable box and provide information below.

<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

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-ingenelheim.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

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1. GENERAL

a. United States Patent Number

6,147,095

b. Issue Date of Patent

11/14/2000

c. Expiration Date of Patent

10/29/2019

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

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E-Mail Address (if available)

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.

2. 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

3. 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

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

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.)

[]

5. No Relevant Patents

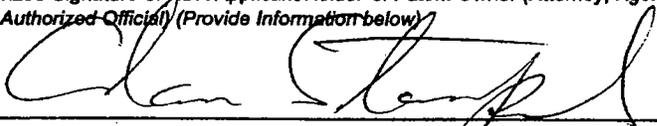
For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably 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

Declaration Certification

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Date Signed

09/14/2004

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NDA Applicant/Holder

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

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900 Ridgebury Road, PO Box 368

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6,169,181

b. Issue Date of Patent

01/02/2001

c. Expiration Date of Patent

05/06/2014

d. Name of Patent Owner

Pharmacia & Upjohn Company LLC

Address (of Patent Owner)

235 East 42nd Street

c/o General Patent Counsel

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Pfizer Inc.

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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.

2. 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?	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> 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?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> 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).	<input type="checkbox"/> Yes <input type="checkbox"/> 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.)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> 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.)	<input type="checkbox"/> Yes <input type="checkbox"/> No
3. 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?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
3.2 Does the patent claim only an intermediate?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> 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.)	<input type="checkbox"/> Yes <input type="checkbox"/> No
4. Method of Use	
<i>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:</i>	
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?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
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? <input type="checkbox"/> Yes <input type="checkbox"/> 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.)
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.	<input type="checkbox"/> Yes

Declaration/Certification

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<input type="checkbox"/> NDA Applicant/Holder	<input checked="" type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
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

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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).		<input type="checkbox"/> Yes	<input type="checkbox"/> 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.)		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
2.6 Does the patent claim only an intermediate?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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.)		<input type="checkbox"/> Yes	<input type="checkbox"/> No
3. 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?		<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
3.2 Does the patent claim only an intermediate?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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.)		<input type="checkbox"/> Yes	<input type="checkbox"/> No
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?		<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> 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?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
Not applicable			
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.			<input type="checkbox"/> Yes

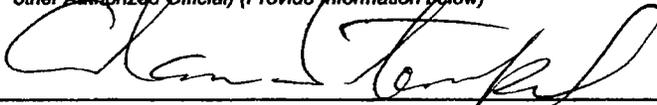
6. Declaration Certification

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)

Date Signed



09/14/2004

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.

NDA Applicant/Holder

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

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City/State

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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

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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 simply 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).

NDA#

NDA#

NDA#

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.")

Investigation #1 YES NO

Investigation #2 YES NO

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?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a

Explain:

! Explain:

Investigation #2

!

YES

!

! NO

Explain:

! Explain:

(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

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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

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:

There are two deferrals for this application

Age/weight range being deferred:

Pediatric PMC # 03 on Approval Letter

Min _____ kg _____ mo. _____ yr. 02 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 18 Tanner Stage _____

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

Age/weight range being deferred:

Pediatric PMC # 04 on Approval Letter

Min _____ kg _____ mo. 2 weeks yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 2 Tanner Stage _____

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:

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

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:

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

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)

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

/s/

Virginia Behr
6/29/05 01:00:11 PM

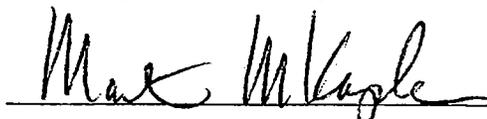
Boehringer Ingelheim
NDA 21-814
(tipranavir) 250mg Capsules

1.3.3 DEBARMENT CERTIFICATION

Certification Requirement Section 306(k)(1) 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:

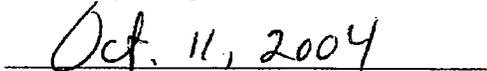
Signature:



Name of Applicant:

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

Date:



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]

6/2/05

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 μ M. 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 isoform 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; pimozone; 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_{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 \geq 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 \geq 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 moderated severity 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 a 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 \geq 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
- \leq 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 Bhore 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 \geq 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. Melisse 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 sulfa drugs; this is important as TPV contains a sulfa moiety. In the RESIST trials, 11% of subjects with a sulfa allergy developed a rash compared to the same percentage in those without a sulfa 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 sulfa 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. Hypertriglyceridemia 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 C_{min}/IC_{50} (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 $\geq 1 \log_{10}$ 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

4. Conduct a human drug-drug interaction study of TPV/r twice daily and tadalafil.

Protocol Submission: August 31, 2005

Final report Submission: Submitted by December 31, 2006

5. Conduct a human drug-drug interaction study of TPV/r twice daily and ribavirin/pegylated IFN alpha 2a.

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 naive patients through the conduct of study 1182.33.

Protocol Submission: Completed

Final report Submission: [1

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

Final report Submission: [1

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 naive 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



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

Tel 301-827-2020
FAX 301-827-2075

M E M O R A N D U M

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: Tanima 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. Kozmaforano, 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

MEMORANDUM

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

DATE: June 3, 2005
TO: Division File, HFD-530
FROM: Tanima Sinha, HFD-530
SUBJECT: **Micro section of TPV label to sponsor.**
NDA 21-814, Aptivus® (Tipranavir) capsules

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.]

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3 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

Tanima Sinha
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CSO
Micro label to BIPI, 6-3-05.

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/s/

Rosemary Johann-Liang
6/6/05 10:03:50 AM

REQUEST FOR CONSULTATION

To (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

- | | | |
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| <input type="checkbox"/> NEW PROTOCOL
<input type="checkbox"/> PROGRESS REPORT
<input type="checkbox"/> NEW CORRESPONDENCE
<input type="checkbox"/> DRUG ADVERTISING
<input type="checkbox"/> ADVERSE REACTION REPORT
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION
<input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING
<input type="checkbox"/> END-OF-PHASE 2a MEETING
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> RESUBMISSION
<input type="checkbox"/> SAFETY / EFFICACY
<input type="checkbox"/> PAPER NDA
<input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER
<input type="checkbox"/> FINAL PRINTED LABELING
<input type="checkbox"/> LABELING REVISION
<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE
<input type="checkbox"/> FORMULATIVE REVIEW
<input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
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II. BIOMETRICS

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| <input type="checkbox"/> PRIORITY P NDA REVIEW
<input type="checkbox"/> END-OF-PHASE 2 MEETING
<input type="checkbox"/> CONTROLLED STUDIES
<input type="checkbox"/> PROTOCOL REVIEW
<input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW
<input type="checkbox"/> PHARMACOLOGY
<input type="checkbox"/> BIOPHARMACEUTICS
<input type="checkbox"/> OTHER (SPECIFY BELOW): |
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III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION
<input type="checkbox"/> BIOAVAILABILITY STUDIES
<input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE
<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS
<input type="checkbox"/> IN-VIVO WAIVER REQUEST |
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IV. DRUG SAFETY

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|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE
<input type="checkbox"/> POISON RISK ANALYSIS |
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V. SCIENTIFIC INVESTIGATIONS

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|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> 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. PDUFA 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: Tanima 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 Databases¹

	0004	0012	0048	0051	0052
HGB	15.6,17.2	15.8,16.4,17,18.1	15.8,16.4,17,18.1	15.8,16.4,17.0,18.1	14.99,15,17
WBC	10.8	10.7	10.7,13.2	10.7	10.5
PLTCT	400	394,400	394,400	394,400	415
SGPT	48,52	32,34,35,43	34,35,43	34,35,43	40
SGOT	36,42,59	34,36	34,36,40	34,36	40
GGT	45,65,73	49,50,61	49,50,51,61	49,50,61	60,65
TBILI	1.29,1.30	1.2,1.23	1.2,1.23	1.2,1.23	1.2,1.23
CHOL	199,199.15,200	218-352, n=17	218-352, n=17	235-320, n=16	199,199.15
TRIGL	198.4,199.99,200	144-327, n=16	124-327, n=22	176-327, n=16	149,149.20
CRE	1.2,1.4,1.5	1.1-1.6, n=8	1.1-1.6, n=7	1.1-1.55, n=7	1.5,1.504

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 Studies¹

Grade		4	12	48	51	52
GGT						
0	<1.25 ULN	7-90	6-76	6-76	8-76	11-81
1	1.25-2.5	59-182	54-152	31-152	50-152	62-162
2	>2.5-5.0	103-364	69-305	103-305	47-305	68-325
3	>5.0-10.0	195-716	109-609	112-610	64-603	112-636
4	>10.0	756-1265	250-3248	403-2921	33-2620	375-2059
SGPT						
0	<1.25 ULN	7-90	6-53	5-53	7-53	11-81
1	1.25-2.5	41-179	20-107	20-107	35-107	62-162
2	>2.5-5.0	128-347	20-208	66-213	29-208	68-325
3	>5.0-10.0	76-511	15-424	27-405	70-424	112-636
4	>10.0	79-939	80-1582	11-1579	39-1096	375-2059
SGOT						

0	<1.25 ULN	10-73	9-44	7-44	11-44	9-49
1	1.25-2.5	41-140	24-90	19-90	22-90	17-100
2	>2.5-5.0	36-255	21-175	27-179	34-178	20-200
3	>5.0-10.0	28-365	22-341	18-360	58-317	35-390
4	>10.0	25-423	65-604	377-737	25-663	24-2830
Total Bilirubin						
0	≤1.0 ULN	0.2-1.3	0.08-1.23	0.18-1.23	0.18-1.23	0.06-1.23
1	>1.0-1.5	1.0-1.8	0.6-1.7	0.47-1.81	1.29-1.81	1.23-1.81
2	>1.5-2.5	2.2-2.8	0.9-3.0	1.5-2.9	1.80-2.80	0.4-2.51
3	>2.5-5.0	3.3-6.1	3.2-4.7	3.1-6.1	3.20-5.20	1.29-5.03
4	>5.0	12.1	na	6.4-19.7	2.50-6.20	1.2-8.9

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/s/

Tanima Sinha
3/17/05 03:44:32 PM
CSO
stats. info req. 3-16-05

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: Tanima 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,
Tanima 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/

Tanima Sinha
3/17/05 03:32:28 PM
CSO
clin info request (2) 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: Tanima 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. 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 1 Number of Subjects with Relevant Protocol Deviations – Resist 1 and 2 FAS 24 Weeks

Treatment group/No. (%) of patients	TPV/r	CPI/r
Total treated	582 (100%)	577 (100%)
Total with relevant protocol deviations	211 (36%)	217 (38%)
Protocol Deviations		
Age < 18	1	0
No protease gene mutations at codons 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V or 90M	6 9	3 4
More than two protease gene mutations at codons 33, 82, 84, 90	17 20	16 21
Less than 2 PIs or less than 3 months of treatment on historical HIV-1 therapy page	4 5	6 10
No NRTI with > 1 month duration or no NNRTI with > 1 month duration	5 4	7 8
Screening viral load < 1000	7 4	1 1
AIDS Defining Event not resolved and treatment less than 2 months	17	18

Treatment group/No. (%) of patients		
	TPV/r	CPI/r
Total treated	582 (100%)	577 (100%)
Total with relevant protocol deviations	211 (36%)	217 (38%)
Protocol Deviations		
Recent drug holiday: Off ARV for >=7 consecutive days within last 3 months	7	3
ALT or AST > DAIDS grade 1	12 15	15 20
Triglycerides at screening > DAIDS grade 2	31 23	38 27
No new or recycled ARV in OBR	29 75	40 86
Wrong T20 stratum	13 21	11 30
Pre-selected background is changed at start of new PI randomization	12	13
OBR of less than 2 non PI ARV drugs	3 3	5 7
Randomized to CPI and prespecified not taken throughout trial or changed	0	7
More than one PI taken at the same time (plus RTV)	3	5
Undetectable PI troughs at any visit despite documented intake of PI	52	44
Immunomodulatory drug used within 30 days of study entry or during study and/or Investigational drug used during study	44	48
Treatment interruption of > 28 day w/in 6 mos period if not due to AE	0	1
Use of contraindicated drugs	1	1

- 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 + ddI 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

STUDY PTNO ITRCDDC

1182_0012	1711	LPV/r
1182_0012	1814	LPV/r
1182_0048	4006	LPV/r
1182_0012	2098	SQV/r
1182_0012	2243	TPV/r
1182_0012	2251	TPV/r
1182_0048	3079	TPV/r
1182_0048	3119	TPV/r
1182_0048	3295	TPV/r
1182_0048	3305	TPV/r
1182_0048	4048	TPV/r
1182_0048	7161	TPV/r
1182_0048	8056	TPV/r

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

STUDY PTNO ITRCDDC

1182_0012	1447	APV/r
1182_0012	4044	APV/r
1182_0048	1117	APV/r
1182_0048	4213	APV/r
1182_0012	2007	IDV/r
1182_0048	6118	IDV/r
1182_0012	1329	LPV/r
1182_0012	1418	LPV/r
1182_0012	1495	LPV/r
1182_0012	1660	LPV/r
1182_0012	2077	LPV/r
1182_0012	2161	LPV/r
1182_0012	3063	LPV/r
1182_0012	4072	LPV/r
1182_0012	4073	LPV/r
1182_0048	1137	LPV/r
1182_0048	6206	LPV/r
1182_0048	9067	LPV/r

1182_0012	1245	SQV/r
1182_0012	1786	SQV/r
1182_0012	3001	SQV/r
1182_0012	1013	TPV/r
1182_0012	1197	TPV/r
1182_0012	1269	TPV/r
1182_0012	1302	TPV/r
1182_0012	1390	TPV/r
1182_0012	1398	TPV/r
1182_0012	1633	TPV/r
1182_0012	1647	TPV/r
1182_0012	1724	TPV/r
1182_0012	1728	TPV/r
1182_0012	1827	TPV/r
1182_0012	2040	TPV/r
1182_0012	2376	TPV/r
1182_0012	3102	TPV/r
1182_0012	4079	TPV/r
1182_0012	4093	TPV/r
1182_0048	1109	TPV/r
1182_0048	4096	TPV/r
1182_0048	6097	TPV/r
1182_0048	6342	TPV/r

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

STUDY	PTNO	ITRCDDC
1182_0012	3041	APV/r
1182_0012	1069	LPV/r
1182_0012	2016	LPV/r
1182_0012	2321	LPV/r
1182_0012	4084	LPV/r
1182_0012	1732	SQV/r
1182_0012	2168	TPV/r
1182_0012	2373	TPV/r
1182_0048	1107	LPV/r
1182_0048	6158	LPV/r
1182_0048	8031	LPV/r
1182_0048	6161	SQV/r
1182_0048	3079	TPV/r
1182_0048	3192	TPV/r
1182_0048	4166	TPV/r

No NRTI with > 1 month duration or no NNRTI with > 1 month duration

STUDY PTNO ITRCDDC

1182_0012 2181 APV/r
1182_0012 1485 IDV/r
1182_0012 1640 LPV/r
1182_0012 2031 LPV/r
1182_0012 4089 LPV/r
1182_0012 2150 TPV/r
1182_0012 2168 TPV/r

1182_0048 4143 APV/r
1182_0048 3284 LPV/r
1182_0048 6161 SQV/r
1182_0048 1247 TPV/r
1182_0048 8006 TPV/r

Screening viral load < 1000

STUDY PTNO ITRCDDC

1182_0012 1106 APV/r
1182_0012 1354 TPV/r
1182_0012 2121 TPV/r
1182_0012 2243 TPV/r

1182_0048 7057 TPV/r

ALT or AST > DAIDS grade 1

1182_0012 1612 APV/r
1182_0012 2089 APV/r
1182_0012 1017 LPV/r
1182_0012 1202 LPV/r
1182_0012 1828 LPV/r
1182_0012 2091 LPV/r
1182_0012 2161 LPV/r
1182_0012 2375 LPV/r
1182_0012 4010 LPV/r
1182_0012 1242 SQV/r
1182_0012 1408 SQV/r
1182_0012 2158 SQV/r
1182_0012 2441 SQV/r
1182_0012 1668 TPV/r
1182_0012 1674 TPV/r
1182_0012 1704 TPV/r
1182_0012 1837 TPV/r

1182_0012	2238	TPV/r
1182_0012	3051	TPV/r
1182_0012	3078	TPV/r
1182_0012	3160	TPV/r
1182_0012	4055	TPV/r
1182_0048	3027	APV/r
1182_0048	3257	APV/r
1182_0048	4143	APV/r
1182_0048	6087	APV/r
1182_0048	1107	LPV/r
1182_0048	1254	LPV/r
1182_0048	2226	SQV/r
1182_0048	1087	TPV/r
1182_0048	4011	TPV/r
1182_0048	4234	TPV/r
1182_0048	6053	TPV/r
1182_0048	6186	TPV/r
1182_0048	7085	TPV/r

Triglycerides at screening > DAIDS grade 2

STUDY	PTNO	ITR	TRIGL
			CDDC
1182_0012	1277	APV/r	1184
1182_0012	1402	APV/r	1098
1182_0012	2163	IDV/r	842
1182_0012	1069	LPV/r	970
1182_0012	1121	LPV/r	784
1182_0012	1327	LPV/r	792
1182_0012	1720	LPV/r	1610
1182_0012	1736	LPV/r	791
1182_0012	1831	LPV/r	860
1182_0012	1853	LPV/r	944
1182_0012	2000	LPV/r	1105
1182_0012	2463	LPV/r	799
1182_0012	3113	LPV/r	1847.653
1182_0012	1957	SQV/r	859
1182_0012	3182	SQV/r	999.1143
1182_0012	1188	TPV/r	937
1182_0012	1297	TPV/r	801

1182_0012	1497	TPV/r	895
1182_0012	1550	TPV/r	769
1182_0012	1591	TPV/r	1630
1182_0012	1655	TPV/r	888
1182_0012	1674	TPV/r	1683
1182_0012	1827	TPV/r	1088
1182_0012	2070	TPV/r	974
1182_0012	2083	TPV/r	775
1182_0012	2123	TPV/r	803
1182_0012	2373	TPV/r	857
1182_0012	3034	TPV/r	1534.101
1182_0012	3123	TPV/r	920.2834
1182_0012	3157	TPV/r	870.682
1182_0012	4079	TPV/r	937.9982

1182_0048	3143	APV/r	1348.096
1182_0048	4231	APV/r	1333.924
1182_0048	5033	APV/r	1647.476
1182_0048	1059	LPV/r	778
1182_0048	4028	LPV/r	876.8822
1182_0048	6039	LPV/r	1018.601
1182_0048	6100	LPV/r	803.3658
1182_0048	4020	SQV/r	1094.774
1182_0048	4179	SQV/r	876.8822
1182_0048	4232	SQV/r	2471.213
1182_0048	6072	SQV/r	1185.12
1182_0048	1122	TPV/r	852
1182_0048	1138	TPV/r	1438
1182_0048	2005	TPV/r	761.736
1182_0048	3003	TPV/r	1043.401
1182_0048	3189	TPV/r	828.1665
1182_0048	4205	TPV/r	818.4234
1182_0048	5034	TPV/r	860.0531
1182_0048	7161	TPV/r	799.8229

No New or Recycled ARV in OBR

STUDY PTNO ITRCDDC

1182_0012	1105	APV/r
1182_0012	1106	APV/r
1182_0012	1131	APV/r
1182_0012	1262	APV/r
1182_0012	1402	APV/r
1182_0012	1411	APV/r
1182_0012	1667	APV/r

1182_0012	1806	APV/r
1182_0012	1900	APV/r
1182_0012	2032	APV/r
1182_0012	2043	APV/r
1182_0012	2266	APV/r
1182_0012	3151	APV/r
1182_0012	3201	APV/r
1182_0012	1103	IDV/r
1182_0012	1463	IDV/r
1182_0012	1073	LPV/r
1182_0012	1113	LPV/r
1182_0012	1147	LPV/r
1182_0012	1225	LPV/r
1182_0012	1423	LPV/r
1182_0012	1490	LPV/r
1182_0012	1622	LPV/r
1182_0012	1763	LPV/r
1182_0012	1831	LPV/r
1182_0012	2005	LPV/r
1182_0012	2077	LPV/r
1182_0012	2088	LPV/r
1182_0012	2108	LPV/r
1182_0012	2174	LPV/r
1182_0012	2256	LPV/r
1182_0012	2375	LPV/r
1182_0012	3013	LPV/r
1182_0012	3046	LPV/r
1182_0012	3122	LPV/r
1182_0012	3150	LPV/r
1182_0012	3196	LPV/r
1182_0012	4025	LPV/r
1182_0012	1108	SQV/r
1182_0012	1189	SQV/r
1182_0012	1543	SQV/r
1182_0012	1650	SQV/r
1182_0012	1732	SQV/r
1182_0012	2155	SQV/r
1182_0012	2441	SQV/r
1182_0012	2498	SQV/r
1182_0012	1029	TPV/r
1182_0012	1075	TPV/r
1182_0012	1077	TPV/r
1182_0012	1080	TPV/r
1182_0012	1161	TPV/r
1182_0012	1176	TPV/r
1182_0012	1215	TPV/r

1182_0012	1243	TPV/r
1182_0012	1308	TPV/r
1182_0012	1352	TPV/r
1182_0012	1369	TPV/r
1182_0012	1488	TPV/r
1182_0012	1489	TPV/r
1182_0012	1491	TPV/r
1182_0012	1499	TPV/r
1182_0012	1555	TPV/r
1182_0012	1570	TPV/r
1182_0012	1593	TPV/r
1182_0012	1619	TPV/r
1182_0012	1630	TPV/r
1182_0012	1655	TPV/r
1182_0012	1656	TPV/r
1182_0012	1658	TPV/r
1182_0012	1659	TPV/r
1182_0012	1674	TPV/r
1182_0012	1688	TPV/r
1182_0012	1729	TPV/r
1182_0012	1738	TPV/r
1182_0012	1764	TPV/r
1182_0012	1794	TPV/r
1182_0012	1827	TPV/r
1182_0012	1847	TPV/r
1182_0012	1880	TPV/r
1182_0012	1924	TPV/r
1182_0012	1968	TPV/r
1182_0012	2113	TPV/r
1182_0012	2123	TPV/r
1182_0012	2251	TPV/r
1182_0012	2252	TPV/r
1182_0012	2280	TPV/r
1182_0012	2497	TPV/r
1182_0012	3045	TPV/r
1182_0012	3117	TPV/r
1182_0012	3160	TPV/r
1182_0012	4024	TPV/r
1182_0012	4031	TPV/r
1182_0012	4039	TPV/r
1182_0048	1204	APV/r
1182_0048	3028	APV/r
1182_0048	3133	APV/r
1182_0048	3268	APV/r
1182_0048	3276	APV/r

1182_0048	4057	APV/r
1182_0048	4111	APV/r
1182_0048	4158	APV/r
1182_0048	4247	APV/r
1182_0048	6038	APV/r
1182_0048	6087	APV/r
1182_0048	1038	LPV/r
1182_0048	2605	LPV/r
1182_0048	3002	LPV/r
1182_0048	3012	LPV/r
1182_0048	3065	LPV/r
1182_0048	3199	LPV/r
1182_0048	4006	LPV/r
1182_0048	4076	LPV/r
1182_0048	4221	LPV/r
1182_0048	5004	LPV/r
1182_0048	5010	LPV/r
1182_0048	6001	LPV/r
1182_0048	6058	LPV/r
1182_0048	6156	LPV/r
1182_0048	6158	LPV/r
1182_0048	6160	LPV/r
1182_0048	7016	LPV/r
1182_0048	7196	LPV/r
1182_0048	8035	LPV/r
1182_0048	8077	LPV/r
1182_0048	3037	SQV/r
1182_0048	3131	SQV/r
1182_0048	4020	SQV/r
1182_0048	4179	SQV/r
1182_0048	5001	SQV/r
1182_0048	5032	SQV/r
1182_0048	6104	SQV/r
1182_0048	6161	SQV/r
1182_0048	6224	SQV/r
1182_0048	1037	TPV/r
1182_0048	1436	TPV/r
1182_0048	2006	TPV/r
1182_0048	3073	TPV/r
1182_0048	3102	TPV/r
1182_0048	3108	TPV/r
1182_0048	3126	TPV/r
1182_0048	3263	TPV/r
1182_0048	4001	TPV/r
1182_0048	4021	TPV/r
1182_0048	4075	TPV/r

1182_0048	4175	TPV/r
1182_0048	4237	TPV/r
1182_0048	4241	TPV/r
1182_0048	6010	TPV/r
1182_0048	6016	TPV/r
1182_0048	6027	TPV/r
1182_0048	6061	TPV/r
1182_0048	6073	TPV/r
1182_0048	6086	TPV/r
1182_0048	6131	TPV/r
1182_0048	6133	TPV/r
1182_0048	6137	TPV/r
1182_0048	6138	TPV/r
1182_0048	6155	TPV/r
1182_0048	6159	TPV/r
1182_0048	8004	TPV/r
1182_0048	8049	TPV/r

OBR of less than 2 non PI ARV drugs

Study	PTNO	ITRCDDC
1182_0012	1131	APV/r
1182_0012	1137	SQV/r
1182_0012	1243	TPV/r
1182_0048	6038	APV/r
1182_0048	3159	LPV/r
1182_0048	6020	LPV/r
1182_0048	3040	SQV/r
1182_0048	5032	SQV/r
1182_0048	4048	TPV/r
1182_0048	8049	TPV/r

Wrong T20 stratum

USUBJID	TRTGRP	PRENFDC	ACTENFDC
1182_0012/001084	CPI/r	Yes	No
1182_0012/001093	CPI/r	Yes	No
1182_0012/001113	CPI/r	Yes	No
1182_0012/001402	CPI/r	Yes	No
1182_0012/001423	CPI/r	Yes	No
1182_0012/001840	CPI/r	No	Yes
1182_0012/001931	CPI/r	Yes	No
1182_0012/002005	CPI/r	Yes	No
1182_0012/002032	CPI/r	Yes	No
1182_0012/002056	CPI/r	Yes	No

1182_0012/002088	CPI/r	Yes	No
1182_0012/002178	CPI/r	No	Yes
1182_0012/002399	CPI/r	Yes	No
1182_0012/004023	CPI/r	No	Yes
1182_0012/001100	TPV/r	Yes	No
1182_0012/001308	TPV/r	Yes	No
1182_0012/001481	TPV/r	No	Yes
1182_0012/001489	TPV/r	Yes	No
1182_0012/001491	TPV/r	Yes	No
1182_0012/001629	TPV/r	No	Yes
1182_0012/001835	TPV/r	No	Yes
1182_0012/001837	TPV/r	No	Yes
1182_0012/002035	TPV/r	No	Yes
1182_0012/002052	TPV/r	No	Yes
1182_0012/002080	TPV/r	No	Yes
1182_0012/002081	TPV/r	No	Yes
1182_0012/002373	TPV/r	Yes	No

1182_0048/003291	CPI/r	No	Yes
1182_0048/006224	CPI/r	No	Yes
1182_0048/002001	CPI/r	Yes	No
1182_0048/002203	CPI/r	Yes	No
1182_0048/002241	CPI/r	Yes	No
1182_0048/003072	CPI/r	Yes	No
1182_0048/003176	CPI/r	Yes	No
1182_0048/003185	CPI/r	Yes	No
1182_0048/003226	CPI/r	Yes	No
1182_0048/004232	CPI/r	Yes	No
1182_0048/004315	CPI/r	Yes	No
1182_0048/005010	CPI/r	Yes	No
1182_0048/006019	CPI/r	Yes	No
1182_0048/006038	CPI/r	Yes	No
1182_0048/008035	CPI/r	Yes	No
1182_0048/008077	CPI/r	Yes	No
1182_0048/003043	TPV/r	No	Yes
1182_0048/003289	TPV/r	No	Yes
1182_0048/004094	TPV/r	No	Yes
1182_0048/001849	TPV/r	Yes	No
1182_0048/002011	TPV/r	Yes	No
1182_0048/003084	TPV/r	Yes	No
1182_0048/003264	TPV/r	Yes	No
1182_0048/008049	TPV/r	Yes	No

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/s/

Tanima Sinha
3/17/05 03:26:37 PM
CSO
Clinical info request to sponsor 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: Tanima 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. Bhore 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. Bhore, the primary statistical reviewer for your application. Please see below for message.

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

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

From: Bhore, Rafia
Sent: Wednesday, March 09, 2005 5:17 PM
To: Sinha, Tanima
Cc: James, Andrea; Johann-Liang, Rosemary; Soon, Guoxing
Subject: -- #8 STAT Queries on Tipranavir NDA 21-814, N000
Importance: High

Hi Tanima.

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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/s/

Tanima Sinha
3/17/05 02:15:27 PM
CSO
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: Tanima 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 DAVG₂₄. 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 DAVG₂₄ 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 TEXPL 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)
 - TEXPL 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 TEXPL - 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
 - TEXPL 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

Overall number of subjects in Resistance dataset from BIPI	1482
Responders	349
Failures	152
D/C While Suppressed	61
D/C Before achieve viral suppression	279
Other	317
"Blank:	324

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

Overall Number in BIBPI dataset	1482
Overall number of subjects in Resistance dataset from FDA	1015
FDA Censored	467
Reasons for Censoring	
D/C While Suppressed Category	61
D/C before achieve viral suppression category	
• Subjects with HIV RNA data only through week 8 (no wk 16-24) and achieved 0.5 log decrease at week 8	5
• Subjects with no week 8-24 HIV RNA data (D/C between weeks 0-4)	45
Other Category	
• Added new ARV or changed PI	28
• Subjects with HIV RNA data only through week 8 (no wk 16-24) and achieved 0.5 log decrease at week 8	11
"BLANK" Category (RESIST 2 subjects censored because did not have week 24 data)	317

FDA Included the following	
Responders	349
Failures	152
D/C While Suppressed	0
D/C Before achieve viral suppression	229
Other	278
"Blank"	7
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 in 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

Overall number of subjects in Resistance dataset from BIPI	1482
Responders	349
Failures	152
D/C While Suppressed	61
D/C Before achieve viral suppression	279
Other	317
"Blank:"	324

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

Overall number of subjects in BIPI dataset	1482
Overall number of subjects in FDA resistance dataset	1409
FDA censored	73
Reasons for Censoring	
D/C before achieve viral suppression category	
• Subjects with no week 8-24 HIV RNA data (D/C between weeks 0-4)	45
Other Category	
• Added new ARV or changed PI	28
FDA Included the following	
Overall number of subjects in Resistance dataset from FDA	1409
Responders	349
Failures	152
D/C While Suppressed	61
D/C Before achieve viral suppression	234
• 45 had no week 8-24 HIV RNA data	
• censored 28/43 who added new ARV or changed PI; remaining 15 subjects had nRTI in class substitution	
Other	289
"Blank:"	324

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/s/

Tanima Sinha

3/17/05 01:29:13 PM

CSO

Microbiology information request to application (3-9-05)

MEMORANDUM

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

DATE: February 25, 2005
TO: Division File, HFD-530
FROM: Tanima Sinha, Regulatory Project Manager
SUBJECT: **Statistics Information Request**
NDA 21-814, tipranavir capsules

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?

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/s/

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