

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-976

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

**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

21-976

NAME OF APPLICANT / NDA HOLDER

Tibotec, 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)

ACTIVE INGREDIENT(S)

Darunavir

STRENGTH(S)

300 mg

DOSAGE FORM

tablet

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 file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

or 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
6,335,460

b. Issue Date of Patent
January 1, 2002

c. Expiration Date of Patent
August 25, 2012

d. Name of Patent Owner
G.D. Searle & Co. LLC
c/o General Patent Counsel
Pfizer Inc.

Address (of Patent Owner)
235 East 42nd Street

City/State
New York, NY

ZIP Code
10017

FAX Number (if available)

Telephone Number
(212) 733-2323

E-Mail Address (if available)

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)

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.		
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

4a. 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 checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2	Patent 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 checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4			
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 approved labeling.) treatment of human immunodeficiency virus (HIV) infection	

4b. 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 checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent) 5	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 checked="" 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 approved labeling.) treatment of human immunodeficiency virus (HIV) infection		

4c. 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 checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent) 6	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 checked="" 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 approved labeling.) treatment of human immunodeficiency virus (HIV) infection		

1. 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 checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent) 7	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 checked="" 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 approved labeling.) treatment of human immunodeficiency virus (HIV) infection		

4e. 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 checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent) 8	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 checked="" 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 approved labeling.) treatment of human immunodeficiency virus (HIV) infection		

4f. 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 Patent Claim Number (as listed in the patent) 15 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 approved labeling.)
treatment of human immunodeficiency virus (HIV) infection

4g. 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 Patent Claim Number (as listed in the patent) 16 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 approved labeling.)
treatment of human immunodeficiency virus (HIV) infection

4h. 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 Patent Claim Number (as listed in the patent) 17 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 approved labeling.)
treatment of human immunodeficiency virus (HIV) infection

4i. 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 Patent Claim Number (as listed in the patent) 18 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 approved labeling.)
treatment of human immunodeficiency virus (HIV) infection

4j. 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 checked="" type="checkbox"/> Yes <input type="checkbox"/> No
4.2 Patent Claim Number (as listed in the patent) 19	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 checked="" 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 approved labeling.) treatment of human immunodeficiency virus (HIV) infection
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 05 December 2005
	
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.	
<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 Alana G. Kriegsman	
Address Office of the General Counsel Johnson & Johnson One Johnson & Johnson Drive	City/State New Brunswick, NJ
ZIP Code 08933	Telephone Number 732-524-1495
FAX Number (if available) (732) 524-2134	E-Mail Address (if available) akriegsm@corus.jnj.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

**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

21-976

NAME OF APPLICANT / NDA HOLDER

Tibotec, 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)

ACTIVE INGREDIENT(S)

Darunavir

STRENGTH(S)

300 mg

DOSAGE FORM

tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

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FDA will not list patent information if you file 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

6,248,775

b. Issue Date of Patent

June 19, 2001

c. Expiration Date of Patent

August 25, 2012

d. Name of Patent Owner

G.D. Searle & Co. LLC
c/o General Patent Counsel
Pfizer Inc.

Address (of Patent Owner)

235 East 42nd Street

City/State

New York, NY

ZIP Code

10017

FAX Number (if available)

Telephone Number

(212) 733-2323

E-Mail Address (if available)

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

ZIP Code

Telephone Number

Telephone Number

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)

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.		
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

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 Patent 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 checked="" 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 approved labeling.)	

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. 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
05 December 2005



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
Alana G. Kriegsman

Address
Office of the General Counsel
Johnson & Johnson
One Johnson & Johnson Drive

City/State
New Brunswick, NJ

ZIP Code
08933

Telephone Number
732-524-1495

FAX Number (if available)
(732) 524-2134

E-Mail Address (if available)
akriegsm@corus.jnj.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

**PATENT INFORMATION SUBMITTED WITH THE
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**For Each Patent That Claims a Drug Substance
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NAME OF APPLICANT / NDA HOLDER

Tibotec, Inc.

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STRENGTH(S)

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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
5,843,946

b. Issue Date of Patent
12/1/1998

c. Expiration Date of Patent
1 December 2015

d. Name of Patent Owner
G.D. Searle & Co. LLC
c/o General Patent Counsel
Pfizer Inc.

Address (of Patent Owner)
235 East 42nd Street

City/State
New York, NY

ZIP Code
10017

FAX Number (if available)

Telephone Number
(212) 733-2323

E-Mail Address (if available)

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

ZIP Code

Telephone Number

Telephone Number

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.
- 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

4a. 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 Patent Claim Number (as listed in the patent) 8 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 approved labeling.)
treatment of human immunodeficiency virus (HIV) infection

4b. 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:	
Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Patent Claim Number (as listed in the patent) 9	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 checked="" 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 approved labeling.) treatment of human immunodeficiency virus (HIV) infection
4c. 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 checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Patent Claim Number (as listed in the patent) 10	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 checked="" 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 approved labeling.) treatment of human immunodeficiency virus (HIV) infection
4d. 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 checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Patent Claim Number (as listed in the patent) 11	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 checked="" 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 approved labeling.) treatment of human immunodeficiency virus (HIV) infection
4e. 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 checked="" type="checkbox"/> Yes <input type="checkbox"/> No	
4.2 Patent Claim Number (as listed in the patent) 12	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 checked="" 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 approved labeling.) treatment of human immunodeficiency virus (HIV) infection

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

 Yes
6. 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
05 December 2005

Alana Kriegsman

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

Alana G. Kriegsman

Address

Office of the General Counsel
Johnson & Johnson
One Johnson & Johnson Drive

City/State

New Brunswick, NJ

ZIP Code

08933

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732-524-1495

FAX Number (if available)

(732) 524-2134

E-Mail Address (if available)

akriegsm@corus.jnj.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

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

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 21-976

SUPPL #

HFD # 530

Trade Name PREZISTA

Generic Name Darunavir

Applicant Name Tibotec, Inc.

Approval Date, If Known June 23, 2006

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 similar investigation was relied on:

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

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

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

Investigation #1 !
IND # YES ! NO
! Explain:

Investigation #2 !
IND # YES ! NO
! Explain:

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

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! 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: Elizabeth Thompson, M.S.

Title: Regulatory Project Manager

Date: June 23, 2006

Name of Office/Division Director signing form: Jeff Murray, M.D., M.P.H.

Title: Deputy Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

CLAIMED EXCLUSIVITY

Pursuant to 21 CFR 314.50(j) Tibotec, Inc. is hereby claiming marketing exclusivity for TMC114* (generic name: darunavir) tablets under the provisions of 21 CFR 314.108(b)(2).

To the best of our knowledge, no drug containing the active moiety in TMC114 (darunavir) tablets has been previously approved under section 505(b) of the Federal Food, Drug, and Cosmetic Act.

* The proprietary name for TMC114 is pending review by FDA and will replace TMC114 once available.

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

/s/

Jeffrey Murray
6/16/2006 04:01:19 PM

PEDIATRIC PAGE

\A/BLA #: 21-976 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

stamp Date: December 23, 2005 Action Date: June 23, 2006

HFD 530 Trade and generic names/dosage form: PREZISTA™ (darunavir) tablets, 300 mg

Applicant: Tibotec, Inc. Therapeutic Class: 7030220 (protease inhibitor)

Indication(s) previously approved: N/A; 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 PREZISTA (darunavir) tablets, co-administered with 100 mg of ritonavir, b.i.d. for the treatment of human immunodeficiency virus (HIV) infection in antiretroviral treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor.**

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

1. Age/weight range being deferred: Pediatric PMC # 03 on Approval Letter

Min _____ kg _____ mo. _____ yr. 6 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 17 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
- X Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): June 30, 2008

2. Age/weight range being deferred: Pediatric PMC # 04 on Approval Letter

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 6 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
- X Adult studies ready for approval
- Formulation needed

Other: Due to complex medical state of neonates and infants, and considering the availability of alternative treatment options in children less than 6 years of age, Tibotec would like to defer the assessment in this age group (<6 years) until additional data have been obtained in children 6-17 years of age.

Date studies are due (mm/dd/yy): June 30, 2011

udies 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 proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

Elizabeth Thompson
Division of Antiviral Products

{See appended electronic signature page}

Regulatory Project Manager

NDA 21-976
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)

PEDIATRIC USE SECTION: REQUEST FOR DEFERRAL OF PEDIATRIC STUDIES

In compliance with 21 CFR 314.55, Tibotec, Inc. is submitting a deferral request for submission of pediatric studies with the original New Drug Application (NDA 21-976) for the accelerated approval of TMC114* (generic name: darunavir) 300 mg tablets in combination with low dose (100 mg) ritonavir (RTV) for the treatment of human immunodeficiency virus (HIV) infection.

Reference is made to the pre-NDA meeting minutes dated 8 July 2005 in which the Division of Antiviral Drug Products (DAVDP) at FDA agreed to the proposed approach regarding the TMC114 pediatric development program and the proposed plan for submission of a request for deferral of pediatric studies with the original NDA.

Reference is also made to the TMC114 pediatric development plan submitted to the IND 62,477 on 1 December 2005 (Serial No. 400), providing a comprehensive package of nonclinical, CMC, PK and clinical information to support the initiation of pediatric program for TMC114 in antiretroviral treatment-experienced children (6 to 11 years of age) and adolescents (12 to 17 years of age).

The pediatric clinical development program of TMC114 initially will focus on the antiretroviral treatment-experienced pediatric children and adolescents between 6 years to 17 years of age given the unmet medical need in this population due to virologic failure and/or tolerability reasons. The pharmacokinetics, safety, tolerability and antiviral activity of TMC114 administered in combination with low dose RTV will be assessed in a Phase II PK/safety study TMC114-C212, to be initiated during 2Q2006. In light of the superior virologic response and the favorable safety profile of TMC114/RTV compared to optimized PI containing regimens used in the control group in the treatment-experienced HIV-infected adult population, it is expected that TMC114/RTV will represent a valid therapeutic option in a treatment-experienced pediatric population.

As described in the pediatric development plan submitted, study TMC114-C212 will consist of two parts, with part I targets to determine the pediatric dose of TMC114/RTV per body weight, and part II to evaluate long-term efficacy, safety and tolerability of the recommended pediatric dose. The recommended adult dose of [REDACTED] will be evaluated in treatment-experienced pediatric patients with a body weight of at least 60 kg. The adult tablet formulation was used [REDACTED]

The current projected dates for the availability of 24 weeks and 48 weeks data from study TMC114-C212 are 1Q2008 and 3Q2008, respectively.

* The proprietary name for TMC114 is pending review by FDA and will replace TMC114 once available.

In addition, as agreed during the pre-NDA meeting, Tibotec will be submitting the juvenile toxicity studies as a postmarketing commitment in supporting the pediatric development program for TMC114.

Subsequent pediatric development for TMC114 will consider its use in treatment-naïve pediatric patients < 6 years of age, pending completion of the juvenile toxicity program and availability of the appropriate pediatric formulation for this age group.

Given the proposed initiation timeline for study TMC114-C212 relative to the submission timeline of the original NDA to support the accelerated approval of TMC114 in treatment-experienced HIV-infected adult patients, Tibotec hereby requests a deferral for the assessment of safety and effectiveness of TMC114 in pediatric patients (ages 17 years and below) as a postmarketing commitment. In addition, due to the complex medical state of neonates and infants, and considering the availability of alternative treatment options in children less than 6 years of age, Tibotec would like to defer the assessment in this age group (<6 years) until additional data have been obtained in children (6 to 11 years of age) and adolescents (12 to 17 years of age).

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

/s/

Jeffrey Murray
6/27/2006 04:45:39 PM

DEBARMENT CERTIFICATION

Tibotec, Inc. certifies that we did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food Drug and Cosmetic Act in connection with this application.

Robin A. Keen

11/21/2005

Robin A. Keen
Sr. Director, Regulatory Affairs

Date

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-976 Supplement # N/A Efficacy Supplement Type SE- N/A

Trade Name: TMC114
Established Name: Darunavir
Strengths: 300 mg tablet

Applicant: Tibotec, Inc.
Agent for Applicant: N/A

Date of Application: 12-22-05
Date of Receipt: 12-23-05
Date clock started after UN: N/A
Date of Filing Meeting: February 10, 2006
Filing Date: February 21, 2006
Action Goal Date (optional): June 9, 2006 User Fee Goal Date: June 23, 2006

Indication(s) requested: Treatment of HIV infection

Type of Original NDA: (b)(1) (b)(2)
OR
Type of Supplement: (b)(1) (b)(2)

NOTE:

- (1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.
- (2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

NDA is a (b)(1) application OR NDA is a (b)(2) application

Therapeutic Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) Type 1, AA
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO
If yes, explain:
- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? N/A YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain: N/A
- If yes, has OC/DMPQ been notified of the submission? YES NO
N/A
- Does the submission contain an accurate comprehensive index? YES NO
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format? All

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A YES NO
- Is it an electronic CTD (eCTD)? N/A YES NO
If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, 5 Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y NO
- PDUFA and Action Goal dates correct in COMIS? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 62,477 and _____
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES NO
If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO
- Risk Management Plan consulted to ODS/IO? N/A YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A YES NO
- Has DOTCDP been notified of the OTC switch application? N/A YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A
YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? N/A YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? N/A YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO
N/A

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 10, 2006

BACKGROUND: TMC114 (Darunavir) is a new protease inhibitor (PI) that was developed in combination with ritonavir for the treatment of HIV-1 infection in antiretroviral treatment-experienced patients. Ritonavir is used as a pharmacokinetic enhancer of TMC114. The recommended dosage is 600mg twice daily taken with 100mg ritonavir twice daily.

TMC114 was granted fast track on November 15, 2004 and granted rolling review on June 6, 2005.

ATTENDEES: Tom Hammerstrom, Vikram Arya, Anitra Denson, Neville Gibbs, Kendall Marcus, Rao Kambhampati, Jules O'Rear, Lisa Naeger, Kellie Reynolds, Sarah Connelly, Andrea James, Charlene Brown, Virginia Behr, Monica Zeballos, Elizabeth Thompson, Debra Birnkrant, Mark Goldberger

ASSIGNED REVIEWERS (including those not present at filing meeting):

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Neville Gibbs
Secondary Medical:	Anitra Denson
Statistical:	Tom Hammerstrom
Pharmacology:	Jim Farrelly
Statistical Pharmacology:	N/A
Chemistry:	Rao Kambhampati
Environmental Assessment (if needed):	N/A
Clinical Pharmacology:	Vikram Arya
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	Lisa Naeger
DSI:	Tony El Hage
Regulatory Project Management:	Elizabeth Thompson
Other Consults:	

Per reviewers, are all parts in English or English translation? YES NO

If no, explain:

CLINICAL FILE REFUSE TO FILE

• Clinical site inspection needed? YES NO

• Advisory Committee Meeting needed? YES, date if known _____ NO

• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS

FILE

REFUSE TO FILE

- Biopharm. inspection needed?

YES NO

PHARMACOLOGY

N/A

FILE

REFUSE TO FILE

- GLP inspection needed?

YES NO

CHEMISTRY

FILE

REFUSE TO FILE

- Establishment(s) ready for inspection?
- Microbiology N/A

YES NO
YES NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- No filing issues have been identified.
- Filing issues to be communicated by Day 74. List (optional): see below

Chemistry

1. Since the drug substance contains 1:1 ratio of the active molecule (TMC114) and ethanol, we recommend that you revise the chemical name, structural formula, molecular formula, and molecular weight of darunavir in the package insert and in the appropriate sections of the NDA.
2. Please provide the anticipated date of submission for the updated stability data for darunavir tablet batches.

Clinical Pharmacology

3. Please submit the following datasets to support the population pk-pd graphical and statistical analyses for TMC114-C926:
 - All analysis datasets should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file.
 - Model codes and output listings should be provided for the ANCOVA and logistic regression models. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

Statistics

4. Please send a corrected copy of the demographics dataset including all baseline covariates, including but not limited to the following:
- indicator of subject used in the interim analysis
 - indicator of subject in the original 278 for trial 202
 - indicator of subject assigned randomly or deterministically
 - country, age, sex, race
 - indicators for each drug in the OBR-- one variable for each drug that could possibly be used by any subject
 - baseline HIV and baseline CD4 count
 - every variable used in the randomization
 - every variable used in any primary or sensitivity analysis
 - number of susceptible NRTI's at baseline
 - number of susceptible NNRTI's at baseline
 - number of susceptible PI's at baseline
 - duration of previous ARV use
 - number of NRTI mutations at baseline
 - number of NNRTI mutations at baseline
 - number of PI mutations at baseline, one variable for each list of mutations

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Convey document filing issues/no filing issues to applicant by Day 74.

Elizabeth Thompson, M.S.
Regulatory Project Manager, HFD-530

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-976	Efficacy Supplement Type SE-	Supplement Number
Drug: PREZISTA™ (Darunavir) tablets		Applicant: Tibotec, Inc.
RPM: Elizabeth Thompson		Division of Antiviral Products HFD-530
Phone # 301-796-1500		
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected Not applicable as this is a 505(b)(1) application</p>	<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p>	
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority • Chem class (NDAs only) • Other (e.g., orphan, OTC) 		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Type I Type AA (HIV)
❖ User Fee Goal Dates		June 23, 2006
❖ Special programs (indicate all that apply)		<input type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input checked="" type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee • User Fee waiver N/A 		<input checked="" type="checkbox"/> Paid UF ID number <u>3006195</u>
<ul style="list-style-type: none"> • User Fee exception N/A 		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
<ul style="list-style-type: none"> • User Fee exception N/A 		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
❖ Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> • Applicant is on the AIP 		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> • Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	5 years claimed marketing: exclusivity summary DFS'd to M. Holovac
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	<input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	N/A

General Information	
❖ Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	() Materials requested in AP letter (X) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes () Not applicable
• Indicate what types (if any) of information dissemination are anticipated Information Advisory, Q & A's	() None (X) Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling June 22, 2006; revised via email June 23	√ June 23, 2006
• Original applicant-proposed labeling	N/A
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	√
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed June 22, 2006; revised via email June 23	√ June 23, 2006
• Reviews	√
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	√ June 22, 2006 eCTD submission (letter dated June 21, 2006)
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	√
❖ Memoranda and Telecons	√
❖ Minutes of Meetings	√
• EOP2 meeting (indicate date)	Type C; November 3, 2004
• Pre-NDA meeting (indicate date)	June 7, 2005
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	EOP2 CMC; December 8, 2004
❖ Advisory Committee Meeting	N/A
• Date of Meeting	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	√
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	√
❖ Microbiology (efficacy) review(s) (indicate date for each review)	√
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	√
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	√
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	√
❖ Biopharmaceutical review(s) (indicate date for each review)	√
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	√
• Clinical studies	√
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) (indicate date for each review)	√
❖ Environmental Assessment	√
• Categorical Exclusion (indicate review date)	√
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	√
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	√
❖ Facilities inspection (provide EER report) see Chemistry review	Date completed: (X) Acceptable () Withhold recommendation
❖ Methods validation (Will not be requested on the basis of the current policy. The dosage form is simple and doesn't involve any unusual/special tests.)	() Completed () Requested (X) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	√
❖ Nonclinical inspection review summary	√
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	√
❖ CAC/ECAC report	√

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

/s/

Virginia Behr
6/23/2006 05:15:29 PM

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

DATE: June 23, 2006

FROM: Jeffrey S. Murray M.D., M.P.H.
Deputy Director
Division of Antiviral Products

SUBJECT: Memorandum for NDA 21- 976 (Prezista, darunavir)

TO: Division files

Tibotec, Inc. submitted an original NDA for darunavir, a new HIV protease inhibitor for the treatment of HIV in treatment-experienced patients. FDA granted Fast Track status and a rolling NDA for darunavir. In addition, darunavir was determined to be an appropriate candidate for accelerated approval. Specifically, darunavir may offer treatment benefit over existing antiretroviral treatment options based on demonstrated clinical activity against clinical isolates resistant to other marketed protease inhibitors.

Please refer to the primary clinical review written by medical officer Neville Gibbs, M.D., M.P.H., the team leader memorandum written by Kendall Marcus, M.D., the microbiology review written by Lisa Naeger, PhD, and the statistical review written by Thomas Hammerstrom, PhD for detailed descriptions of study designs and analyses. Briefly, this application is primarily supported by data from two randomized, controlled, Phase 2b, dose-finding studies in heavily treatment-experienced HIV patients comparing control to several doses of darunavir co-administered with low-dose ritonavir. In these studies the control consisted of one or two of several investigator selected protease inhibitors (PIs), most boosted with ritonavir. Darunavir and control were added to an "optimized" antiretroviral regimen selected according to resistance testing and prior treatment history. Given the extensive treatment history among trial participants, the marketed PI controls in these studies were essentially ineffective or partially effective at best.

Similar to other studies in heavily treatment-experienced subjects, these two protocols allowed subjects not having an adequate virologic response by 12 weeks to exit and receive darunavir/ritonavir in a roll-over study. Given the primary endpoint of a 1 log decrease in HIV-RNA, these patients are considered treatment failures at the time of exit.

Both studies showed that darunavir/ritonavir at all doses had substantial and unambiguous antiviral efficacy that was superior to control. In one of the two studies, the highest dose of darunavir, 600 mg twice daily, produced the best virologic responses (numerically) compared to other doses. Therefore the dose of darunavir for marketing is 600 mg co-administered with ritonavir 100 mg twice daily. It is common for the highest tolerated dose of an antiretroviral to be chosen for marketing to allow a margin of activity for patients with reduced drug susceptibility and to perhaps allow for more "forgiveness" for missed or late doses. In addition, pharmacokinetic/pharmacodynamic analyses of these studies suggest that the 600 mg twice daily dose is associated with better virologic activity, particularly for patients with decreases in phenotypic susceptibility to darunavir. Pharmacodynamic modeling also suggested that higher doses of darunavir would not result in additional antiviral activity.

The safety and tolerability of darunavir boosted with ritonavir is similar to that of other boosted protease inhibitors on the market. Gastrointestinal symptoms such as nausea and diarrhea are among the most common adverse reactions. Similar to some other boosted protease inhibitors, darunavir is also associated with increases in total cholesterol and LDL. A potentially serious adverse drug reaction associated with darunavir/ritonavir is drug rash which has infrequently been severe (one case of Stevens Johnson Syndrome in an ongoing study) and has been associated with fever and/or transaminases elevations in several cases. Discontinuations due to drug eruption are not common (< 1%). Also because darunavir contains a sulfa moiety in its chemical structure, the label will direct prescribing physicians to use additional caution if prescribing darunavir to patients with a history of sulfa rash. It should be noted that rash can occur in the absence of a prior history of sulfa allergy.

The clinical and statistical reviewers noted that there were more deaths in the pooled darunavir arms compared to the control arms in both studies. In fact, in the original submission, all but one death occurred among patients receiving darunavir. However, the mortality rate on the darunavir arms was similar to that of previous studies in similar populations. The striking finding was the near absence of mortality on the control arms. Upon further inspection of the study data, it appeared that there was a substantial difference in the follow-up of patients randomized to controls who had chosen to exit the protocol. Specifically, four times as many patients randomized to control compared to darunavir dropped out of the study prior to taking drug, most likely because some subjects were unhappy with being randomized to control. In addition, a substantial number of subjects randomized to control did not roll-over to another darunavir protocol and were not included for follow-up for clinical or late occurring endpoints. During the review process, the applicant was able to retrieve vital status in all but one of the randomized patients, receiving darunavir and/or control, revealing a comparable incidence of death among patients randomized to darunavir and control arms. In addition, there were no patterns regarding the cause of death that would point to a safety signal for darunavir.

Although differences in longer term follow-up caused an initial appearance of an imbalance in mortality between darunavir and control, sensitivity analyses (performed by Thomas Hammerstrom) showed that the virologic response endpoint was not appreciably affected by differences in discontinuations.

During a May 2005 advisory committee for tipranavir (a protease inhibitor approved in June 2005 for treatment-experienced patients), some committee members questioned why the observed differences in virologic response did not translate into a mortality benefit in the tipranavir studies and the previously conducted enfuvirtide studies. Some have raised this issue to challenge the validity of HIV-RNA as a surrogate. However, one must realize that studies are now conducted with escape clauses for virologic failure, such that patients are not required to endure a clinical endpoint prior to changing to a new treatment. Historically, in the 13 studies designed to assess clinical endpoints prior to 1997 (in which participants randomized to controls were required to have a documented clinical endpoint before given access to the study drug), every treatment comparison in which at least a 0.5 log difference in viral load was observed over 16-24 weeks also showed a difference in clinical progression of HIV. The fact that there have been no differences in mortality in contemporary studies, for which treatment decisions and endpoints are based on HIV-RNA levels, means that study designs are now ethically designed with safeguards protecting participants. In other words, the studies have achieved their intended goals of allowing the evaluation of differences in HIV-RNA without measurably placing participants at increased risk of progression and mortality if randomized to a suboptimal control.

Similar to other trials in heavily treatment-experienced subjects, a relatively small proportion of women were enrolled in these trials. Despite the relatively small number of women, the difference in virologic response between darunavir and control in women was large and consistent with the overall response. Therefore, virologic efficacy of darunavir in women is not in question; however, a larger safety database in women at the time of traditional approval will be important to determine any potential safety issues.

Based on the scientific data included in this application in which subjects treated with darunavir/ritonavir had substantially larger decreases in viral load and increases in CD4 cell counts, I recommend accelerated approval for darunavir. Darunavir 600 mg twice daily with ritonavir 100 mg twice daily in combination with other antiretrovirals will be indicated for the treatment of HIV in adult treatment experienced patients, such as those with HIV strains resistant to more than one protease inhibitor. This new protease inhibitor has demonstrated activity in patients harboring clinical isolates resistant to many other approved protease inhibitors and therefore fulfills a clinical need. In addition darunavir is reasonably tolerated with an acceptable risk-benefit profile.

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

/s/

Jeffrey Murray
6/23/2006 02:18:14 PM
MEDICAL OFFICER

Edward Cox
6/23/2006 02:48:52 PM
MEDICAL OFFICER

**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; White Oak Mail Stop 4447
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: October 20, 2005

NDA# 21-976

NAME OF DRUG: Prezista
 (Darunavir Film Coated Tablets)
 300 mg

NDA HOLDER: Tibotec, Inc.

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

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anti-Viral Products (HFD-530), for assessment of the proprietary name, "Prezista" regarding potential name confusion with other proprietary and/or established drug names. Container labels, carton, and insert labeling were not submitted for review and comment at this time.

The sponsor submitted two proposed proprietary names for consideration: [REDACTED] (primary) and Prezista (secondary). The first proposed name, [REDACTED], was found unacceptable by the Division of Drug Marketing, Advertising, and Communications (DDMAC) [REDACTED]. The Division of Anti-Viral Drug Products concurs with DDMAC's objection to the name [REDACTED], therefore [REDACTED] will not be discussed further in this review (see ODS Consult #05-0299, dated November 23, 2005). Only Prezista will be reviewed by DMETS from a safety perspective.

PRODUCT INFORMATION

Prezista is a protease inhibitor indicated for treatment of Human Immunodeficiency Virus-1 (HIV-1) infection in antiretroviral treatment-experienced patients. It will be supplied as 300 mg orange oval shaped film-coated tablets. The proposed dose is 600 mg (2 tablets) by mouth twice daily with food, taken in conjunction with 100 mg of ritonavir. Ritonavir is used as a pharmacokinetic enhancer of Prezista. Prezista is proposed to be packaged in a bottle of 120 count tablets.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases^{3,4} for existing drug names which sound-alike or look-alike to Prezista to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁵. The Saegis⁶ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies for each proposed name consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

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

1. DDMAC has no objections to the tradename "Prezista" from a promotional perspective.
2. The Expert Panel identified five proprietary names that were thought to have the potential for confusion with Prezista. These products are listed in Table 1 (page 4), along with the dosage forms available and usual dosage.

¹ MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

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

³ AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-05, and the electronic online version of the FDA Orange Book.

⁴ F.D.A. Phonetic and Orthographic Computer Analysis (POCA)

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁶ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Table 1: PREZISTA: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form		Other
Prezista	Darunavir Tablets, film-coated Bottle of 120 tablets		N/A
Pentasa	Mesalamine (5-ASA) Capsules, extended-release: 250 mg, 500 mg	1 g 4 times daily for a total dose of 4 g for up to 8 weeks.	LA
Prinzide	Hydrochlorothiazide/Lisinopril Tablets: 12.5 mg/20 mg, 25 mg/20 mg, 12.5 mg/10 mg	Initially, one tablet daily of either the 12.5 mg/10 mg or 12.5 mg/20 mg dosage ratio of HCTZ and Lisinopril, when blood pressure is not responsive to Lisinopril or HCTZ monotherapy. Adjust dosage based on clinical response.	LA
Evista	Raloxifene Hydrochloride Tablets: 60 mg	1 Tablet (60 mg) orally once daily. Supplement calcium if dietary intake is inadequate	SA
Prazosin	Prazosin Capsules: 1 mg, 2 mg, 5 mg Tradename: Minipress and various generics	Initially, 1 mg PO given 2 to 3 times per day. The first dose can be given at bedtime to minimize orthostatic hypotension. The average dosage is 6 mg/day to 15 mg/day PO, given in divided doses. Some patients may need higher doses up to 40 mg/day. When adding additional hypotensive agents or diuretics to prazosin therapy, decrease the dosage of prazosin to 1 mg to 2 mg PO three times per day, then gradually increase as needed. <u>Elderly:</u> Initially, 1 mg PO given 1 to 2 times per day.. <u>Children:</u> Initially, 5 mcg/kg PO every 6 hours. Increase dosage gradually to 25 mcg/kg PO every 6 hours.	LA
Propecia	Finasteride Tablets: 1 mg	1 mg PO once daily. Daily use for more than 3 months is necessary before benefit is observed. Continued use is recommended to sustain benefit.	SA

*Frequently used, not all-inclusive.

**LA (look-alike), SA (sound-alike)

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

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary names to determine the degree of confusion of Prezista with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The set of studies (i.e., inpatient, outpatient, and verbal study for each name) employed a total of 124 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescription were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Prezista (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: <i>Prezista 300mg #120 # tabs BID</i>	"Prezista 300 mg, number 120, take 2 tablets twice a day"
Inpatient RX: <i>Prezista 300mg 2 tablets twice daily</i>	

2. Results for Prezista:

One respondent in the verbal study misinterpreted the proposed name, Prezista, as Evista. Evista is a currently marketed U.S. product. The remaining misinterpretations were misspelled/phonetic variations of the proposed name, Prezista. See Appendix A for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

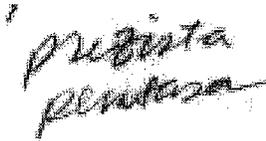
In reviewing the proprietary name Prezista, the primary concerns identified were related to potential look-alike and sound-alike confusion with Pentasa, Prinzide, Evista, Prazosin, Propecia, and [REDACTED]. Upon further review of the names gathered from the EPD, independent analysis, and POCA, the name [REDACTED] was not reviewed further due to a lack of convincing look-alike/sound-alike similarities with Prezista, in addition to numerous differentiating product characteristics such as the product strength, indication for use, frequency of administration, and dosage form.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. One respondent in the verbal study interpreted the proposed name, Prezista, as Evista, an already existing marketed drug product. The remaining misinterpretations were misspelled/phonetic variations of the proposed name, Prezista.

1. Pentasa was identified as a name with similar appearance to Prezista. Pentasa is a brand of extended-release mesalamine capsules that is used as an anti-inflammatory agent in treating ulcerative colitis and, to a lesser extent, Crohn's disease, although clinical response is believed to be due to a local effect.

The two names have some orthographic similarities. Both names begin with the letter 'P' and end with the letter 'a' which contributes to their look-alike properties. However, the middle portions of the name look different (-entas- vs. -rezist-) when scripted. Additionally, the letter 't' in each name contributes an upstroke in different positions of the name which may help to differentiate the two names.

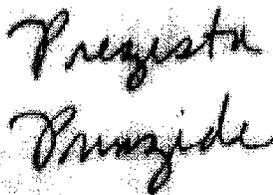
Another differentiating factor is the product strength. Since Prezista is available in only one strength it is possible for the strength to be omitted on a prescription. However, Pentasa is available in two strengths (250 mg and 500 mg) so the strength should be present on a prescription which may help to differentiate between the two names. Prezista is proposed to be given in conjunction with Ritonavir and taken with food so it is likely that additional prescription modifiers, such as "take with food" or "take with 100 mg Ritonavir" will be present on a prescription for Prezista that may help to differentiate the two names. Additionally, the two products have different prescribed doses (1 gram vs. 600 mg) and different frequencies of administration (four times daily vs. twice daily) which may help to differentiate between the two names. Therefore, despite some orthographic similarities between Prezista and Pentasa, distinguishing characteristics such as the dose, frequency of administration, and prescription modifiers on the prescription will help minimize the potential for confusion between the two names.



2. Prinzide was identified as a name with similar appearance to Prezista. Prinzide is a tradename formulation of the drugs Lisinopril and Hydrochlorothiazide combined in an oral formulation for the treatment of hypertension. Hydrochlorothiazide is a thiazide diuretic and Lisinopril is an angiotensin-converting enzyme inhibitor.

Both names begin with the prefix 'Pr-' which contributes to their look-alike properties. Additionally, the letter 'z' in Prinzide and Prezista when scripted can contribute a downstroke in similar positions of each name. However, the endings of each name are distinctive (-ide vs. -sta) and may help to differentiate between the two names. The product strengths may also be a distinguishing factor. Since Prezista is available in only one strength, it is possible for the strength to be omitted on a prescription. However, Prinzide is available in three strengths (12.5 mg/20 mg, 25 mg/20 mg, and 12.5 mg/10 mg) so the strength should be present on a prescription which may help to differentiate between the two names. Additionally, Prezista is proposed to be given in conjunction with Ritonavir and taken with food so it is likely that additional prescription modifiers,

such as “take with food” or “take with 100 mg Ritonavir” will be present on a prescription for Prezista that may help to differentiate the two names. Furthermore, we note that anti-retroviral therapy for HIV is typically given as a combination of three or four anti-retroviral drugs. Additional prescriptions for HIV medications that may accompany a prescription for Prezista may help to differentiate between the names Prezista and Prinzide. Prezista and Prinzide have different frequencies of administration (once daily vs. twice daily) which may help to differentiate between the two names. Therefore, despite some orthographic similarities between Prezista and Prinzide, distinguishing characteristics such as the strength, frequency of administration, and prescription modifiers on the prescription will help minimize the potential for confusion between the two names.

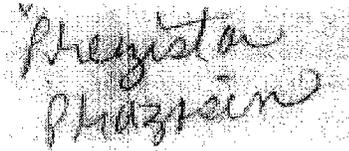


3. Evista was identified as a name that may sound similar to Prezista. Evista is a prescription brand of raloxifene hydrochloride, a selective estrogen receptor modulator used in the treatment of osteoporosis and osteoporosis prophylaxis in postmenopausal women. One respondent in the DMETS verbal study interpreted the proposed name as Evista. The dose of Evista is 60 mg (1 tablet) taken once daily. The two names share the same suffix, ‘-ista’ which contributes to their rhyming properties. However, the prefixes for each name, ‘E-’ for Evista and ‘Prez-’ for Prezista remain distinguishable by sound and may help to differentiate between the two names. Both Evista and Prezista are available in just one strength (60 mg vs. 300 mg), therefore the strength may be omitted with a verbal order. However, because the dose of Prezista is 600 mg, and the tablet strength is 300 mg, it is likely that either the dose and/or strength will be included in the verbal order for Prezista. The milligram strength of the prescription when spoken (“sixty” vs. “three hundred” or “six hundred”) may also help to differentiate between the two drug names on a verbal order. Additionally, a verbal order for Prezista may contain the directions “take two tablets”, in which case the number of tablets per dose may help differentiate from a prescription for Evista, which is ordered as one tablet per dose. Furthermore, the dosing frequency for Prezista is twice a day whereas the dosing frequency for Evista is once a day. The inclusion of these prescription modifiers on a verbal order may minimize the potential for confusion between the two names.

It is possible for either drug to be ordered with the directions “dispense one month supply, take as directed,” in which case the verbal pronunciation of the name would be the differentiating factor. Due to the varied dosage regimen for each of the antiretroviral drugs, they are typically not ordered “as directed.” Additionally, Prezista is taken in conjunction with Ritonavir and treatment-experienced HIV patients are typically on a two to four drug antiretroviral regimen. Therefore, it is likely that the patient will have accompanying prescriptions for additional antiretroviral drugs. Moreover, it is typical for HIV patients to use the same pharmacy for all their prescriptions, so the knowledge of the patient’s HIV positive status as well as an existing patient profile of HIV medications may help to differentiate between the two names. Thus, despite some phonetic similarities, the different product characteristics of each drug such as the dose, and dosing frequency will help minimize the potential for confusion between the two names.

4. Prazosin was identified as a name that may look similar to Prezista. Prazosin is the established name for Minipress Capsules, a prescription antihypertensive agent. There are several generic formulations of Prazosin available on the market. The initial dose is 1 mg orally two to three times a day. The dose is titrated to the desired response. The average dose of Prazosin is 6 mg to 15 mg per day in divided doses, although some patients may require up to 40 mg per day in divided doses. Prazosin is marketed in three strengths, 1 mg, 2 mg, and 5 mg.

The two names share some orthographic similarities due to the shared prefix, 'Pr-'. Additionally, it is possible for each name to contain a downstroke from a scripted letter 'z' in similar positions within each name. However, the remaining portions of each name still remain distinctive and may help to differentiate between the two names (see below). Additionally, the name Prezista contains an additional upstroke from the letter 't' which may help to differentiate between the two names. The two products share the overlapping dosing frequency (twice a day vs. two to three times a day), and may share overlapping instructions for use (take two) if the dose is expressed in the number of dosage units. However, if the milligram strength or milligram dose is written on the prescription it will also help differentiate between the two names ("Prezista 300 mg, take two tablets" vs. "Prazosin 2 mg, take two capsules"). Thus, any prescription modifiers present on the prescription may help differentiate between the two names. Overall, the orthographic differences, as well as any prescription modifiers and the different product characteristics of each drug such as the dosing regimen, strength and dose will help minimize the potential for confusion between the two names.

A handwritten comparison of the names 'Prezista' and 'Prazosin'. The word 'Prezista' is written in a cursive script with a distinct upstroke on the letter 't'. Below it, 'Prazosin' is written in a similar cursive script, but without the upstroke on the 't'. The two words are written close together to highlight their orthographic similarities.

5. Propecia was identified as a name that may sound similar to Prezista. Propecia is the tradename for the prescription drug finasteride, which is indicated for the treatment of male pattern hair loss (i.e., androgenetic alopecia), in patients with mild to moderate hair loss of the vertex and anterior mid-scalp area.

The similarity in sound stems from the fact that both of the names have three syllables. The suffixes of the two names, '-pecia' for Propecia and '-zista' for Prezista can sound similar due to the sound of the letter 'e' in Propecia and the letter 'i' in Prezista which may be pronounced as the letter 'e'. Furthermore, the letter 'a' at the end of each name is the terminal syllable and is pronounced with emphasis like the phonetic "-uh". Despite these similarities, the prefixes of each name 'Pre-' for Prezista and 'Pro-' for Propecia sound different due to the prominence of the vowels and different sound of each vowel and may help to differentiate between the two names. Both Propecia and Prezista are available in just one strength (1 mg vs. 300 mg), therefore the strength may be omitted on a prescription. However, because the dose of Prezista is 600 mg, and the tablet strength is 300 mg, it is likely that either the dose and/or strength will be included on the prescription. Additionally, a verbal order for Prezista may contain the directions "take two tablets", in which case the number of tablets per dose may help differentiate from a prescription for Propecia, which is ordered as one tablet per dose. Furthermore, the dosing frequency for Prezista is twice daily, whereas the dosing frequency for Propecia is

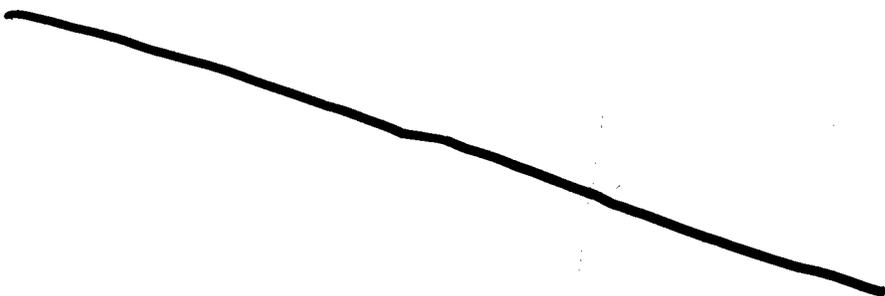
once daily. The presence of the dosing frequency on an order may help to differentiate between the two names. Thus, the phonetic differences, in addition to the product characteristics of each drug such as frequency of administration or number of tablets per dose will help decrease the potential for confusion between the two names.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

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

A. CONTAINER LABEL (120 count bottle)

1. Ensure that the established name is at least one-half the size of the proprietary name in accordance with 21 CFR 201.10(g)(2) on all labels and labeling.
2. Since this drug will be packaged in a “unit of use” container, ensure that the container will have a Child Resistant Closure in accordance with the Poison Prevention Act.
3. Revise the “Each tablet contains...” statement to read “Each tablet contains darunavir ethanolate equivalent to 300 mg of darunavir”.

4. 

B. INSERT LABELING

1. The sections of the package insert labeling for Prezista seem out of order. For example, the Description of Clinical Studies section follows the INDICATIONS AND USAGE section. Please follow the FDA template for the ordering of these sections in accordance with 201.56(d)(1).
2. CONTRAINDICATIONS and PRECAUTIONS Sections

Table 5 (under the CONTRAINDICATIONS section) lists the “Drugs That Are Contraindicated with TRADENAME/rtv” and Table 6 (under the PRECAUTIONS section) lists the “Drugs That Should Not Be Coadministered with TRADENAME/rtv.” We question how a clinician is to distinguish between these categorizations. Please clarify the difference between these products that are “contraindicated” and those that “should not be coadministered with” in regards to Prezista. Should all of the drugs in Table 6 be considered contraindicated?

3. PRECAUTIONS Section
Information for Patients

- a. The first sentence of the fourth paragraph should be revised to read “Patients should be advised to take TRADENAME with food and Ritonavir every day as prescribed.” As currently written, the recommendation to take TRADENAME with Ritonavir does not appear until the third sentence where it may be missed by the reader.
- b. Reprint the Information for Patient at the end of the package insert in accordance with CFR 201.57(f)(2).

4. DOSAGE AND ADMINISTRATION Section

DMETS recommends avoiding the use of all abbreviations in the labels and labeling since they are often misread and may lead to medication errors (i.e., “q.d.”, “b.i.d.”, etc.). As evidenced by our post-marketing surveillance, abbreviations and acronyms may be misinterpreted. We note that the Joint Commission for Accreditation of Hospitals (JCAHO), 2006 Hospitals National Patient Safety Goals includes the goal: Improve the effectiveness of communication among caregivers. A requirement to meet this goal is that each hospital must ‘Standardize a list of abbreviations, acronyms and symbols that are not to be used throughout the organization’. The abbreviation “q.d.” is specifically listed as a dangerous abbreviation, acronym or symbol. Additionally, the Institute for Safe Medication Practices also publishes an “ISMP List of Error-Prone Abbreviations, Symbols, and Dose Designations” in which they also recommend avoiding the use of the abbreviation “q.d.” Postmarketing experience has shown that “q.d.” (once daily) may be confused with “q.i.d.” (four times daily), especially if the period after the letter “q” or the tail of the letter “q” is misinterpreted as the letter “i”. Revise accordingly (i.e., “q.d.” to read “daily”, “b.i.d.” to read “twice daily”, etc.).

C. PATIENT INSERT LABELING

1. DMETS recommend that the proposed patient information be reviewed by the Division of Surveillance, Research, and Communication Support (DSRCS) to ensure comprehension level and format.
2. How does TRADE NAME work? Section

We recommend that you revise the second paragraph to read “TRADE NAME is always taken with and at the same time as 100 mg of ritonavir (NORVIR), in combination with other anti-HIV medicines. TRADE NAME should also be taken with food.”

Inpatient	Outpatient	Verbal
Prezista	Prevista	Pazista
Prezista	Prevista	Pozista
Prezista	Prevista	Pazisa
Preziola	Previta	Zessa
Prezista	Previta	Pisiza
Prezita	Prevista	Prevista
Prezista	Previta	Previtsta
Prezista	Prerista	Evista
Prezista	Previta	Pozista
Prezista	Previta	Prozeesta
Prezista	Previta	Pazista
Prezista	Previta	Pazesza
Prezida	Previta	Pazista
Prezista	Previta	Promisa
Prezista	Prevista	Pazista
Prezista	Previta	Pezista
Prozista	Previta	
Prezista	Prevista	
Prezista	Precista	
Prezista	Prevista	
Prezista	Previta	
Prezista		

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

/s/

Laura Pincock
4/5/2006 08:52:41 AM
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung
4/5/2006 09:02:12 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
4/7/2006 07:55:25 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
4/7/2006 03:42:42 PM
DRUG SAFETY OFFICE REVIEWER

REQUEST FOR CONSULTATION

TO (Office/Division): John Senior, M.D. OPSS

FROM (Name, Office/Division, and Phone Number of Requestor):

Neville Gibbs, M.D., DAVP
301-796-0718

DATE
March 15, 2006

IND NO.
062477

NDA NO.
021976

TYPE OF DOCUMENT
paper

DATE OF DOCUMENT
3/15/2006

NAME OF DRUG
TMC114/RTV

PRIORITY CONSIDERATION
priority

CLASSIFICATION OF DRUG
HIV protease inhibitor

DESIRED COMPLETION DATE
4/17/2006

NAME OF FIRM: Tibotec Virco

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG SAFETY

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

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Requesting opinion on the hepatic signals occurring during the clinical development program of TMC114, a protease inhibitor (sulfonamide). The MO review "Hepatic Safety of TMC114/RTV" will be emailed to John Senior. Copies of the narratives of the SAEs and the schematic of the design of the development program will be hand delivered to John Senior.

SIGNATURE OF REQUESTOR
Neville Gibbs, M.D.

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF PHARMACOEPIDEMIOLOGY AND STATISTICAL SCIENCE

DATE: 5 April 2006

FROM: John R. Senior, M.D., Associate Director for Science, Office of
Pharmacoepidemiology and Statistical Sciences (OPaSS), HFD-030

TO: Debra Birnkrant, M.D., Director, Division of Antiviral Products, HFD-530
Neville Gibbs, M.D., Medical Officer, DAVP

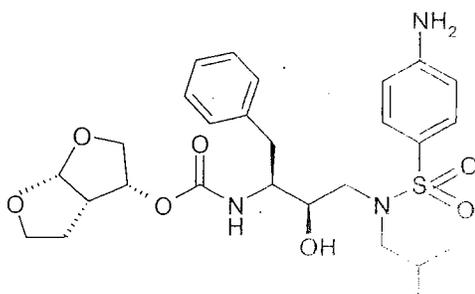
VIA: Mark Avigan, M.D., Director, Division of Drug Risk Evaluation
(DDRE), HFD-430
Paul Seligman, M.D., Director, OPaSS, HFD-030

SUBJECT: Cases of possible liver injury in patients treated with darunavir (TMC114)
under IND 62,477 and NDA 21-976; Office of Drug Safety, Division of Drug
Risk Evaluation consultation request PID #060218

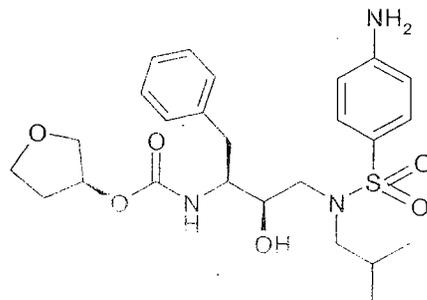
Documents reviewed:

- 1) Consultation request dated 15 March 2006, from Dr. Neville Gibbs, DAVP, 22:6385, 301-796-0718, requesting hepatology opinion on "hepatic signals" occurring during development of the new sulfonamide protease inhibitor TMC114 (darunavir) reported in New Drug Application 21-976 submitted for review and evaluation 23 December 2005.
- 2) Brief medical safety review by Dr. Gibbs on "Hepatic Safety of TMC114/RTV," with tabulated numbers of patients showing various degrees of elevation of serum bilirubin, alanine and aspartate aminotransferase and alkaline phosphatase activities in studies C202 and C213, and some thumbnail sketches of individual patients showing abnormalities.
- 3) Listings of 30 cases for which closer inspection was requested.
- 4) Chemistry, toxicology, biopharmaceutic reviews for IND 62,477 (no NDA 21-976 reviews posted yet to the Document File System).

TMC114, now called generically darunavir, is a new protease inhibitor developed to treat human immunodeficiency virus (HIV) infection resistant to other protease inhibitors (Koh, et al., 2003).



TMC114 (darunavir)



amprenavir

The new drug is structurally similar to amprenavir (Agenerase, GlaxoSmithKline), the fifth protease inhibitor available for clinical use (approved 15 April 1999; NDA 21-007), but amprenavir has no reported hepatotoxicity. Other protease inhibitors (nelfinavir, ritonavir, and saquinavir) are reported to stimulate hepatic triglyceride synthesis (Lenhard, et al., 2000), but amprenavir does not, nor does it inhibit the hepatic enzyme uridine diphosphoglucuronosyl transferase -1A1 and cause jaundice, as do indinavir and atazanavir (Kempf, et al., 2006).

Dr. Gibbs pointed out that many of the anti-retroviral agents developed so far have shown some degree of liver toxicity in preclinical and clinical studies (Sulkowski, 2004), but that the preclinical repeat-dose studies in rats exposed to TMC114 and ritonavir (RTV) appeared to the toxicology reviewer to be adaptive responses with induction of cytochrome P450 enzymes. From the tabulations of elevations in serum total bilirubin (TBL) concentration, alanine (ALT) and aspartate (AST) aminotransferase or alkaline phosphatase (ALP) activities. He noted no increases in peak values in patients treated with TMC111 and RTV at various doses in the controlled studies, compared to control patients.

He cited one case (#0052 in Study C215), a 45-year-old Afro-american man who was "rolled over" from the control treatment arm of Study C202 (where he was #5507) into the extension study C215 in which he received TMC114 with ritonavir (used to prolong the concentration of unmetabolized TMC114, darunavir), along with abacavir, tenofavir (TNV) and lamivudine (3TC), in addition to clarithromycin, triamterine-hydrochlorothiazide (Dyazide), furosemide, flucatisone, medinite, salbutamol, ramipril and valciclovir for his concomitant esophageal candidiasis, thrush, toxoplasmosisdiarrhea, neuropathy, herpes zoster, wasting syndrome, hypertension, and depression. After 114 days on darunavir-ritonavir he showed elevated serum activities of ALT, AST and gammaglutamyltransferase (GGT) >5 times the upper limit of the normal or reference range (xULN) and ALP activity >2.6 xULN, with a dip in ALT 5 days later but rebound at 135 days. Study drug was withdrawn permanently after 145 days of exposure because of the persisting serum enzyme activity elevations. From the more detailed case report, it appears that serum bilirubin was not measured, but there was no increase in serial prothrombin times.

Comment: The cited reference to the Navarro-Senior paper mistakenly cites the combination of ALT >3 xULN and ALP >2 xULN as Definition #1 indication of liver injury, and Definition #2 as the combination of TBL >2 xULN and ALT or ALP elevation as cholestatic injury. The paper makes argument that combined ALT and TBL elevations, when not cholestatic (ALP elevation) suggest possibly serious liver injury if caused by a drug. This patient did not show such serious injury, only elevated serum enzyme activities. It is a function of the liver to clear bilirubin from the plasma, conjugate it and excrete it into the bile, and another function to synthesize coagulation factors such as prothrombin. But regulation of plasma enzyme activities is not a function of the liver. Although elevations may suggest liver injury, they are not specific. It is too bad the study protocols did not call for measuring serial serum bilirubin levels. It is unclear why the sponsor chose to monitor using GGT in these studies, which is generally taken to indicate cholestasis, but also reflects alcohol use. The combination of drug-induced hepatocellular (but not cholestatic) elevation of ALT and TBL has come to be called "Hy's Law" and suggests possibly serious liver injury. The cholestatic indicators, ALP and GGT, do not have this significance. Please see recent editorials by Kaplowitz, Temple, and me recently published in the April 2006 issue of Pharmacoeconomics and Drug Safety for more detailed explanations.

Among the 4 other patients mentioned briefly because of elevated serum aminotransferase or GGT enzyme activity elevations (Cases 215-0408, C215-0500, C202-6401, C202-6405), there were none who showed clinical or laboratory evidence of serious liver disease or injury. Study drug administration was interrupted temporarily in another 9 patients (C215-0032, C215-0065, C215-0413, C215-0268, C215-0128, C215-0016, C215-0153, C202-6610, C202-1501). None of them showed any serious hepatic injury with loss of function, but mainly elevated serum ALT or AST elevations or on-drug serum bilirubin increases. Of perhaps greater interest are the 8 cases mentioned in Section E, 4 of whom had liver biopsies done.

Comment: In searching out the additional information for these individual cases, it is important to know how well other causes than TMC114 may have been ruled out. Both other diseases and other drugs must be excluded, which may be very difficult in this population of patients who have many problems and usually are on many drugs. Enzyme rises alone are not so important in determining severity as are associated (concurrent or subsequent) loss of overall liver function, as measured by rises in total bilirubin or prothrombin time. Liver biopsy may be of interest and somewhat helpful, but is almost never definitive in proving causation by drug, despite statements by pathologists that the findings may be "compatible with" drug causation. Also to be taken with a grain or more of salt are the diagnoses by investigators and their opinions of causality or how well the drug may be implicated; they are often wrong.

The 4 cases that did not have liver biopsy done are mentioned with very little detail. Two of them are among the 30 for which more information was provided, but there is not enough information given or available to comment on C202-3505 or PAA-2722. Case C213-0120, a 51-year-old German man, had very far advanced AIDS with only 16 CD4+ cells/ μ L, fatty liver since 2001, pneumocystis pneumonia, wasting syndrome, HIV-leukoencephalopathy, mycobacteriosis, chronic diarrhea, and developed multi-organ failure after sepsis from his Port-a-cath infection. Case C202-6610, a 37-year-old Argentinian man, is reported to have developed hepatitis on 26 September 2005 but had showed no ALT or AST elevations on 5 September, only some slight alkaline phosphatase elevation with rise in bilirubin or GGT. It is unclear on what information the diagnosis of hepatitis was made, but he is said to have developed orchitis and meningitis in late September, from which he is said to have recovered and no attribution was made to TMC114 causation.

Among the 4 cases of suspected hepatotoxicity, Case C215-0333 was a 39-year-old Caucasian woman from France who had an elective liver biopsy done for evaluation of viral hepatitis B and C that predated administration of TMC114. The biopsy specimen showed low intensity chronic inflammation with mononuclear cells, slight fibrosis with rare bridging, minimal steatosis, but severe fibrosis or cirrhosis or active inflammation. The changes were attributed to her viral hepatitis infections and not to experimental drug. Case C213-0077 was a 48-year-old Frenchman with an 18-year history of HIV infection said to have developed "cholestasis" after 169 days of TMC114 treatment but his alkaline phosphatase activity and total bilirubin were normal, although his ALT was 243 U/L (5.65 xULN), AST 192 U/L (5.33 xULN), and his GGT elevated to 4.70-8.75 xULN. Liver biopsy showed macrovesiculat steatosis, ballooned hepatocytes, and neutrophilic infiltrate.

Comment: The data from the second case above do not support a diagnosis of cholestasis, but rather more strongly indicate probable alcoholic liver disease not likely attributable to TMC114. The first case above obviously had pre-existing chronic viral hepatitis B/C.

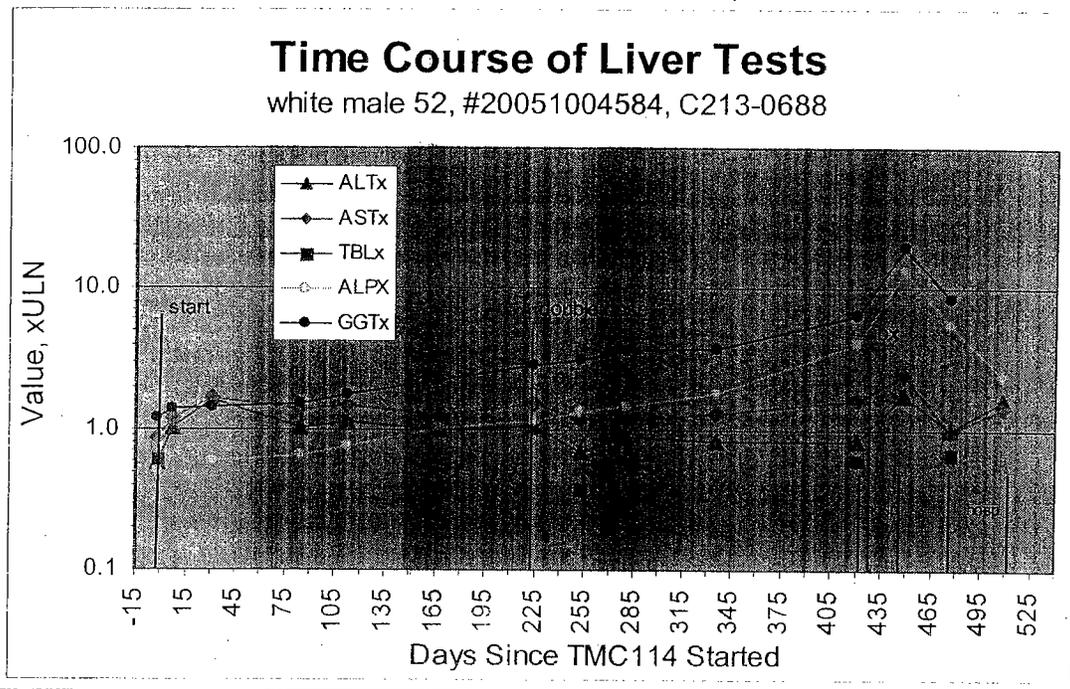
Additional information for the other two cases with liver biopsies was not found among the 30 cases listed and printouts supplied by Ms Anne Marie Russell, but were discussed in more detail in the material from Dr. Gibbs. Case C207-0019 (BE-JNJFOC-20050100783) was a 36-year-old Belgian man with a history of chronic alcohol abuse, prior elevations of GGT and AST, treated for two weeks with TMC114 during which he admitted to drinking 3 “units” of wine daily. He was admitted for liver biopsy two weeks later with greater elevations of ALT to 1483 U/L and AST 1748 U/L, GGT 545 U/L and ALP 679 U/L, total bilirubin rose to 10.7 mg/dL a week later. The biopsy findings were not described in detail, but were interpreted as “compatible with drug-induced hepatitis” but not with alcohol-induced hepatitis.

Comment: In cases such as this it is difficult if not impossible to be certain that the experimental drug may or may not have caused added injury to an already damaged liver, The levels of serum transaminase noted were greater than usually seen from alcohol alone, but it may be that the underlying injury from alcohol may have aggravated what might have been minor or inapparent TMC114-induced injury or impaired the adaptive recovery from it. In this, I concur with the sponsor and investigator that the observed findings probably were TMC114-induced, but the alcohol abuse may have contributed. Not a clean case for attribution.

In considering the last of the cases, C213-0688, for whom the most complete information was provided in the 4th MedWatch report of ██████████ (CH-JNJFOC-20051004584), this is perhaps the most difficult to understand. The patient was a 52-year-old Swiss man, reported by Professor Opravil because he was found to have recent-onset ascites, suspected of cirrhosis, and hospitalized ██████████. Extensive workup failed to reveal a cause for his ascites, portal hypertension, and hepatomegaly. He had HIV since 1995, Pneumocystis jiroveci pneumonia, oral leukoplakia and candidiasis, elevations in GGT, ALP, AST and ALT since April 2005 after being on TMC114 since 23 August 2004, plus didanosine, tenofovir, lamivudine, Bactrim, and pravastatin. He had a history of very moderate alcohol use, weight loss of about 7 kg down to 59 kg, crampy abdominal pains. His liver was palpated 10 cm below the rib margin, and ascitic fluid showed 400 cells/mL, 87% macrophages, but no malignant cells or acid-fast bacilli, and culture was negative. Magnetic resonance cholangiopancreatography was said to show cirrhosis and slight splenomegaly, and esophageal varices indicative of portal hypertension. Endoscopic retrograde cholangiopancreatography showed normal biliary and pancreatic ductal systems. Transjugular liver biopsy showed portal hypertension, areas of necrosis, apoptosis, steatosis and bile duct impairment, but no severe fibrosis or cirrhosis, and this was more persuasive than the MRCP imaging suggesting cirrhosis. There was nothing to suggest either hemochromatosis or Wilson’s disease. Failing all else, a suspicion of drug-induced liver disease was postulated. A second hospitalization ██████████, consultation by hepatologists, and additional negative workup for rare problems failed to disclose a cause for the recurring ascites.

The common causes of chronic liver disease with cirrhosis, use of alcohol and hepatitis B or C, appear to have been excluded. And none of the uncommon causes were substantiated either. The diagnosis of drug-induced liver injury was considered, but unclear as to which drug caused it.

Comment: The very good work-up in Switzerland of this patient, with no clear diagnosis for the portal hypertension and ascites but without cirrhosis on transjugular biopsy, leaves us with no good explanation. Drug-induced liver injury is usually acute, and seldom produces chronic liver problems such as this. Noncirrhotic portal hypertension, or "hepatoportal sclerosis," is a rare type of periportal sclerosing fibrosis with phlebosclerotic and fibrotic occlusion of intrahepatic branches of the portal vein and deposition of collagen in the space of Disse that has been attributed to inorganic arsenicals, vinyl chloride, toxic doses of vitamin A, and drugs taken for cancer chemotherapy or bone marrow transplant (Zimmerman, 1999). These lesions are not described in the report of the transjugular biopsy. It might be a good idea to ask the company to forward slides made from the biopsy for review by Dr. Zachary Goodman at the Armed Forces institute of Pathology, located on the grounds of the Walter Reed Army Medical Center in Washington, DC. His supplemental review might be very instructive in this very difficult case.



Displayed on the graph above is the progression of laboratory test abnormalities over the period almost a year-and-a-half that this patient was exposed to TMC114. There is very little evidence of severe hepatocellular injury, with ALT barely elevated AST a bit more so, but the cholestatic measures of ALP and especially GGT are notable. It is not clear from the history what may have triggered the increase in serum enzyme activities just after the first hospitalization (19 October to 10 November 2005).

This case should not be considered closed until a better explanation for the findings is reached. The latest report to Med Watch (#4 follow-up) of 28 February 2006 is very good, but still leaves many questions.

Recommendations:

- 1) I do not find clear evidence of darunavir-induced liver toxicity in the data accrued so far. There are a couple of cases that suggest possible contributing injury to pre-existing liver problems, but definite attribution of causality is difficult in patients with such prolonged and complex illness and exposure to so many drug.
- 2) I suggest that the biopsy slides for case C213-0688 (CH JNJFOC-20051004584) be forwarded to Dr. Zachary Goodman, hepatopathologist at the Armed Forces Institute of Pathology, Walter Reed Army Medical Center, Washington, DC for his review and opinion. Please ask the company to send as much information as possible, including all data and reports, as well.
- 3) We should keep alert for more cases, especially those in which acute liver injury, as indicated by elevations of serum ALT and AST are combined with or followed by rises in either total serum bilirubin or plasma prothrombin time, or by symptoms of liver disease.
- 4) There does not yet seem to be an indication for special labeling of darunavir as causing clearcut liver injury, but please keep me posted.

John R. Senior, M.D.

cc: ODS DDRE PID#D060
M. Avigan, ODS/DDRE
S. Birdsong, ODS/DDRE
P. Seligman, OPaSS
D. Birnkrant, DAVP
N. Gibbs, DAVP

REFERENCES

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

/s/

John Senior
6/23/2006 04:12:00 PM
MEDICAL OFFICER

Cannot find consultation request of 15 March 2006 in
DFS, so have linked this to N 21976
N 000 FG 22 Dec 2005, as has
Dr, Gibbs done in his medical review of
23 June 2006.

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: May 12, 2006

TO: Elizabeth Thompson, Regulatory Project Manager
Neville Gibbs, M. D., Medical Officer
Division of Antiviral Drug Products, HFD-530

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-976

APPLICANT: Tibotec Inc.

DRUG: TMC114 (darunavir) 300 mg twice a day dose/RTV 100mg.

THERAPEUTIC CLASSIFICATION: priority Review

INDICATION: Treatment of HIV-1 infection

CONSULTATION REQUEST DATE: February 1, 2006

DIVISION ACTION GOAL DATE: June 23, 2006

PDUFA DATE: June 30, 2006

I. BACKGROUND:

Tibotec Inc. submitted TMC114 (darunavir) to FDA for marketing approval under NDA 21-976. TMC 114 is a new HIV-1 protease inhibitor (PI) that is being used in combination with low dose (100 mg) ritonavir (RTV) and other antiretroviral agents for the treatment of HIV-1 infection. The antiretroviral agents (e.g. zidovudine, videx, lamivudine, virmune) are known to act at an early stage in the HIV-1 life cycle, while the protease inhibitors (e.g. fortavase, crixivan) act at a later stage during the viral replication. At present, there is no single drug or combination drug treatment that is effective in stopping the progression of the HIV-1 disease. A triple combination regimen is considered the standard of care and, when effective, significantly reduces the emergence of resistance.

medications (rifampin, warfarin, phenytoin and telithromycin, respectively) while participating in the study; Five subjects (1511, 1513, 1526, 1529, and 1536) had their scheduled visits conducted outside the allowed visit windows; and six subjects (1502, 1513, 1518, 1519, 1527, and 1529) did not take a few doses of their study medication orally within the 30 minute time frame required by the protocol. In general, the records reviewed were accurate (with the exception of the four subjects who received prohibited medications) and found no significant problems that would impact the results. The clinical investigator acknowledged the inspectional observations. The review division will be advised of the observations and will determine whether to exclude from the final analyses the four subjects who took prohibited medications. There were no limitations to this inspection.

The remaining data appear acceptable in support of the pending application.

B. Protocols C202 and C215

1. Timothy Wilkin, M.D.

Observations noted below are based on an email summary statement from the FDA field investigator; the EIR for this inspection is currently pending. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

At this site a total of 23 subjects were screened and enrolled in the two protocols; Protocol C202 enrolled 15 subjects; and protocol C215 enrolled 8 subjects. Informed consent for all subjects was verified and no regulatory violations found. The medical records were reviewed in depth and compared source data, case report forms to data listings for primary efficacy endpoint and adverse events for 5 subjects in study C202 and 3 subjects in study C215. The adverse events experienced by study subjects during the study were accurately reported in the case report forms and to the IRB in a timely manner.

No Form FDA 483 was issued at the close of the inspection. The medical records reviewed disclosed no findings that would reflect negatively on the reliability of the data. In general, the records reviewed were accurate and found no significant problems that would impact the results. There were no limitations to this inspection.

The data appear acceptable in support of the pending application.

2. Gerald Pierone, M.D.

At this site a total of 30 subjects were screened for the two protocols. For study protocol C202, twenty(20) subjects were screened, 9 subjects were reported as screen failures, eleven (11) subjects were enrolled in the study, and four (4) subjects were discontinued for disease condition and adverse events. For study protocol C215, ten subjects were screened, nine (9) subjects randomized, two subjects withdrew consent, and subject 0045 died from pneumonia. Informed consent for all subjects was verified and no regulatory violations found. The medical records were reviewed in depth and compared source data, case report forms to data listings for primary efficacy endpoint and adverse events for four subjects in study C202 and four subjects in study C215. The adverse events experienced by study subjects during the study were accurately reported in the case report forms and to the IRB in a timely manner (except for two subjects: subject 0455 in study protocol C215 experienced a grade 4 hemoglobin abnormality of 6.1g/dl requiring transfusion and this adverse event was not reported to the sponsor and IRB; and subject 0503 in study protocol C202 was hospitalized on 6/26/04 for cytomegalovirus pancreatitis and this adverse event was notreported to the sponsor until 10/27/04).

A Form FDA 483 was issued at the close of the inspection for failure to report the two serious adverse events experienced by subjects 0455 and 0503 as noted above. The medical records reviewed disclosed no findings that would reflect negatively on the reliability of the data. In general, the records reviewed were accurate and found no significant problems that would impact the results.

There were no limitations to this inspection.

The data appear acceptable in support of the pending application.

3. Corklin Steinhart, M.D.

Observations noted below are based on an email summary statement from the FDA field investigator; the EIR for this inspection is currently pending. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

At this site a total of 35 subjects were screened for the two protocols. For study protocol C202, twenty two (22) subjects were screened and 16 subjects were enrolled. For study protocol C215, thirteen (13) subjects were screened, and 10 subjects were enrolled. Three subjects withdrew consent. Informed consent for all subjects was verified and no regulatory violations found. The medical records were reviewed in depth and compared source data, case report forms to data listings for primary efficacy endpoint and adverse events for 9 subjects in study C202 and seven subjects in study C215. The adverse events experienced by study subjects during the study were accurately reported in the case report forms and to the IRB in a timely manner.

No Form FDA 483 was issued at the close of the inspection. The medical records reviewed disclosed no findings that would reflect negatively on the reliability of the data. In general, the records reviewed were accurate and found no significant problems that would impact the results. There were no limitations to this inspection.

The data appear acceptable in support of the pending application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspections of Drs. Berger, Wilkin, Pierone and Steinhart did not identify any significant observations that would compromise the integrity of the data. As noted above, observations related to Drs. Wilkin, and Steinhart are based on an email summary from the FDA field investigator; the EIRs for these inspections are currently pending. Overall, the data appear acceptable in support of the pending application. Should any of the pending EIRs contain additional information that would affect the application, the information will be forwarded to the review division as soon as it becomes available.

Antoine El-Hage, Ph.D.
Regulatory Pharmacologist
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

Request for Clinical Inspections

Site # (Name and Address)	Protocol #	Number of Subjects	Indication
Site #005 + #905 Gerald Pierone Treasure Coast Infectious Disease Consultants 3715 7th Terrace Vero Beach, FL 32960	C202 + C215	18 + 9	Treatment of HIV-1 infection
Site #003 + #903 Corklin Steinhart Steinhart Medical Associates 3661 South Miami Avenue Suite 806 Miami, FL 33133	C202 + C215	12 + 10	Treatment of HIV-1 infection

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (presented at Mid-Cycle meeting) April 5, 2006. We intend to issue an action letter on this application by (division action goal date) June 9, 2006. The PDUFA due date for this application is June 23, 2006.

Should you require any additional information, please contact Elizabeth Thompson at 301-796-0824.

Concurrence:

Kendall Marcus, M.D., Medical Officer Team Leader, Medical Team Leader
Neville Gibbs, M.D., M.P.H., Medical Officer, Medical Reviewer

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(White Oak Mail Stop 4447)

DATE RECEIVED: October 6, 2005	DESIRED COMPLETION DATE: January 6, 2006	ODS CONSULT #: 05-0238-1
DOCUMENT DATE: September 23, 2005 and December 22, 2005	PDUFA DATE: June 23, 2006	

TO: Debra Birnkrant, MD
Director, Division of Anti-Viral Products
HFD-530

THROUGH: Linda Kim-Jung, Pharm.D., Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support

FROM: Laura L. Pincock, Pharm.D., Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME: Prezista
(Darunavir Film Coated Tablets)
300 mg

NDA #: 21-976

NDA SPONSOR: Tibotec, Inc.

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name "Prezista." DMETS considers this a final review. However, if approval of the application is delayed beyond 90 days from the signature date of this review, then the name and its labels and labeling must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the container labels, carton and insert labeling revisions outlined in Section III of this review in order to minimize potential user error.
3. DDMAC finds the proprietary name "Prezista" acceptable from a promotional perspective.
4. DMETS recommends that you submit the proposed patient information labeling to the Division of Surveillance, Research, and Communication Support (DSRCS) for consultation.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-796-0538.

REQUEST FOR CONSULTATION

TO (Office/Division): **OPSS/ODS/DMETS**
Director, Division of Medication, Errors and Technical Support (DMETS)

FROM (Name, Office/Division, and Phone Number of Requestor):
OND/OAP/DAVP
Elizabeth Thompson, RPM
Division of Anti-Viral Products, 301-796-0824

DATE 10-5-05	IND NO. 62477	NDA NO.	TYPE OF DOCUMENT trade name review	DATE OF DOCUMENT 9-23-05
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NAME OF DRUG TMC114	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG 7030220 (protease inhibitor)	DESIRED COMPLETION DATE within 90 days
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NAME OF FIRM: **Tibotec, Inc.**

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG SAFETY

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

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review sponsor's request for proprietary name.
Dosage form: 300 mg orange oval shaped film-coated tablet; Frequency: 600 mg twice daily with ritonavir (100mg) twice daily with food; ritonavir is used as a pharmacokinetic enhancer of TMC114; Indication of use: treatment of HIV-1 infection in antiretroviral treatment experienced patients; Route of administration: oral
No available draft package insert or container and carton labels are available at this time.

SIGNATURE OF REQUESTOR

METHOD OF DELIVERY (Check one)

- DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.		
DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		PRESCRIPTION DRUG USER FEE COVERSHEET
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm		
1. APPLICANT'S NAME AND ADDRESS TIBOTEC INC Jenny Lin 1020 STONY HILL ROAD SUITE 300 YARDLEY PA 19067 US	4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 021976	
2. TELEPHONE NUMBER 609-730-7516	5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:	
3. PRODUCT NAME Darunavir	6. USER FEE I.D. NUMBER PD3006195	
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY		
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO		
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: Department of Health and Human Services Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852 An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.		
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE <i>J. Lin</i>	TITLE MANAGER, REGULATORY AFFAIRS	DATE 8/30/2005
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$672,000.00		
Form FDA 3397 (12/03)		

IBE_PRMT_CLOSE_G

Print Cover sheet

RECORD OF FDA/INDUSTRY MEETING

Date of Meeting: November 3, 2004
IND: 62,477
Drug: TMC114 (along with low dose ritonavir)
Sponsor: Tibotec, Inc.
Indication: Treatment of HIV-1
Type of Meeting: Type C

Center for Drug Evaluation and Research Participants:

Mark Goldberger, M.D., Office of Drug Evaluation (ODE) 4 Director
David Roeder, M.S., ODE 4 Associate Director for Regulatory Affairs

Division of Antiviral Drug Products (DAVDP) Participants:

Debra Birnkrant, M.D., Director
Jeffrey Murray, M.D., M.P.H., Deputy Director
Rosemary Johann-Liang, M.D., Medical Team Leader
Andrea James, M.D., Medical Officer
Lisa Naeger, Ph.D., Microbiology Reviewer
Guoxing Soon, Ph.D., Statistics Team Leader
Tom Hammerstrom, Ph.D., Statistics Reviewer
James Farrelly, Ph.D., Pharmacology/Toxicology Team Leader
Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader
Kimberly Bergman, Pharm.D., Clinical Pharmacology Reviewer
Kendall Marcus, M.D., Medical Team Leader
Virginia L. Behr, Chief, Project Management Staff
David Araujo, Pharm.D., Regulatory Project Manager
Monica Zeballos, Pharm.D., Regulatory Project Manager

Tibotec, Inc. Participants:

Marie-Pierre de Bethune, Ph.D., VP, Clinical Virology
Frederic Godderis, Senior Director, Global Compound Development Team
Andrew Hill, Ph.D., Senior Consultant, Biostatistics
Richard Hoetelmans, Ph.D., Director, Clinical Pharmacology
Eric Lefebvre, M.D., Director, Global Clinical Development
Jenny Lin, Pharm.D., Manager, Global Regulatory Affairs
Manal Morsy, M.D., Ph.D., MBA, Senior Director, Global Regulatory Affairs
Wim Parys, M.D., Vice President, Global Clinical Development

Thomas Pituk, Ph.D., R.Ph., Senior Director, CMC Global Regulatory Affairs

Araz Raouf, Ph.D., MBA, Director, Global Preclinical Development

Paul Stoffels, M.D., President, Tibotec

Karin Van Baelen, Pharm.D., Vice President, Global Regulatory Affairs

Tony Vangeneugden, M.Sc., Director, Biostatistics

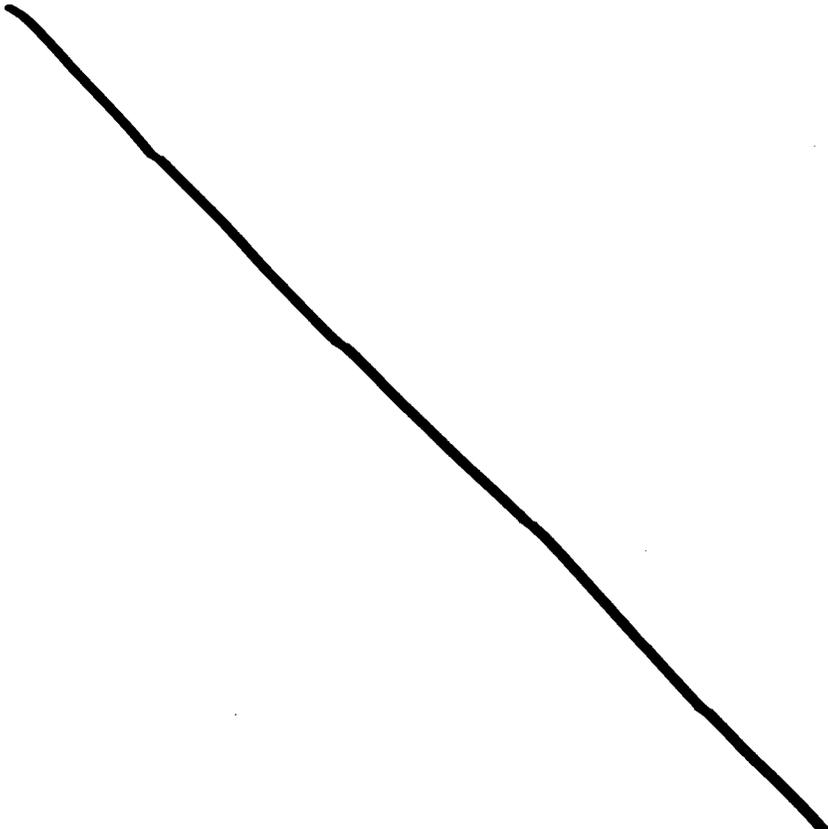
Hilde Walgraeve, Ph.D., Director, Global Regulatory Affairs

Background	
This meeting was held at the request of the sponsor, Tibotec, Inc. The meeting was requested on September 17, 2004 (SN137) and the meeting background package was submitted on October 15, 2004 (SN152; for list of sponsor's questions, see Attachment A). The most recent face to face meeting between DAVDP and the sponsor was held on August 6, 2003 to discuss the overall development plan for TMC114.	
Objectives	
To discuss:	
<ul style="list-style-type: none"> - The development plan towards submission of an NDA under accelerated approval - Results of the Week 16 and Week 24 interim analyses from two dose-finding studies (TMC114-C202 and TMC114-C213). 	
Sponsor Presentation	Tibotec: presented efficacy results from Weeks 16 and 24 from studies TMC114-C202 and TMC114-C213, as well as expected numbers of subjects in the safety database. Extensive dialogue between parties occurred during the presentation and many of the questions listed below were discussed. See Questions/Topics below for key points and conclusions.
DAVDP opening statement	DAVDP: focused meeting towards: <ul style="list-style-type: none"> -data necessary for filing an NDA under accelerated approval based upon dose-finding studies TMC114-C202 and TMC114-C213. -number of subjects in the safety database -general comments about requirements for traditional approval
Questions /Topics	Discussion Points /Conclusions
Clinical Development: Accelerated Approval	
1. Proposed dose of TMC114/RTV 600/100 mg BID in treatment-experienced patients	DAVDP: proposed dose is acceptable for an accelerated approval NDA package. <ul style="list-style-type: none"> -however, since plateau in drug activity has not been reached at this dose, DAVDP requested that Tibotec continue to explore higher doses
2. All patients on treatment with TMC114/RTV, including patients from TMC114-C202, are switched to the TMC114/RTV 600/100 mg b.i.d. dose regimen when 300 patients in TMC114-C213 reached their primary endpoint, pending confirmation of a sustained antiviral activity and safety of this dose regimen at the Week 24 interim analysis	DAVDP: <ul style="list-style-type: none"> -agreed -noted that subjects who discontinue the control arm while maintaining adequate virologic response but who discontinue because the DSMB recommends stopping the control arm cannot be considered virologic failures at time of discontinuation. Sensitivity analyses should be done considering such control subjects as virologic successes. Tibotec: <ul style="list-style-type: none"> -will communicate extension of study and dose switch to

	<p>600mg/100mg TMC114/ritonavir to investigators -noted that their DSMB would allow subjects to continue on the control group if virologically suppressed, and the DSMB is supportive of switching the test arm subjects to 600mg/100mg TMC114/ritonavir which is the intended market dose.</p>
<p>3. Analysis demonstrating statistically superior antiviral efficacy at Week 24 in change versus baseline of the log₁₀ plasma viral load of TMC114/RTV 600/100 mg b.i.d. in comparison to a control PI regimen, will demonstrate a clear clinical benefit of TMC114/RTV in the treatment-experienced patient population, and will qualify both studies TMC114-C202 and TMC114-C213 as two independent, adequate and well-controlled studies supporting accelerated approval of TMC114/RTV</p>	<p>DAVDP: -noted that the sponsor had never indicated that these Phase 2 trials would be relied upon as the pivotal trials to support NDA approval. -stated that the studies were not designed to serve as primary basis for approval -agreed that efficacy data looks promising, but have concerns about number of subjects in the safety database, especially the numbers in the control arm -asked for approximate numbers at 24 weeks of subjects in the TMC114 and control arms -primary efficacy endpoint: virologic response should be defined as percent with at least a one log drop between baseline and week 24 or percent BLQ at week 24 -asked the sponsor to submit an exact data analyses plan that specifies the primary efficacy endpoint.</p> <p>Tibotec: -stated that there will be 300+ number of subjects in the TMC114 arm (at 600/100mg BID dose) at 24 weeks for the safety database -stated that there will be approximately 40 subjects in the control arm at 24 weeks for the safety database -agreed to submit their data analysis plan</p>
<p>4. Proposed safety database considered adequate to support accelerated approval for TMC114 in the treatment-experienced patient population</p>	<p>DAVDP: -need to increase number of subjects expected in the safety database by at least 200 subjects -concerned about inability to observe safety signal due to small number of subjects, especially in the control arms of the studies -concerned about several cardiac safety reports from ongoing studies -per sponsor's request, decided that sponsor could recruit subjects co-infected with HIV and HBV.</p> <p>Tibotec: -noted that a high percentage of subjects had cardiac problems at baseline -have not switched subjects to the 600mg/100mg TMC114/ritonavir dose yet -will reopen enrollment of study TMC114-C213 at the 600mg/100mg TMC114/ritonavir dose and recruit additional subjects to study TMC114-C202 in order to increase the number of subjects treated with 600mg/100mg TMC114/ritonavir in the safety database. -will supplement the control group safety database with the control data from proposed study TMC114-C214 (this study in less treatment experienced subjects should be ongoing at the time of accelerated approval NDA submission)</p>
<p>Microbiology</p>	

<p>5. Planned resistance determinations to study clinical development of resistance</p>	<p>DAVDP: -noted that the planned resistance determinations to study clinical development of TMC114 are adequate at this time. -requested submission of Week 24 resistance data in the template format.</p> <p>Tibotec: -agreed and requested a copy of the updated template.</p> <p><i>NOTE: the updated resistance template was electronically mailed to Tibotec on November 8, 2004.</i></p>
<p>Pharmacokinetics</p>	
<p>6. Co-administration of TMC114/RTV with other drug products based on drug-drug interaction studies with TMC114/RTV 400/100 mg b.i.d. is adequate to support the use of these products in combination with TMC114/RTV 600/100 mg b.i.d.?</p>	<p>DAVDP: -agreed that the drug interaction studies are supportive.</p>
<p>7. Study in patients with renal impairment not warranted?</p>	<p>DAVDP: -did not agree -requested submission of mass balance study report</p> <p>Tibotec: -mass balance study report will be submitted soon</p>
<p>Additional Pharmacokinetics Discussion:</p> <p>Dose adjustment questions from DAVDP</p> <p>Renal impairment</p>	<p>DAVDP: -why no dose adjustments recommended for use with saquinavir/ritonavir, nevirapine, and pravastatin?</p> <p>Tibotec: -do not recommend dosing of TMC114 with saquinavir/ritonavir or pravastatin. Mechanism of action not understood, still investigating cause. For saquinavir/ritonavir, may be due to protein binding -nevirapine: no interaction observed in HIV infected subjects, so no dose adjustment recommended</p> <p>DAVDP: noted that studies in subjects with renal impairment are not required for accelerated approval, but should be completed soon thereafter (possibly as postmarketing commitments)</p> <p>Tibotec: agreed.</p>
<p>Nonclinical</p>	
<p>8. Completed, ongoing and planned non-clinical toxicology and non-clinical pharmacokinetic studies for TMC114 adequate to support an application for accelerated approval for the treatment-</p>	<p>DAVDP: -agreed that the studies are adequate -reminded sponsor to submit requests for special protocol assessments for carcinogenicity protocols</p>

experienced patient population?	
Indication	
9. Proposed Indication	DAVDP: -the proposed Indication in the labeling will be limited to the population studied; in this instance, the Indication would be limited to heavily treatment-experienced subjects with ongoing measurable viremia (similar to the current enfuvirtide indication).
Fast Track	
10. TMC114 development program in HIV-1 infected treatment-experienced patient population eligible for fast-track designation?	DAVDP: -TMC114 is eligible for fast track designation. -will issue a letter granting fast track status
Clinical Development: Traditional Approval	DAVDP General Comment: sponsor must perform additional studies to satisfy traditional approval requirements; need two adequate and well controlled studies to serve as confirmatory studies, one of which should enroll treatment-naïve subjects if the sponsor desires to expand the indication to the broad HIV-infected population.



	<p>Tibotec: -agreed to select a clinically meaningful endpoint and submit an amended protocol -asked whether international recruitment of subjects was allowed given the need to possibly increase enrollment numbers with below the limit of detection endpoint.</p> <p>DAVDP: -international recruitment is allowed as long as a percentage of the subjects are U.S. based and the characteristics of the international subjects are similar to the U.S. population</p>
14. Proposed safety monitoring plan for TMC114-C214 protocol summary	DAVDP: awaits amended protocol
Pediatric Program	
15. Overall approach for the pediatric program?	<p>DAVDP: -overall approach is acceptable -encouraged sponsor to develop formulation</p> <p>Tibotec: -working to identify optimal oral formulation for pediatric population; syrup versus powder -planning a PACTG study with NIH to enroll pre-teens; initiate early 2005</p>
Expanded Access Program	
16. Proposed Expanded Access Program	<p>DAVDP: program is acceptable. -timing is critical -do not interfere with enrollment of subjects needed to increase safety database -will need to submit treatment IND</p> <p>Tibotec: will submit a treatment IND, which will be assigned a new IND number. Will not be submitted under IND 62,477.</p>

Demographics

Action Items Summary

- Tibotec will submit their analysis plan for assessing the efficacy of TMC114 in trials TMC114-C202 and TMC114-C213 as two independent, adequate and well-controlled studies supporting accelerated approval of TMC114/RTV
- Tibotec will amend protocol TMC114-C214 and will submit for DAVDP review and comment
- Tibotec will submit a treatment IND for their expanded access program
- DAVDP will issue a letter granting fast track status for TMC114

Virginia L. Behr, November 3, 2004

blank

Attachment A**OVERALL DEVELOPMENT PROGRAM TO SUPPORT ACCELERATED APPROVAL****Clinical Development Program**

1. Does the Division agree with the proposed dose of TMC114/RTV 600/100 mg b.i.d as the recommended dose for the treatment of HIV-1 infection in treatment-experienced patients?
2. Does the Division agree that all patients on treatment with TMC114/RTV, including patients from TMC114-C202, are switched to the TMC114/RTV 600/100 mg b.i.d. dose regimen when 300 patients in TMC114-C213 have reached their primary endpoint, pending confirmation of a sustained antiviral activity and safety of this dose regimen at the Week 24 interim analysis?
3. Does the Division agree that an analysis demonstrating statistically superior antiviral efficacy at Week 24 in change versus baseline of the log₁₀ plasma viral load of TMC114/RTV 600/100 mg b.i.d. in comparison to a control PI regimen, will demonstrate a clear clinical benefit of TMC114/RTV in the treatment-experienced patient population, and will qualify both studies TMC114-C202 and TMC114-C213 as two independent, adequate and well-controlled studies supporting accelerated approval of TMC114/RTV?
4. Is the proposed safety database of approximately 300 patients for 6 months and approximately 100 patients for one year on the recommended dose considered adequate to support accelerated approval for TMC114 in combination with low dose RTV for the treatment of HIV-1 infection in the treatment-experienced patient population?

Microbiology:

5. Does the Division consider the planned resistance determinations to study clinical development of resistance adequate?

Overall Pharmacokinetic Program:

6. Does the Division agree that the recommendations for co-administration of TMC114/RTV with other drug products based on drug-drug interaction studies with TMC114/RTV 400/100 mg b.i.d. is adequate to support the use of these products in combination with TMC114/RTV 600/100 mg b.i.d.?

7. Does the Division agree that a study in patients with renal impairment is not warranted?

Overall Non-Clinical Development Program:

8. Does the Division agree that the completed, ongoing and planned non-clinical toxicology and non-clinical pharmacokinetic studies for TMC114 are adequate to support an application for accelerated approval for the treatment-experienced patient population?

Proposed Indication:

9. Does the Division agree with the proposed indication?

Fast Track Application/Rolling Submission

10. Does the Division consider the TMC114 development program in HIV-1 infected treatment-experienced patient population eligible for fast-track designation?

DEVELOPMENT PROGRAM

Trials TMC114-C202 and TMC114-C213

Design of the Proposed Trial TMC114-C214

12. Does the Division consider the design of TMC114-C214 adequate to support traditional approval for the use of TMC114/RTV in HIV-1 infected treatment-experienced patient population?
13. Does the Division consider the proposed maximum allowable difference of 0.4 \log_{10} in the primary parameter time averaged difference (DAVG) in study TMC114-C214 acceptable?
14. Does the Division consider the proposed safety monitoring plan outlined in the Flowchart of the TMC114-C214 protocol summary acceptable?

Pediatric Program

15. Does the Division agree with the overall approach for the pediatric program?

EXPANDED ACCESS PROGRAM

16. Does the Division agree with the proposed Expanded Access Program?

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 62,477

Tibotec, Inc.
Attention: Jenny Z. Lin, Pharm.D.
1020 Stony Hill Road, Suite 300
Yardley, PA 19067

Dear Dr. Lin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TMC-114 tablets.

We also refer to the meeting between representatives of your firm and the FDA on December 8, 2004. The purpose of the meeting was to discuss specific Chemistry, Manufacturing, and Control (CMC) aspects of the pharmaceutical development of TMC114 and the potential submission of a New Drug Application (NDA).

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

If you have any questions, call Virginia Behr, Chief, Project Management Staff, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

Stephen P. Miller, Ph.D.
Chemistry Team Leader for the
Division of Antiviral Drug Products
DNDC III, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Enclosure

RECORD OF DAVDP/INDUSTRY MEETING

Date of Meeting: December 8, 2004

Sponsor: Tibotec, Inc. (Tibotec)

IND: 62,477

Drug: TMC114 (along with low dose ritonavir)

Indication: Treatment of HIV-1

Type of Meeting: Type B

Division of Antiviral Drugs (DAVDP) Participants:

Rosemary Johann-Liang, M.D., Medical Team Leader
Stephen Miller, Ph.D., Chemistry Team Leader
George Lunn, Ph.D., Chemistry Reviewer
Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader
Kimberly Bergman, Pharm.D., Clinical Pharmacology Reviewer
Virginia L. Behr, Chief, Project Management Staff
Elizabeth Thompson, Regulatory Project Manager

External Participants:

Jenny Lin, Pharm.D., Manager, Global Regulatory Affairs, Tibotec
Dirk De Smaele, Ph.D., Director, Full Development Teams, J&JPRD
Luc Janssens, Ph.D., Director, CMC Regulatory Affairs, Tibotec
Andrew Kuzmission, Ph.D., Assistant Director, Analytical Development,
J&JPRD
Hartmut Zinser, Ph.D., Group Leader, Chemical R&D, Cilag
Aniruddha Railkar, Ph.D., Senior Scientist, Pharmaceutical Development,
J&JPRD
Jan A. Rosier, Ph.D., VP ChemPharm Development, Tibotec
Thomas Pituk, Ph.D., R.Ph., Senior Director, CMC Global Regulatory Affairs,
Tibotec
Hilde Walgraeve, Ph.D., Director, Global Regulatory Affairs, Tibotec

Background:

Tibotec plans to submit a new drug application (NDA) in December, 2005, for TMC114 300 mg tablets for the treatment of HIV infection. A meeting between Tibotec and DAVDP was held on November 3, 2004 to discuss the clinical development of TMC114. This meeting was held to discuss specific Chemistry, Manufacturing, and Control (CMC) aspects of the pharmaceutical development of TMC114 and the potential submission of a New Drug Application (NDA). The sponsor submitted their questions to FDA on November 9, 2004 to IND 62,477.

(SN164).

Presentation: During their brief presentation, Tibotec addressed a few questions that DAVDP had posed to the sponsor via telephone facsimile correspondence on December 2, 2004. The questions faxed to Tibotec are listed below, with a summary of Tibotec's response (in italics) during this meeting.

1. Please supply details of the specifications and [redacted] procedures for the [redacted] and also supply details of the final [redacted] step.

Starting material purities and specifications were discussed. [redacted]

compounds. [redacted]

2. It appears that TMC114 is a low solubility drug. Please justify the omission of a [redacted] specification.

[redacted] *were no significant differences in bioavailability.* [redacted]

3. Please describe any plans you have to develop a pediatric formulation. [redacted]

[redacted]

4. Please clarify the role of the silicon dioxide in the tablet formulation.

[redacted]

Discussion:

Tibotec posed the following questions in their submission dated November 9, 2004 (SN164):

Question 1

Tibotec proposes _____ as starting materials in the synthesis of TMC114. Does the Division agree with this proposal?

DAVDP response

The _____ starts further back but the _____ are also defined in the _____ so the difference is not so great. Apparently, _____ are _____ intermediates. DAVDP requested that the sponsor supply details of the specifications and _____ procedures for the _____ the final _____ step.

Generally the impurities in the starting materials are not carried through to the drug substance although the _____. The acceptance criteria _____ for unspecified impurities or _____ in the proposed starting materials are reasonable.

It is reassuring that the _____ can determine all the likely _____. This provides added reassurance that new impurities will be detected.

Tibotec presented an analysis of criticality, including carry over of impurities, to show how they arrived at their specifications.

Question 2

Does the Division agree that _____ of the drug substance is sufficiently characterized?

DAVDP Response

Tibotec will submit the report in the NDA.

Question 3

DAVDP Response

This approach is acceptable. DAVDP asked the sponsor to justify the acceptance criteria for _____ in their NDA submission.

Question 4

DAVDP Response

Question 5

Because the _____ is extremely unlikely, Tibotec believes it is justified that the _____ should not be taken into account for analytical method development, specification setting and toxicological qualification. Does the Division agree with this approach?

DAVDP agreed.

Question 6

Tibotec proposes to _____ will be demonstrated during the manufacturing of the registration stability batches and the corresponding registration stability studies. Does the Division agree with this approach?

DAVDP Response

In general, DAVDP finds the approach acceptable. However, for the time being the sponsor should continue to collect data on the _____ by using the _____. If sponsor decides to remove this test, a justification should be included in the NDA.

Question 7

Tibotec requests the Division's agreement on the proposed drug substance specification parameters and acceptance criteria contained within this briefing document, recognizing that specification limits will be evaluated and may be revised prior to NDA submission.

DAVDP Response

DAVDP noted that this is an issue that will be decided during the NDA review process. The sponsor should be prepared to support the impurity limits by toxicological qualification and manufacturing capability. [REDACTED] so the sponsor should justify the limit for [REDACTED]

It appears that TMC114 is a low solubility drug. DAVDP recommended that the sponsor justify the omission of a [REDACTED] specification in the NDA.

Tibotec stated that the NDA will contain [REDACTED] data on batches representative of commercial process/equipment to support their process capability justification.

Question 8

Tibotec requests the Division's agreement on the proposed drug product specification parameters and acceptance criteria contained within this briefing document, recognizing that specification limits will be evaluated and may be revised prior to NDA submission.

DAVDP Response

These will be decided during the NDA review process. DAVDP has no comments at this time, but the sponsor should be prepared to support the omission of tests for [REDACTED]

Question 9

Does the Division agree that the dissolution method developed for this product is acceptable?

DAVDP Response

This is another issue that will be decided during the NDA review process and DAVDP has no comments at this time. However, it would be helpful if Tibotec would submit an expanded justification of the method.

Question 10

Tibotec will perform drug substance registration stability studies in accordance with the protocol provided in this Briefing Document. Does the Division agree that the drug substance registration stability protocol, as currently designed, will provide the data needed to establish the stability of the drug substance?

DAVDP Response

The protocol appears appropriate, but please to continue to monitor for [REDACTED]

Question 11

Tibotec proposes to perform drug product registration stability studies in accordance with the protocol provided in this Briefing Document. Does the Division agree with the proposed drug product registration stability protocol?

DAVDP Response

The protocol appears appropriate. In particular please to continue to monitor for [REDACTED]

Tibotec confirmed that the omission of dissolution testing (Table 9, p. 24) was an oversight.

Question 12

Does the Division agree that given Tibotec's plan for a submission of the NDA for accelerated approval, [REDACTED] stability data for drug substance and [REDACTED] stability data for drug product can be considered adequate at time of submission, with additional stability data to be provided during the review period?

DAVDP Response

In keeping with ICH Q1A(R) DAVDP expects to get [REDACTED] of data on the drug product at the time of filing. However, if the clinical trial results indicate a clear benefit to patients of having TMC114 approved as early as possible, DAVDP could accept the [REDACTED] stability data as proposed. It may be best to reassess this timing issue when more clinical results are available (e.g., pre-NDA meeting). The expiration dating period will reflect the amount of data submitted. DAVDP can accept [REDACTED] stability data on the final product submitted to the NDA and [REDACTED] of stability data on the drug substance during the NDA review period. An 18 month expiry must be based upon [REDACTED] of stability data.

DAVDP asked for the scale of manufacturing for the stability batches. *Tibotec responded that these are commercial scale batches.*

Question 13

Tibotec proposes to use the electronic Common Technical Document (eCTD) format for the NDA for TMC114. Because of hyperlinking and the ability to navigate easily within this format, Tibotec also proposes to structure the Module 2 - Quality Overall Summary as a cross reference to Module 3 - Quality, using appropriate hyperlinks. Does the Division agree with this proposal?

DAVDP Response

More information might be available prior to submission of the NDA for TMC114. In the event that a Guidance is issued before the NDA submission DAVDP recommends that the sponsor follow the Guidance; if not, the sponsor should use their best judgment.

Question 14

To meet the requirement for submission of executed batch records, Tibotec proposes to submit executed batch documentation for one registration stability batch. This is with the understanding that FDA may review any batch records during site inspections and that any additional executed batch records not submitted in the NDA would be provided to the Division upon request. Is this approach acceptable to the Division?

DAVDP Response: Tibotec's proposal is acceptable.

Actions:

- The sponsor will submit the details of the dissolution method development.
- DAVDP will follow up with the sponsor regarding use of ritonavir boosting in bioequivalence studies.
- The sponsor will submit the details of their formal bioequivalence study.

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

/s/

Stephen Paul Miller
1/7/05 01:35:52 PM



Food and Drug Administration
Rockville MD 20857

IND 62,477

Tibotec, Inc.
Attention: Jenny Z. Lin, Pharm.D.
1020 Stony Hill Road, Suite 300
Yardley, PA 19067

Dear Dr. Lin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TMC-114 tablets.

We also refer to the meeting between representatives of your firm and the FDA on November 3, 2004. The purpose of the meeting was to discuss the results of the interim analysis from studies TMC114-C202 and C213 and the potential submission of a New Drug Application (NDA) under accelerated approval regulations.

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

If you have any questions, call Virginia Behr, Chief, Project Management Staff, at (301) 827-2335.

Sincerely,

{See appended electronic signature page}

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



Food and Drug Administration
Rockville MD 20857

IND 62,477

Tibotec, Inc.
Attention: Jenny Lin, Pharm D
Manager, US Regulatory Affairs
1020 Stony Hill Road, Suite 300
Yardley, PA 19067

Dear Dr. Lin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for TMC114 tablets.

We also refer to the meeting between representatives of your firm and the FDA on June 7, 2005. The purpose of the meeting was to discuss the proposed content and format of your planned NDA submission in support of accelerated approval for use of TMC114 in combination with low dose (100 mg) ritonavir (RTV) for the treatment of HIV-1 infection.

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

If you have any questions, call Elizabeth Thompson, Regulatory Project Manager, at (301) 827-2419.

Sincerely,

{See appended electronic signature page}

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

Enclosure



MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 7, 2005
TIME: 11:00 am
LOCATION: S400
APPLICATION: IND 62,477
DRUG NAME: TMC114
SPONSOR: Tibotec, Inc.
TYPE OF MEETING: Type B Pre-NDA meeting

FDA Participants:

Dave Roeder, M.S., Associate Director for Regulatory Affairs
Jeff Murray, M.D., MPH, Deputy Division Director
Debra Birnkrant, M.D., Division Director
Mark Goldberger, M.D., MPH, Office Director
George Lunn, Ph.D., Chemistry Reviewer
Jim Farrelly, Ph.D., Pharmacology Team Leader
Jules O'Rear, Ph.D., Microbiology Team Leader
Kimberly Bergman, Pharm.D., Clinical Pharmacology Reviewer
Kellie Reynolds, Pharm.D., Clinical Pharmacology Team Leader
Thomas Hammerstrom, Ph.D., Statistical Reviewer
Neville Gibbs, M.D., Medical Officer
Anitra Denson, M.D., Medical Officer
Melisse Baylor, M.D., Medical Officer
Andrea James, M.D., Medical Officer
Rosemary Johann-Liang, M.D., Medical Officer Team Leader
Fran Weiss, Regulatory Information Specialist, OIM
Elizabeth Thompson, M.S., Regulatory Project Manager
Anthony DeCicco, RPh, Chief, Project Management Staff
John Lazor, Pharm.D., Director, Division of Pharmaceutical Evaluation 3, OCPB

Tibotec, Inc. Participants:

Marie-Pierre de Bethune, Ph.D., Vice President, Clinical Virology
Dirk De Smaele, Ph.D., Director, Global Chem-Pharm Team Leader
Frederic Godderis, MSc, Senior Director, Global Compound Development Team Leader
Eric Lefebvre, M.D., Director, Global Clinical Development
Jenny Lin, Pharm.D., Manager, Global Regulatory Affairs
Leslie Krause, M.D., Senior Director, Drug Safety
Lieve Molenaers, Pharm.D., Director, Document Management & Submissions Operation

Wim Parys, M.D., Vice President, Global Clinical Development
Thomas Pituk, Ph.D., RPh, Senior Director, CMC Global Regulatory Affairs
Araz Raoof, Ph.D., MBA, Director, Global Preclinical Development
Vanitha Sekar, Ph.D., Director, Clinical Pharmacology
Karin Van Baelen, Pharm.D., Vice President, Global Regulatory Affairs
Tony Vangeneugden, MSc, Director, Biostatistics
Hilde Walgraeve, Ph.D., Director, Global Regulatory Affairs

BACKGROUND:

This meeting was held at the request of the sponsor. Tibotec submitted a meeting package on May 6, 2005 in preparation for the June 7, 2005 pre-NDA meeting. In a facsimile dated June 3, 2005, the Division of Antiviral Drug Products provided reviewers' comments to the questions posed by Tibotec, Inc. in the briefing package.

MEETING OBJECTIVES:

To discuss the proposed content and format of an NDA submission in support of accelerated approval for use of TMC114 in combination with low dose (100 mg) RTV for the treatment of HIV-1 infection.

To address the questions submitted by the sponsor.

DISCUSSION POINTS:

Comments to the following questions were provided by facsimile to Tibotec, Inc. on June 3, 2005. Tibotec submission questions are listed first, followed by FDA response in bold. Additional comments, if any, from the June 7, 2005 Pre-NDA meeting are located below the initial reviewer comments.

ADEQUACY OF EFFICACY AND SAFETY DATABASE TO SUPPORT ACCELERATED APPROVAL

1. Does the Division agree that Tibotec has addressed the Division's request for assessing the efficacy of TMC114 in trials TMC114-C202 and TMC114-C213 and would therefore consider these two trials as two independent, adequate and well-controlled studies supporting the filing and review of the accelerated approval NDA for TMC114?

Yes

2. Does the proposed safety database including 400 TMC114 treated patients on the recommended dose for 6 months and 102 patients on the recommended dose for one year adequately address the Division's request for supporting the filing and review of the accelerated approval NDA for TMC114?

Yes

ACCELERATED APPROVAL NDA SUBMISSION PLAN

Submission schedule following rolling review process

3. Is the detailed submission plan for rolling review of the TMC114 accelerated approval NDA and the updated submission schedule for the Nonclinical section of the NDA acceptable to the Division?

This is acceptable from both a Chemistry, Manufacturing & Controls and a Pharmacology/Toxicology point of view.

Proposed content of the accelerated approval NDA

QUALITY (CMC)

4. Does the Division agree with the proposal of submitting the TMC114 drug substance data and information in a DMF and submitting the drug product data and information in the NDA?

This is not ideal, for the reasons outlined in our previous response, but we have no objection to your proposal.

5. Does the Division agree that the proposed Drug substance and Drug product stability data are adequate? Does the Division agree that the available stability data are adequate to support an 18-month expiration date?

Yes, the proposed stability data is adequate. The expiration date is an issue that will be decided during the review process.

Following further internal discussions DAVDP agrees that an expiration date of 18 months could be justified by [REDACTED] of data at the time of NDA submission together with [REDACTED] of data in the stability update, provided the quality of the data is satisfactory. The expiration date is a review issue and the final date will be decided in the course of the NDA review.

NONCLINICAL

6. Does the Division agree with the proposed approach (6 month cut-off prior to the accelerated approval NDA submission date) of including data from all ongoing preclinical studies or externally published studies to be included in the Nonclinical Overview and Nonclinical Summary?

Yes

7. Does the Division agree with the proposal of providing the data line listings electronically as scanned files and that the study protocols for the nonclinical studies will be submitted upon request?

Yes

CLINICAL

Clinical Pharmacology and Biopharmaceutics

8. Does the Division agree that the list of clinical pharmacology and biopharmaceutics studies proposed to be included are adequate to support the filing and review of the accelerated approval NDA for TMC114?

Yes, we agree that the clinical pharmacology and biopharmaceutics studies are adequate for review. Please be prepared to discuss an overall summary of the drug interaction potential for TMC114 from a mechanistic perspective at the June 7, 2005 pre-NDA meeting. Also, provide a rationale for extrapolating interaction data from other TMC114/ritonavir dosing regimens to the 600/100 BID regimen.

June 7, 2005: Tibotec presented slides on drug interaction studies and the rationale for extrapolating interaction data from other TMC114 dosing regimens to the 600/100 mg BID regimen. The Division found Tibotec's rationale acceptable and thanked Tibotec for their presentation.

9. Does the Division agree with the proposed approach for the submission of PK/PD analyses?

We agree with the proposed approach for submission of PK/PD analyses.

June 7, 2005: Tibotec presented slides on the PK and PK/PD of TMC114 in HIV infected individuals. In response to an FDA request, Tibotec also discussed the role of therapeutic drug monitoring (TDM) for TMC114. The Sponsor's exposure-response analysis indicates exposure is significantly associated with antiviral response and that IQ (TMC114 plasma concentration/TMC114 fold-change in EC_{50} at baseline) is the strongest predictor of efficacy. Tibotec believes the relationship is driven by the fold-change in EC_{50} , rather than the C_{min} . DAVDP and Office of Clinical Pharmacology and Biopharmaceutics (OCPB) indicated the potential utility of TDM deserves further consideration.

10. Does the Division agree with the proposed plan for the analysis and submission of the population PK data for TMC114?

Yes, we agree with your proposed plan for the analysis and submission of population PK/PD data.

11. Based on the findings from trial TMC114-C109, does the Division agree that a trial in subjects with renal impairment is not warranted?

Based on the data available, we do *not* agree that a renal impairment study is not warranted. We request a complete clinical study report for TMC114-C109 (mass balance study) in addition to information from the absolute bioavailability study TMC114-C114 in order to determine if a study in renally impaired subjects is required.

June 7, 2005: Tibotec responded by agreeing with the Division's comment and announced that they would be submitting the appropriate data. The Division noted that this would be a review issue. If a renal impairment study is needed, it can be conducted as a post marketing commitment.

Virology

12. Does the Division agree that the proposed lists of Virology Research Reports are adequate to support the filing and review of the accelerated approval NDA for TMC114?

Yes, the list of Virology Reports is adequate to support filing.

13. Is the proposal of submitting exploratory analyses of genotypic profiles of patients from trials TMC114-C202 and TMC114-C213 in the December 2005 submission acceptable to the Division?

Please submit baseline genotypes and phenotypes of all patients from studies C202 and C213 in the HIV Resistance Template format, and the baseline and failure timepoint genotypes and phenotypes of all virologic failures from both the TMC114 and control groups in studies C202 and C213. In an effort to get as much resistance data as possible, please provide genotypes and phenotypes as mentioned above from the rollover study C215. In addition, if available, please provide the Cmin and IQ data in the template datasets.

June 7, 2005: Tibotec presented slides and had the following questions (FDA responses are shown in bold):

Does the Division agree that earlier timepoints (week 8 or week 12) could be considered as endpoint, especially for non-responders in this study?

The Division agrees with the earlier timepoints (week 8, week 12) as endpoints; however, we would like to see the 24 week data when available (Tibotec mentioned this would be around 1Q 2006).

Please advise as to the preferred list to be used in the analyses.

Please use the following modified FDA list (including D30, V32, M36, M46, I47, G48, I50, F53, I54, G73, V82, I84, N88, L90).

Does the Division agree with the time of submission of December 2005 for the reports of the available clinical virology exploratory analyses?

Yes

14. Is it acceptable to the Division that Tibotec will provide genotyping data of the GAG cleavage sites based on unidirectional sequencing for samples with deletions or insertions?

Yes. Please use one column for each GAG cleavage site including all amino acid substitutions at the cleavage site, e.g. A431V and other substitutions at the NC-P1 cleavage site would be in the same column, in the respective cell for the patient sample. Leave the cell blank if there is no change in the GAG cleavage site. For deletions, identify the amino acids deleted, e.g. L449-P453.

Clinical Efficacy and Safety

15. Is the proposed outline of Summary of Clinical Efficacy (Module 2.7.3) and Summary of Clinical Safety (Module 2.7.4) acceptable to the Division? Does the Division agree that the proposed Statistical Analysis Plans for ISE and ISS for the controlled data would adequately characterize the efficacy and safety profile of TMC114?

Yes

16. Does the Division agree with the proposal of not providing separate ISE or ISS reports in Module 5 given the level of details that will be provided for the Summary of Clinical Efficacy (Module 2.7.3) and Summary of Clinical Safety (Module 2.7.4), with the supporting statistical output to be provided under Module 5?

Yes

17. Is the proposal for inclusion of patient narratives and the proposed format of the patient narratives acceptable to the Division?

Yes

18. Does the Division agree with the proposed reporting of safety and efficacy data from the ongoing Phase II trials (TMC114-C202, TMC114-C213, TMC114-C215, and TMC114-C208) in the December 2005 submission?

No. We recommend submitting individual Study Reports in December 2005 rather than in September 2005.

June 7, 2005: This question was further discussed at the Pre-NDA meeting and concluded with the Division requesting one submission of the Summary of Clinical Safety (SCS) and Summary of Clinical Efficacy (SCE) in December 2005 whereas individual study reports will be submitted in September 2005. (Tibotec noted that they will not be submitting individual study reports for TMC114-C215 and TMC114-C208).

19. Does the Division agree with the proposal of providing only SAE reports in the format of line listings with appended CIOMS-1 forms for the ongoing trials TMC114-C214 or TMC114-C209 in the December 2005 submission?

Yes

Literature References

20. Is the proposal for the submission of literature references acceptable to the Division?

Yes

Proposed safety update during the accelerated approval NDA review

21. Does the Division agree with the proposed content, data cut-off and timeline of submitting the safety update report during the accelerated approval NDA review period?

Yes

June 7, 2005: The Division mentioned that they would like further time to discuss the proposed safety update internally. In the end the Division found the safety update proposal acceptable.

Proposed format of accelerated approval NDA

22. Does the Division agree with the proposed approach regarding compilation of the eCTD?

Yes

June 7, 2005: the Division strongly suggests promptly submitting a sample eCTD to Mr. Ken Edmunds. The email address for submissions was provided to Tibotec at the meeting by Elizabeth Thompson, Regulatory Project Manager.

23. Does the Division agree with the proposal on the definition of the element 'duration' in the STF?

Yes

24. Does the Division agree with the proposal of providing the draft labeling in Microsoft WORD and PDF format?

Yes

25. Does the Division agree with the proposed format of including the Virology Summary under the folder of Module 2.7 "Clinical Summary"?

Yes

POST APPROVAL COMMITMENTS

Studies to support traditional approval

26. Does the Division agree that by conducting the proposed Phase III studies TMC114-C214 and TMC114-C211, Tibotec would have fulfilled _____

Yes

June 7, 2005: The Division has no further comments.

Carcinogenicity studies

27. Does the Division agree that the completion of the carcinogenicity studies will not be required at the time of the submission for _____

Yes, we agree; however, submit the results of the individual carcinogenicity studies as soon as the final audited reports are ready.

Pediatric program

28. Does the Division agree with the proposed approach regarding the TMC114 pediatric program and the proposed plan for submission of the pediatric studies?

Yes. Please be prepared to discuss studies assessing the PK, safety and feasibility of administering a crushed pediatric tablet.

EXPANDED ACCESS PROGRAM

29. Does the Division agree with the proposed approach for initiation of the first phase of Expanded Access Program (TMC114-C226) in September 2005 and the second phase 6 months prior to the anticipated approval date of the NDA?

Yes

June 7, 2005: The Division clarified that they agree with the approach for the first phase of Expanded Access Program (EAP) where patients with limited treatment options requiring TMC114 to construct a viable antiretroviral regimen would have access to TMC114. _____

The Division asked Tibotec to share their EAP press release (submitted to FDA on June 9, 2005, SN293; Division finds acceptable). Tibotec stated that they plan to

submit a Treatment IND for their EAP in July/August 2005, and that the EAP would be limited to the first phase only.

GENERAL

30. Recognizing that the decision regarding a need for an FDA Advisory Committee Meeting prior to the approval of an NDA will be addressed during the review, does the Division believe that the TMC114 accelerated approval NDA will be subjected to an FDA Advisory Committee Meeting based on the available data presented in this package supporting the NDA?

Yes

In addition, we have the following comments:

Clinical

Section 5.2.2.3.4 of your Pre-NDA Backgrounder: Request for additional CRFs

Although a 10 day turnaround is reasonable for a large request (e.g. > 10 subjects), there will likely be several instances where one or two CRFs are requested in which case 10 days is not an acceptable turnaround time. We would expect you to turnaround small requests in 2-3 business days in an effort to facilitate a rapid and efficient review process.

Clinical Pharmacology

Your background package indicates PK/PD analyses of efficacy and safety for patients who complete 24 weeks of treatment in the Phase IIb studies will be submitted in the NDA. You also indicate that preliminary analyses suggest exposure is significantly associated with antiviral response and that IQ (TMC114 plasma concentration/TMC114 fold-change in EC₅₀ at baseline) is a strong predictor of response. Please present a brief summary of these results at the meeting.

Based on your findings, it seems that adequate exposure, in relation to virus susceptibility, may be critical for assuring the best opportunity for a successful outcome for the individual patient. At the preNDA meeting on June 7, 2005 please discuss the role of Therapeutic Drug Monitoring for TMC114.

DISCUSSION POINTS continued:

The Revised Proposal for TMC114 CTD Module 5.3.7 (SN 275; May 13, 2005) was also discussed at the Pre-NDA meeting on June 7, 2005. Tibotec had the following questions (FDA responses in bold):

1. Is the proposal for submitting data tabulation and annotated waveform datasets acceptable to the Division?

Yes

2. Is the proposal for submitting CRFs acceptable to the Division?

Yes

3. Please clarify the comment regarding "traditional format"?

Currently there is no application available to the FDA reviewers to view data in CDISC format. Therefore, depending on what the reviewers find upon review of the sample datasets we may request that data be provided in SAS transport files with pre-specified domains in a horizontal format. If revised datasets are needed, DAVDP will be in contact and the specifics can be discussed at that time.

4. Is the proposal for submitting analysis datasets acceptable to the Division?

Yes

5. Does the Division agree that the data format and proposed variables to be included in the PK datasets for the clinical pharmacology and biopharmaceutics studies are adequate?

Yes

ACTION ITEMS:

1. CDISC CD-rom samples sent by Tibotec, Inc. on June 3, 2005 for Division review. The Division will notify Tibotec, Inc. if there are any problems with format. It was also noted that Tibotec, Inc. might need to come in for presentation of their CDISC format (**FDA received CDISC samples on June 7, 2005 in SN289**).
2. Tibotec, Inc. will contact Ken Edmunds via eCTD email address provided to them in reference to the timing of these submissions.
3. The Division will provide feedback on how to proceed if datasets are over 100MB (**upon further discussion with OIM, datasets will be acceptable up to 250MB; please contact Regulatory Project Manager if datasets will exceed this**).
4. Microbiology will provide feedback for which HIV Resistance mutation list to use (**see question # 13 for updated response**).

5. Tibotec plans to submit their pediatric proposal in July 2005.
6. Tibotec, Inc. plans to submit as general correspondence their press release announcing EAP programs (**submitted June 9, 2005 in SN293**). Tibotec also mentioned that they would be submitting a Treatment IND in July/August 2005.

ATTACHMENTS/HANDOUTS:

Tibotec slides presented at June 7, 2005 Pre-NDA meeting were officially submitted to the Division on June 9, 2005 (SN292).

**Appears This Way
On Original**

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Wednesday, June 21, 2006 6:17 PM
To: Thompson, Elizabeth
Subject: FW: updated PMCs
Importance: High
Attachments: PMCs.doc; emfafert.txt

Beth,

For your reference, I have included the edits in your version in track changes.

Regarding the 24 week data where I have noted in my letter as well as the submission of PSUR, I wanted to include that in order to capture what's discussed and agreed. I will leave it up to you to decide whether appropriate to include in the final action letter.

Jenny

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Wednesday, June 21, 2006 1:46 PM
To: Lin, Jenny [TIBUS]
Subject: updated PMCs

As promised, here are updated PMC's with minor edits and dates.

<<PMCs.doc>>

Please let me know if you will be able to provide a response letter to these today.

Beth

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Wednesday, June 21, 2006 6:04 PM
To: Thompson, Elizabeth
Subject: RE: updated PMCs
Importance: High
Attachments: TMC114-20060621-FDA COR_PMC.pdf; emfalert.txt

Beth,

Please find attached a response letter to the PMC. Please feel free to call me after you reviewed this.

Jenny

Jenny Lin, Pharm.D.
Global Regulatory Affairs
Tibotec Inc.
1020 Stony Hill Rd. Suite 300
Yardley, PA 19067
Phone: (609) 730-7516
Fax: (609) 730-7501

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Wednesday, June 21, 2006 1:46 PM
To: Lin, Jenny [TIBUS]
Subject: updated PMCs

As promised, here are updated PMC's with minor edits and dates.

<<PMCs.doc>>

Please let me know if you will be able to provide a response letter to these today.

Beth

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Wednesday, June 21, 2006 5:40 PM
To: Thompson, Elizabeth
Subject: RE: final labeling (USPI June 21, 2006)
Attachments: emfalert.txt

Beth,

Minor edit that we missed in our version: There are two places in the microbiology section where we mentioned "Phase 2 studies..." should be Phase 2b studies, to be consistent with the Clinical studies section.

Jenny

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

From: Lin, Jenny [TIBUS]
Sent: Wednesday, June 21, 2006 5:21 PM
To: Elizabeth. Thompson (E-mail)
Subject: RE: final labeling (USPI June 21, 2006)
Importance: High

Beth,

Attached are the annotated and clean versions of the USPI for PREZISTA incorporating FDA comments as received and discussed since June 16, 2006.

Please let me know if you have any questions after your review.

Jenny

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

From: Lin, Jenny [TIBUS]
Sent: Wednesday, June 21, 2006 2:12 PM
To: 'Thompson, Elizabeth'
Subject: RE: final labeling
Importance: High

Beth,

Here is the container label attached.

We will send the USPI within two hours (doing editorial check now).

TBD for USPPi (trying to get consensus on the last issue identified).

If we have the final USPPi as well today, these will all be included in an official eCTD submission of tomorrow.

Jenny

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]

Sent: Wednesday, June 21, 2006 2:00 PM

To: Lin, Jenny [TIBUS]

Subject: final labeling

Jenny,

I know you are still working on the PPI. For the final label, I will need PI, PPI, and carton labeling sent to me (email is fine and then follow up with official submission once you hear back from me that we agree). I need both clean and annotated versions (I will be using the clean for comparison to mine). If any of these are available you can send now.

Beth

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Wednesday, June 21, 2006 4:15 PM
To: Thompson, Elizabeth
Cc: Cruzan, Susan M
Subject: RE: Press Contact for NDA 21-976 (PREZISTA; darunavir)

Beth,

Thank you very much.

Karen Manson (Communications, Tibotec) will be contacting Susan shortly.

Jenny

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Wednesday, June 21, 2006 1:39 PM
To: Lin, Jenny [TIBUS]
Cc: Cruzan, Susan M
Subject: Press Contact for NDA 21-976 (PREZISTA; darunavir)

Jenny,

Your press person can contact Susan Cruzan in the FDA Press Office. Her number is 301-827-6248 and I have included her on this email. Please let me know if I can be of further help.

Regards,

Beth

Elizabeth Thompson, M.S.
LTJG, USPHS
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6317
Silver Spring, MD 20993
Phone (301) 796-0824
Fax (301) 796-9883
Email: Elizabeth.Thompson@fda.hhs.gov

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Wednesday, June 21, 2006 12:08 PM
To: Thompson, Elizabeth
Subject: RE: PREZISTA annotated USPPI (June 19, 2006)

Attachments: TMC114-20060619-USPPI-Ann.pdf; emfalert.txt



TMC114-20060619- emfalert.txt (1 KB)
USPPI-Ann.pdf ...

pdf version attached (including the rash wording)

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

From: Lin, Jenny [TIBUS]
Sent: Monday, June 19, 2006 4:33 PM
To: Elizabeth. Thompson (E-mail)
Subject: PREZISTA annotated USPPI (June 19, 2006)
Importance: High

Hi Beth,

Please refer to the FDA comments received on June 16, 2006 regarding the US Patient Package Insert (USPPI).

Please find attached our annotated USPPI in responding to the comments received.

In addition, we would like to request clarification regarding the deletion of the adverse event " in the USPPI (please refer to the attached USPPI for further details).

Thanks very much.

Jenny

Jenny Lin, Pharm.D.
Global Regulatory Affairs
Tibotec Inc.
1020 Stony Hill Rd. Suite 300
Yardley, PA 19067
Phone: (609) 730-7516
Fax: (609) 730-7501

>
>

Subject: micro comments

Jenny,

We accept all micro revisions as you have proposed with the exception of the following:

Please change

to

In a supportive analysis of Studies TMC114-C213 and TMC114-C202 and the TMC114-C215/C208 analysis, examining subjects not taking enfuvirtide, the presence at baseline of three or more of the substitutions V11I, V32I, L33F, I47V, I50V, I54L or M, G73S, L76V, I84V or L89V was associated with a decreased virologic response to PREZISTA/rtv (the proportion of subjects achieving viral load <50 plasma HIV RNA copies/mL was 50%, 22% and 10% when the baseline genotype had 0-2, 3 and >4 of these mutations, respectively).

Please let me know if you find this acceptable.

Beth

| Page(s) Withheld

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

 § 552(b)(5) Deliberative Process

 § 552(b)(5) Draft Labeling

Sent: Tuesday, June 20, 2006 2:27 PM
To: Thompson, Elizabeth
Subject: PMC

Beth,

When is the latest you need to receive the letter regarding PMC? Is tomorrow ok?

Jenny

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Monday, June 19, 2006 4:33 PM
To: Thompson, Elizabeth
Subject: PREZISTA annotated USPPI (June 19, 2006)

Importance: High

Attachments: TMC114_20060619_USPPI_Ann_FDAsubmission 19Jun06.doc; emfalert.txt



TMC114_20060619 emfalert.txt (1 KB)
_USPPI_Ann_FDAs..

Hi Beth,

Please refer to the FDA comments received on June 16, 2006 regarding the US Patient Package Insert (USPPI).

Please find attached our annotated USPPI in responding to the comments received.

In addition, we would like to request clarification regarding the deletion of the adverse event "constipation" in the USPPI (please refer to the attached USPPI for further details).

Thanks very much.

Jenny

Jenny Lin, Pharm.D.
Global Regulatory Affairs
Tibotec Inc.
1020 Stony Hill Rd. Suite 300
Yardley, PA 19067
Phone: (609) 730-7516
Fax: (609) 730-7501

>
>

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Monday, June 19, 2006 9:45 AM
To: Thompson, Elizabeth
Subject: RE: SAS file
Attachments: death.xpt; emfalert.txt

Hi Beth,

Apparently (after confirming with our Statistician) something was wrong with the xpt file that I sent last Friday. Here is the corrected version if Dr. Hammerstrom still needs it.

Jenny

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

From: Lin, Jenny [TIBUS]
Sent: Friday, June 16, 2006 11:39 AM
To: Elizabeth. Thompson (E-mail)
Subject: SAS file
Importance: High

Hi Beth,

As requested, please find attached a SAS-dataset and a SAS-export file which reflect the status update I provided (including the most recent update so now we have disposition information on 133 subjects)

Please note that deaths reported in the NDA & NDA safety update are not included.

Jenny

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Monday, June 19, 2006 9:35 AM
To: Thompson, Elizabeth
Subject: RE: PREZISTA USPI following June 14, 2006 FDA labeling telecon
Attachments: TMC114_20060616_AnnLabel_Submitted to FDA 16Jun06.pdf

Hi Beth,

Here is the pdf version for the annotated label. I will look into sending you the word version via CD-Rom perhaps.

Jenny

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Monday, June 19, 2006 9:06 AM
To: Lin, Jenny [TIBUS]
Subject: RE: PREZISTA USPI following June 14, 2006 FDA labeling telecon

Jenny,

I can open the clean document, but not the annotated. Can you try to resend again (may need the pdf version)? It would definitely be helpful to have the word document at some point. I am not sure what is wrong and why it won't allow me to open it.

Beth

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

From: Lin, Jenny [TIBUS] [mailto:JLin10@TIBUS.JNJ.COM]
Sent: Friday, June 16, 2006 6:18 PM
To: Thompson, Elizabeth
Subject: PREZISTA USPI following June 14, 2006 FDA labeling telecon
Importance: High

Beth,

>

Please find attached the annotated and clean versions of the United States Package Insert (USPI) reflecting changes as discussed/agreed during the June 14, 2006 FDA labeling teleconference, as well as those following the teleconference with the exception of the proposed IQ text which I have provided a response to you separately

> Regarding the annotated USPI, the left-hand column contains the FDA
> proposed revisions from June 6, 2006, June 14, 2006 (MICROBIOLOGY
> comments), and June 16, 2006. The right-hand column contains the

6/21/2006

> comments from Tibotec.

>

Outstanding issues to be followed up:

> * As agreed during June 14 telecon a proposed sentence regarding
> <400 copies/mL for POWER 1 & 2 in the Description of Clinical Studies
> section has been included. Please let me know whether the sentence is
> acceptable.

* Our responses to the FDA post-telecon microbiology revisions
have been included. Please let me know whether it's acceptable.

> * Please note that we are still working on text regarding Skin
> Rash, and reviewing the FDA revisions received today regarding Sulfa
> Allergy.

>

Please also note the following additional editorial changes:

> * The following text is used throughout to refer to POWER 1, POWER
> 2, and the POWER 3 analysis: "Studies TMC114-C213 and TMC114-C202 and
> the TMC114-C215/C208 analysis" (in that order), as we need to use "the
> TMC114-C215/C208 analysis" to accurately describe the results analyzed
> for those studies and included in the USPI.

* Revised more instances of "patients" to "subjects".

> Please let me know if you have any questions.

Thanks very much.

Jenny

Jenny Lin, Pharm.D.
Global Regulatory Affairs
Tibotec Inc.
1020 Stony Hill Rd. Suite 300
Yardley, PA 19067
Phone: (609) 730-7516
Fax: (609) 730-7501

> Annotated USPI

> Clean USPI

>

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Friday, June 16, 2006 1:55 PM
To: Thompson, Elizabeth
Subject: post marketing
Importance: High

Beth,

In following up to our conversation this morning, please find below requested information regarding the race in subjects screened in C211 & C214 (note: information extracted from eDC, actual numbers may vary)

C214 (out of 793 screened):

412 Caucasian/white
147 Black
118 Hispanic
71 Asian/Oriental
21 other
24 unspecified

C211 (out of 847 screened):

333 Caucasian/white
199 Black
180 Hispanic
105 Asian/Oriental
10 other
20 unspecified

In addition, just to confirm C202/C213/C215 extension of treatment period from 96 to 144 weeks (amendment submitted in Feb 2006).

Jenny

Jenny Lin, Pharm.D.
Global Regulatory Affairs
Tibotec Inc.
1020 Stony Hill Rd. Suite 300
Yardley, PA 19067
Phone: (609) 730-7516
Fax: (609) 730-7501

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Friday, June 16, 2006 11:46 AM
To: Thompson, Elizabeth
Subject: Ananalysis on sulfonamide allergy

Importance: High

Attachments: Display saf 254 rash related events tabulation of all events by history of su.doc; emfalert.txt



Display saf 254 rash related ... emfalert.txt (1 KB)

Hi Beth,

Per discussion at the June 14 FDA label telecon, please find attached the rash analysis by sulfonamide allergy as requested.

Also the reference where to find this analysis in December NDA submission (display SAF.254).

0003/m5/53-clin-stud-rep/535-rep-effic-safety-stud/treatment-of-hiv-1-infection-01/5353-rep-analys-data-more-one-stud/tmc114-c910/any-dose/tmc114-c910-anal-saf-ae.pdf

Jenny

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Friday, June 16, 2006 11:39 AM
To: Thompson, Elizabeth
Subject: SAS file
Importance: High
Attachments: deaths.xpt; deaths.sas7bdat; emfalert.txt

Hi Beth,

As requested, please find attached a SAS-dataset and a SAS-export file which reflect the status update I provided (including the most recent update so now we have disposition information on 133 subjects)

Please note that deaths reported in the NDA & NDA safety update are not included.

Jenny

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Wednesday, June 14, 2006 11:56 PM
To: Thompson, Elizabeth
Subject: RE: STATUS UPDATE: JUNE 14 (final version)
Importance: High
Attachments: TMC114-20060614-FDA-RtQ.pdf; emfalert.txt

Beth,

In following up to our teleconference this morning, please find attached our complete response to the FDA request. At this time, we have included patient disposition information for 132 subjects (out of 133 in total) in the attached response.

In addition, following what we discussed during the teleconference, we would like to provide the updated TMC114 (29) and control (7) counts per ITT analysis, as in the below table. (note: one more deceased subject 213-0238 reported today is reflected in the table as well as the attached response document.)

TMC114 Reported in original NDA (N=18)	TMC114 Reported in NDA safety update (N=1)	TMC114 Randomized not treated (N=2)	TMC114 Treated but deceased after discontinued (N=8)	Control Reported in original NDA (N=2)	Control Reported in NDA safety update (N=1)	Control Randomized not treated (N=3)	Control Treated but deceased after discontinued (N=1)
202-0701	202-1103	202-0520	213-0007	213-0664	202-1013	213-0004	202-1524
202-1401		202-4919	213-0107	213-0504		213-0671	
202-1519			213-0236			213-0049	
202-1804			202-0202				
202-2614			202-0502				
202-3124			202-0503				
202-3503			202-1701				
202-4905			202-6401				
202-4907							
202-5101							
202-5603							
213-0066							
213-0068							
213-0120							
213-0139							
213-0414							
213-0668							
213-0677							

Thanks very much.

Jenny

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

From: Lin, Jenny [TIBUS]
Sent: Tuesday, June 13, 2006 9:50 PM
To: Elizabeth. Thompson (E-mail)
Subject: STATUS UPDATE: JUNE 13

Importance: High

Beth,

Please find attached status update for today. At this time, we have included patient disposition information for 123 subjects (out of 133 in total).

Please note the following:

- 1) these 123 subjects include those lost to follow up, as noted in the attached tables.
- 2) we have received updates for two deceased subjects (202-0520 and 213-0049) who did not receive treatment in studies C202 or C213, however received treatment in study C215. This update is reflected in the attached.

In addition, we would like to provide the following information regarding deaths reported in study C214 (TMC114 Phase III treatment experienced study) if the review team would find it helpful:

- 1) about 600 subjects were randomized in the study (last subject started treatment on February 1, 2006) with all subjects treated for at least 16 weeks.
- 2) two deaths were reported in C214 to date, one in each treatment arm.

Thanks again for the opportunity to discuss this over a telecon tomorrow. Please feel free to let me know if you or the review team has any additional questions prior to our call tomorrow morning, otherwise we will prepare to address them during the call.

The dial-in information will be the same as before, and below is the tentative list of attendees from Tibotec:

Wim Parys, MD - VP Clinical Development
Karin Van Baelen, PharmD - VP Regulatory Affairs
Eric Lefebvre, MD - Medical Leader, TMC114
Tony Vangeneugden, MSc - Biostatistics Leader, TMC114
Melissa Cefalone - Clinical Trial Leader, TMC114
Jenny Lin, PharmD - US Regulatory Liaison, TMC114

Jenny

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

From: Lin, Jenny [TIBUS]
Sent: Monday, June 12, 2006 11:39 PM
To: Elizabeth. Thompson (E-mail)
Subject: STATUS UPDATE: JUNE 12
Importance: High

Beth,

Please find attached status update as of today, which we had included patient disposition information for 114 subjects (out of 133 in total).

Please let me know whether it's possible to receive feedback from the Review team/Division Director via a brief teleconference before Thursday. It would be greatly appreciated.

Thanks very much.

Jenny

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Global Regulatory Affairs
Tibotec Inc.
1020 Stony Hill Rd. Suite 300

Yardley, PA 19067
Phone: (609) 730-7516
Fax: (609) 730-7501

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

From: Lin, Jenny [TIBUS]
Sent: Friday, June 09, 2006 7:09 PM
To: 'Thompson, Elizabeth'
Subject: STATUS UPDATE: JUNE 9

Beth,

As discussed during the telecon of June 7th, please find attached our draft response to the Division's request based on information we obtained as of today. Out of the total 133 subjects we were trying to obtain the requested information, we have received responses regarding 97 subjects and included in this update. Please note that we will continue to follow up on the remaining 36 subjects (currently left as blank in the draft version), as well those lost to follow up.

I intend to provide you another update on Monday.

In addition, we would like to request a brief teleconference with the review team prior to next Thursday (preferably Tuesday based on availability) for an interim feedback on this issue. It would be greatly appreciated if that can be arranged.

Thanks very much for your help.

Jenny

Jenny Lin, Pharm.D.
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Tibotec Inc.
1020 Stony Hill Rd. Suite 300
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Phone: (609) 730-7516
Fax: (609) 730-7501

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Wednesday, June 14, 2006 7:14 PM
To: Thompson, Elizabeth
Subject: Response to Chemistry comments on DMF [REDACTED]

Importance: High

Attachments: None001.PDF; emfalert.txt



None001.PDF (243 KB)
emfalert.txt (1 KB)

Beth,

FYI. Fax sent to Karl Stiller, Regulatory Project Manager today in responding to the 6/8/2006 FDA letter received regarding DMF # [REDACTED]

If possible, could you please also assist in facilitating the review process? The amendment to DMF [REDACTED] is planned on or before June 19, 2006 via electronic submission.

Thanks very much for your help.

Jenny

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Tibotec Inc.
1020 Stony Hill Rd. Suite 300
Yardley, PA 19067
Phone: (609) 730-7516
Fax: (609) 730-7501

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Wednesday, June 14, 2006 12:15 PM
To: Thompson, Elizabeth
Subject: RE: attendees for today's teleconference
Importance: High

Thanks Beth,

Here is the list of Tibotec attendees:

Wim Parys, MD - VP Global Clinical Development
 Marie-Pierre de Bethune, PhD - VP Global Clinical Virology
 Diego Miralles, MD - VP Global Clinical Development
 Eric Lefebvre, MD - Global Medical Leader, TMC114
 Piet De Doncker, PhD - VP Compound Development Team Leader
 Tony Vangeneugden, MSc - Biostatistics Leader, TMC114
 Ben Van Baelen, MSc - Biostatistician, TMC114
 Richard Hoetelmans, PhD - Sr. Director Clinical Pharmacology
 Vanitha Sekar, PhD - Clinical Pharmacology Leader, TMC114
 Marc Ceuppens MD - Director Drug Safety
 Karin Van Baelen, PharmD - VP Global Regulatory Affairs
 Hilde Walgraeve, PhD - Global Regulatory Leader, TMC114
 Lisa Hartline, BA - US Labeling Manager
 Jenny Lin, PharmD - US Regulatory Liaison, TMC114

In addition, here is the dial-in number:

Toll Free Dial In Number: (877)807-4596

PARTICIPANT 838898
CODE:

Jenny

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Wednesday, June 14, 2006 8:49 AM
To: Lin, Jenny [TIBUS]
Subject: attendees for today's teleconference

Jenny,

Below please find today's attendees:

Gibbs, Neville	Medical Officer
Denson, Anitra	Medical Officer
Arya, Vikram	Clinical Pharmacology Reviewer
Reynolds, Kellie	Clinical Pharmacology Team Leader
Hammerstrom, Thomas	Statistics Reviewer
Soon, Guoxing	Statistics Team Leader
Naeger, Lisa	Microbiology Reviewer
O'Rear, Julian	Microbiology Team Leader

Marcus, Kendall	Medical Officer Team Leader
Behr, Virginia L	Chief, Project Management Staff
DeCicco, Anthony W	Chief, Project Management Staff
Murray, Jeffrey S	Deputy Division Director
Birnkrant, Debra B	Division Director
Roeder, David L	Associate Director, Regulatory Affairs
Cox, Edward M	Deputy Office Director

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Wednesday, June 14, 2006 11:56 AM
To: Thompson, Elizabeth
Subject: RE: Peds protocol: SN469 (TMC114-c212)

Hi Beth,

We plan to initiate enrollment at the end of June 2006 for pediatric patients (> 50 kg), and end of August 2006 for pediatric patients (<50 kg).

Please let me know if you need more specific information regarding this.

Jenny

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Wednesday, June 14, 2006 10:24 AM
To: Lin, Jenny [TIBUS]
Subject: Peds protocol: SN469 (TMC114-c212)

Jenny,

Can you tell me when you plan to start enrolling patients in your pediatric study?

Thanks,

Beth

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Tuesday, June 13, 2006 4:16 PM
To: Thompson, Elizabeth
Subject: Annotated USPI for PREZISTA (JUNE 13, 2006)

Importance: High

Attachments: TMC114_20060613_AnnLabel_Submitted to FDA 13Jun06.doc; Microbiology
correspondence_June13.doc; emfalert.txt



TMC114_20060613 Microbiology emfalert.txt (1 KB)
_AnnLabel_Submi...orrespondence_Ju..

Hi Beth,

As discussed, please find attached annotated USPI for discussion during the labeling teleconference of tomorrow (June 14, 2006).

In addition, I would like to forward a correspondence from Dr. Marie-Pierre de Bethune (VP, Clinical Virology) in following up to our Microbiology teleconference of yesterday and the revised Table 2 received from the review team.

Thank you very much, please let me know after you have reviewed and ready to discuss the logistics for tomorrow.

Jenny

Jenny Lin, Pharm.D.
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1020 Stony Hill Rd. Suite 300
Yardley, PA 19067
Phone: (609) 730-7516
Fax: (609) 730-7501

>
>

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Tuesday, June 13, 2006 9:50 PM
To: Thompson, Elizabeth
Subject: STATUS UPDATE: JUNE 13
Importance: High
Attachments: TMC114-20060613-FDA-RtQ.pdf; emfalert.txt

Beth,

Please find attached status update for today. At this time, we have included patient disposition information for 123 subjects (out of 133 in total).

Please note the following:

- 1) these 123 subjects include those lost to follow up, as noted in the attached tables.
- 2) we have received updates for two deceased subjects (202-0520 and 213-0049) who did not receive treatment in studies C202 or C213, however received treatment in study C215. This update is reflected in the attached.

In addition, we would like to provide the following information regarding deaths reported in study C214 (TMC114 Phase III treatment experienced study) if the review team would find it helpful:

- 1) about 600 subjects were randomized in the study (last subject started treatment on February 1, 2006) with all subjects treated for at least 16 weeks.
- 2) two deaths were reported in C214 to date, one in each treatment arm.

Thanks again for the opportunity to discuss this over a telecon tomorrow. Please feel free to let me know if you or the review team has any additional questions prior to our call tomorrow morning, otherwise we will prepare to address them during the call.

The dial-in information will be the same as before, and below is the tentative list of attendees from Tibotec:

Wim Parys, MD - VP Clinical Development
Karin Van Baelen, PharmD - VP Regulatory Affairs
Eric Lefebvre, MD - Medical Leader, TMC114
Tony Vangeneugden, MSc - Biostatistics Leader, TMC114
Melissa Cefalone - Clinical Trial Leader, TMC114
Jenny Lin, PharmD - US Regulatory Liaison, TMC114

Jenny

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

From: Lin, Jenny [TIBUS]
Sent: Monday, June 12, 2006 11:39 PM
To: Elizabeth. Thompson (E-mail)
Subject: STATUS UPDATE: JUNE 12
Importance: High

Beth,

Please find attached status update as of today, which we had included patient disposition information for 114 subjects (out of 133 in total).

Please let me know whether it's possible to receive feedback from the Review team/Division Director via a brief teleconference before Thursday. It would be greatly appreciated.

Thanks very much.

Jenny

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Global Regulatory Affairs
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1020 Stony Hill Rd. Suite 300
Yardley, PA 19067
Phone: (609) 730-7516
Fax: (609) 730-7501

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

From: Lin, Jenny [TIBUS]
Sent: Friday, June 09, 2006 7:09 PM
To: 'Thompson, Elizabeth'
Subject: STATUS UPDATE: JUNE 9

Beth,

As discussed during the telecon of June 7th, please find attached our draft response to the Division's request based on information we obtained as of today. Out of the total 133 subjects we were trying to obtain the requested information, we have received responses regarding 97 subjects and included in this update. Please note that we will continue to follow up on the remaining 36 subjects (currently left as blank in the draft version), as well those lost to follow up.

I intend to provide you another update on Monday.

In addition, we would like to request a brief teleconference with the review team prior to next Thursday (preferably Tuesday based on availability) for an interim feedback on this issue. It would be greatly appreciated if that can be arranged.

Thanks very much for your help.

Jenny

Jenny Lin, Pharm.D.
Global Regulatory Affairs
Tibotec Inc.
1020 Stony Hill Rd. Suite 300
Yardley, PA 19067
Phone: (609) 730-7516
Fax: (609) 730-7501

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Monday, June 12, 2006 1:30 PM
To: Thompson, Elizabeth
Subject: FW: Clarification for Microbiology
Importance: High

Hi Beth,

After post meeting discussion with Marie-Pierre today, only the following clarification we would like to receive from the Micro review team at this time. (please refer to the Microbiology comments received via email on June 6, 2006.)

There were couple of others originally requested by our team, however Marie-Pierre felt that the one below is more urgent in obtaining clarification of the methodology used by the Micro review team.

We understand that there is a possibility this may not be addressed prior to our labeling telecon on Wednesday, therefore we would appreciate a response at the earliest convenience of the review team.

Thanks very much, and again we really appreciate that the review team had made themselves available this morning for the telecon.

Jenny

MICROBIOLOGYClinical Studies of darunavir/ritonavir in treatment-experienced subjects

The Sponsor's analysis demonstrated that the amino acid position "I15" was not observed in at least 10% of virologic failures, when considering rebounders and never suppressed and the amino acid position "G73S" was not observed in at least 10% of any of these subgroups.

The FDA's analysis demonstrated that changes at amino acid positions "I15" and "G73" occurred in 14% and 19%, respectively, of virologic failures from the three studies and, thus, should be included in substitutions that developed in 10-20% of virologic failures. The FDA's analysis included any change at these sites.

The Sponsor requests clarification regarding the FDA's methodology for their analyses. The Sponsor is unable to reproduce the percentages of virologic failures for "I15" and "G73" as provided by FDA.

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Friday, June 09, 2006 7:49 AM
To: Thompson, Elizabeth
Subject: STATUS UPDATE: JUNE 8
Attachments: emfalert.txt

Hi Beth,

As discussed during the telecon of June 7th, please find below status update based on information we obtained yesterday. I am currently working on the tables and hoping to provide you with a more complete picture (to also include those who are alive) of the 4 categories of patients we are following up by end of today.

Control patients who randomized and did not receive treatment (N=20):

213-0004: Died on [REDACTED] (Mycobacteriosis)
213-0671: Died in [REDACTED] (unknown)

TMC114 patients who randomized and did not receive treatment (N=17):

202-4919: Died on [REDACTED] (End stage AIDS)
202-0520: Died on [REDACTED] (AIDS-related anemia)

Jenny

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]

Sent: Monday, June 05, 2006 1:52 AM

To: Thompson, Elizabeth

Hi Beth,

Greetings from Orlando.

If possible, could you please bring up the two questions below, either during the labeling meeting or another time as you deem appropriate:

1) Please refer to the FDA version of USPI received on May 18th, and the deletion of the paragraph regarding supportive long term efficacy data up to 48 weeks from POWER 1 & 2 (page 15 of annotated version), our team felt that additional clarification on the deletion of this paragraph would be very helpful as the efficacy data up to 48 weeks from POWER 1 & 2 were described in the Summary of Clinical Efficacy in NDA 21-976. In addition, we would like to receive some guidance regarding the additional information that the review team is looking for if the team felt that the available data included in the NDA is not substantial to support the inclusion of 48 weeks efficacy data from POWER 1 & 2 in the USPI.

2) Please refer to the stability update amendment submitted in February 2006 as per previous agreement with the Chemistry review team at the pre-NDA meeting. This amendment provided **██████** DP stability data (updating the **██████** data submitted in NDA 21-976) to support an increase in the expiration date to 18 months for darunavir tablets. We would really appreciate any feedback the review team can provide at this time regarding the expiration date for darunavir tablets.

As always, thanks very much for your help.

Jenny

Jenny Lin, Pharm.D.

Global Regulatory Affairs

Tibotec Inc.

1020 Stony Hill Rd. Suite 300

Yardley, PA 19067

Phone: (609) 730-7516

Fax: (609) 730-7501

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Thursday, June 01, 2006 6:26 PM
To: Thompson, Elizabeth
Subject: NDA 21-976: Revised MICROBIOLOGY section of the USPI

Attachments: TMC114-20060601-AnnLabel.doc; TMC114-20060601-USPI.doc; emfalert.txt



TMC114-20060601-TMC114-20060601-emfalert.txt (1 KB)
AnnLabel.doc (... USPI.doc (66 K...

Beth,

As discussed and agreed during our May 24, 2006 Microbiology teleconference, attached are the Tibotec annotated and clean running text versions of the MICROBIOLOGY section of the USPI.

Please let me know if you have any questions regarding the proposed revisions, and we are looking forward to receiving feedback from the Microbiology review team.

Jenny

Jenny Lin, Pharm.D.
Global Regulatory Affairs
Tibotec Inc.
1020 Stony Hill Rd. Suite 300
Yardley, PA 19067
Phone: (609) 730-7516
Fax: (609) 730-7501

> Annotated version of USPI
>
> Clean Running Text version of USPI
>
>

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Thursday, June 01, 2006 2:58 PM
To: Thompson, Elizabeth
Subject: RE: chemistry section of PI and container label
Attachments: 20060518comments_Chemistry.pdf; emfalert.txt

Beth,

Please find attached our responses to the Chemistry comments received in below email as well as those received as part of the FDA annotated version of the USPI via email on May 18, 2006.

I have included with the response the revised Chemistry sections of the USPI and the revised container label. No changes are necessary to the USPI.

Please let me know if the Chemistry reviewer would agree to the proposed revisions or if he has any additional questions/requests.

Thanks very much in advance.

Jenny

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Global Regulatory Affairs
Tibotec Inc.
1020 Stony Hill Rd. Suite 300
Yardley, PA 19067
Phone: (609) 730-7516
Fax: (609) 730-7501

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Friday, May 19, 2006 9:40 AM
To: Lin, Jenny [TIBUS]
Subject: chemistry section of PI and container label

Jenny,

The following comments are in reference to the container label. The third comment also pertains to the USPI. After speaking with the reviewer, he is in agreement with DMETS on the wording and proposes the following be used "Each tablet contains darunavir ethanolate equivalent to 300 mg of darunavir." Please change the PI, PPI, and carton label accordingly.

1. Increase the prominence of the "120 Tablets"
2. Decrease the size of the graphic to about 50%.
3. The proposed statement doesn't reflect the presence of ethanolate solvate in the tablet. One could interpret that each

tablet contains 300 mg of darunavir which is equivalent to mg of darunavir ethanolate.

I hope that this clears things up for the chemistry section. Please don't hesitate to contact me for questions regarding this or to provide rationale if Tibotec does not agree with the above changes.

Beth

Elizabeth Thompson, M.S.
LTJG, USPHS
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6317
Silver Spring, MD 20993
Phone (301) 796-0824
Fax (301) 796-9883
Email: Elizabeth.Thompson@fda.hhs.gov

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Friday, June 02, 2006 1:24 PM
To: Thompson, Elizabeth
Subject: SJS - F/U report submitted: SN 494
Attachments: Medwatch form 20060503263(1).pdf; emfalert.txt

Beth,

I would like to inform you that we have received follow-up information regarding this case (the Follow-up #1 15-day IND safety report will be submitted today- SN 494).

The MedWatch report is attached as FYI, providing additional information received on May 26, 2006:

The patient slowly recovered. A skin biopsy was consistent with Stevens-Johnson syndrome (SJS). The patient was monitored in the intensive care unit, but no treatment for SJS was given. He was discharged from the hospital on _____, when the event was considered stabilized.

Please let me know if you have any questions.

Jenny

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

From: Lin, Jenny [TIBUS]
Sent: Friday, May 19, 2006 3:34 PM
To: 'Thompson, Elizabeth'
Subject: TMC114 7-day Safety Report: SN 488

Hi Beth,

Please find attached a 7-day Safety Report for TMC114. This is regarding a patient enrolled in the TMC114-C211 treatment-naive study (CRF ID 211-0344) who experienced the SAE of Stevens-Johnson Syndrome.

A copy of attached report was also provided to you via fax.

As discussed, please contact me if you or the review team has any questions regarding this case.

Thanks very much.

Jenny

Jenny Lin, Pharm.D.
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Tibotec Inc.
1020 Stony Hill Rd. Suite 300
Yardley, PA 19067
Phone: (609) 730-7516
Fax: (609) 730-7501

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Thursday, June 01, 2006 10:54 AM
To: Thompson, Elizabeth
Subject: RE: oral contraception study
Attachments: TMC114-C131synopsis.pdf; emfalert.txt

Beth,

As requested, please find attached the study report synopsis from study TMC114-C131.

Please let me know if you have any questions or if the team has any additional request.

Jenny

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Thursday, June 01, 2006 9:02 AM
To: Lin, Jenny [TIBUS]
Subject: RE: oral contraception study

Jenny,

Yes, the team would still like to see this.

Beth

From: Lin, Jenny [TIBUS] [mailto:JLin10@TIBUS.JNJ.COM]
Sent: Wednesday, May 31, 2006 4:35 PM
To: Thompson, Elizabeth
Subject: RE: oral contraception study

Hi Beth,

Is the review team still expecting the report from oral contraception study (TMC114-C131) at this time? just wanted to follow up.

Jenny

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

From: Lin, Jenny [TIBUS]
Sent: Monday, May 08, 2006 1:02 PM
To: 'Thompson, Elizabeth'
Subject: RE: oral contraception study

Beth,

Thank you for clarifying. I will go back to the team to see if study report synopsis can be put together before the Clinical Research Report is finalized. Otherwise I will provide the finalized CRR around end of May.

Jenny

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Monday, May 08, 2006 12:29 PM
To: Lin, Jenny [TIBUS]
Subject: FW: oral contraception study

Jenny,

A top line report is all that is needed at this time. We are just looking to see if the results were expected or unexpected. Please let me know if this addresses your questions discussed earlier on the phone.

Beth

From: Thompson, Elizabeth
Sent: Wednesday, May 03, 2006 3:01 PM
To: 'Lin, Jenny [TIBUS]'
Subject: oral contraception study

Jenny,

We are trying to determine if this study is complete, and if so, the Division feels that this data is crucial to the review for the NDA and would like to have it submitted. Please contact me so we can discuss this.

Beth

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Tuesday, May 23, 2006 3:08 PM
To: Thompson, Elizabeth
Subject: RE: microbiology telecon
Attachments: Request for Microbiology telecon.doc; emfalert.txt

Hi Beth,

As promised, I am forwarding the requested background information prepared by Marie-Pierre de Bethune, PhD, VP Clinical Virology.

We would greatly appreciate the opportunity to discuss specifically the attached 4 questions with the Microbiology review team tomorrow, if possible.

In addition to Dr. de Bethune, we will have a few representatives from Regulatory & Clinical.

Thanks very much in advance and I look forward to receiving your feedback.

Jenny

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

From: Lin, Jenny [TIBUS]
Sent: Monday, May 22, 2006 2:42 PM
To: 'Thompson, Elizabeth'
Subject: RE: microbiology telecon

Hi Beth,

We are looking for additional guidance/clarification from the microbiology review team prior to moving forward with our internal discussion in regards to the microbiology section of the label, therefore the earlier we have this telecon, the earlier we will be able to reach an agreement on the proposed text.

If the review team desires to receive the background information earlier than EOB tomorrow, I can also explore the possibility.

Jenny

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Monday, May 22, 2006 2:25 PM
To: Lin, Jenny [TIBUS]
Subject: RE: microbiology telecon

Jenny,

After speaking with the microbiology review team, they feel that there will not be enough time to review the requested information in order to have a teleconference on Wednesday and would like to extend the date to June 1st. I will have to check the calendar here for the medical reviewer and team leader first to see if this date is good for them.

Beth

From: Lin, Jenny [TIBUS] [mailto:JLin10@TIBUS.JNJ.COM]
Sent: Monday, May 22, 2006 12:41 PM
To: Thompson, Elizabeth
Subject: RE: microbiology telecon

Hi Beth,

Thank you very much for following up on our request. The proposed date and time is fine with us and we appreciate very much this opportunity.

I intend to provide you the requested background (list of topics/questions) for the teleconference by end of tomorrow.

Please confirm the list of attendees from the review team and I will follow up with our list & dial-in information.

Jenny

Jenny Lin, Pharm.D.
Global Regulatory Affairs
Tibotec Inc.
1020 Stony Hill Rd. Suite 300
Yardley, PA 19067
Phone: (609) 730-7516
Fax: (609) 730-7501

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Monday, May 22, 2006 9:17 AM
To: Lin, Jenny [TIBUS]
Subject: microbiology telecon

Jenny,

The only date on the calendar for the next two weeks I can schedule is this Wednesday (24th) from 12-1pm. I spoke with the microbiology team, and in order to have this teleconference, they would like to have some proposed background and questions to help prepare them for the direction of this meeting. Is this possible? Also, please let me know if this date/time is ok, otherwise we will need to reschedule for sometime in June.

Beth

Elizabeth Thompson, M.S.
LTJG, USPHS
Regulatory Project Manager

FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6317
Silver Spring, MD 20993
Phone (301) 796-0824
Fax (301) 796-9883
Email: Elizabeth.Thompson@fda.hhs.gov

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
ent: Monday, May 15, 2006 5:33 PM
To: Thompson, Elizabeth
Subject: NDA 21-976: Revised draft USPI and USPPI for PREZISTA

Attachments: PREZISTA_USPI_Annotated_VERSION 1_Submit to FDA_05152006.doc;
PREZISTA_USPI_Clean_VERSION 1_Submit to FDA_05152006.doc;
PREZISTA_USPI_Annotated_VERSION 2_Submit to FDA_05152006.doc;
PREZISTA_USPI_Clean_VERSION 2_Submit to FDA_05152006.doc;
PREZISTA_USPPI_Annotated_Submit to FDA_05152006.doc;
PREZISTA_USPPI_Clean_Submit to FDA_05152006.doc; emfalert.txt



PREZISTA_USPI_Annotated_VERSION 1_Submit to FDA_05152006.doc; PREZISTA_USPI_Clean_VERSION 1_Submit to FDA_05152006.doc; PREZISTA_USPI_Annotated_VERSION 2_Submit to FDA_05152006.doc; PREZISTA_USPI_Clean_VERSION 2_Submit to FDA_05152006.doc; PREZISTA_USPPI_Annotated_Submit to FDA_05152006.doc; PREZISTA_USPPI_Clean_Submit to FDA_05152006.doc; emfalert.txt (1 KB)

Beth,

As agreed during our May 10 teleconference to discuss several comments received regarding TMC114 labeling, please find attached below revised versions of the United States Package Insert (USPI) and the United States Patient Package Insert (USPPI) for review prior to your labeling meeting of this Wednesday. Both annotated and clean versions are provided for the USPI and USPPI.

Please note that the following revisions were incorporated:

- 1) USPI: Revisions to the DESCRIPTION section per previous discussion and agreement with the Chemistry reviewer.
- 2) ~~PREZISTA_USPI_Annotated_VERSION 1_Submit to FDA_05152006.doc~~
- 3) USPI: Revision of POWER 3 data to be described separately from POWER 1 & POWER 2 in tabular format or in text per discussion during May 10 teleconference.
- 4) USPI: Proposal to include the p-value in the last sentence of the paragraph regarding the results of POWER 1 & POWER 2 in the Description of Clinical Studies section.
- 5) USPI & USPPI: Incorporation of DMETS comments.
- 6) Editorial revisions.

Please let me know if you have any questions regarding these revisions.

We look forward to receiving the Division's comments following Wednesday's meeting.

Jenny

Jenny Lin, Pharm.D.
Global Regulatory Affairs
Tibotec Inc.
1020 Stony Hill Rd. Suite 300
Yardley, PA 19067
Phone: (609) 730-7516
Fax: (609) 730-7501

- > USPI Version 1 (with skin rash and POWER 3 retained in a tabular
- > format)
- > Annotated Version Clean Running Text Version
- >
- >

> USPI Version 2 (with skin rash and POWER 3 in text)
> Annotated Version Clean Running Text Version
>
>
> USPPI
> Annotated Version Clean Running Text Version
>
>
>

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Friday, May 12, 2006 4:02 PM
To: Thompson, Elizabeth
Subject: RE: FDA request on NDA 21-976: Liver biopsy slides
Attachments: AFIP consult report.pdf

Beth,

Please find attached a copy of the AFIP consultation report for the liver biopsy slides received in the mail from Dr. Zachary Goodman.

Jenny

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Tuesday, May 02, 2006 10:29 AM
To: Lin, Jenny [TIBUS]
Subject: RE: FDA request on NDA 21-976: Liver biopsy slides

Thanks Jenny. I received your voicemail message, and if Dr. Goodman cannot process the request until his return that will be fine.

Beth

From: Lin, Jenny [TIBUS] [mailto:JLin10@TIBUS.JNJ.COM]
Sent: Tuesday, May 02, 2006 10:22 AM
To: Thompson, Elizabeth
Subject: FW: FDA request on NDA 21-976: Liver biopsy slides

FYI

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

From: Lin, Jenny [TIBUS]
Sent: Tuesday, May 02, 2006 10:11 AM
To: 'Goodman, Zachary D. Dr.'
Subject: RE: FDA request on NDA 21-976: Liver biopsy slides

Dear Dr. Goodman,

I have received response from ~~_____~~ this morning who clarified that you may keep the DPAS stained slide if needed, however the H&E stained slide should be returned.

I sincerely hope that you will still be able to review the slides today?

Thank you very much in advance.

Jenny

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

From: Goodman, Zachary D. Dr. [mailto:Zachary.Goodman@afip.osd.mil]

Sent: Monday, May 01, 2006 4:33 PM

To: Lin, Jenny [TIBUS]

Subject: RE: FDA request on NDA 21-976: Liver biopsy slides

_____ sent 2 slides and asked that they both be returned. I will hold the case until you find out if we can keep one.

By the way, I'll be out of the office from May 3 to 17. If I don't hear from you before then, it will have to wait until I return.

Z. Goodman

From: Lin, Jenny [TIBUS] [mailto:JLin10@TIBUS.JNJ.COM]

Sent: Monday, May 01, 2006 12:58 PM

To: Goodman, Zachary D. Dr.

Cc: Elizabeth. Thompson (E-mail)

Subject: RE: FDA request on NDA 21-976: Liver biopsy slides

Dear Dr. Goodman,

The slides are on their way to you via TNT (http://www.tnt.com/country/en_us.html tacking #: GD 240229622 WW) and scheduled for delivery to you **today**.

The completed consultation request form should accompany the package, and here is a copy of the form with attachment for your reference.

We have informed the sender that at least one slide will be kept at AFIP and I believe for those slides that are wish to be returned to _____ will be marked as such. If that is not the case, please let me know.

As this consultation was requested on behalf of the Division of Antiviral Products at CDER, FDA in reference to NDA 21-976, please feel free to contact me or Beth Thompson (Regulatory Project Manager, DAVP 301-796-0824) should you need further information to be provided on this case.

Thanks very much in advance.

Jenny

Jenny Lin, Pharm.D.

Global Regulatory Affairs

Tibotec Inc.

1020 Stony Hill Rd. Suite 300

Yardley, PA 19067

Phone: (609) 730-7516

Fax: (609) 730-7501

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

From: Goodman, Zachary D. Dr. [mailto:Zachary.Goodman@afip.osd.mil]

Sent: Tuesday, April 25, 2006 11:57 AM
To: Lin, Jenny [TIBUS]
Subject: RE: FDA request on NDA 21-976: Liver biopsy slides

The correct address is:

Zachary Goodman, M.D., Ph.D.
Hepatic Pathology
Armed Forces Institute of Pathology
14th Street and Alaska Ave, NW
Washington, DC 20306

Please fill out the attached Consultation Request Form and send it with the case. The report and invoice will go to whoever is named on the form as the contributor.

Be sure to send the slides by an express delivery service, such as Fedex, not regular mail.

Also, please be aware that we must retain at least one diagnostic slide. All of the material cannot be returned.

Z. Goodman

From: Lin, Jenny [TIBUS] [mailto:JLin10@TIBUS.JNJ.COM]
Sent: Tuesday, April 25, 2006 10:50 AM
To: Goodman, Zachary D. Dr.
Cc: Elizabeth. Thompson (E-mail)
Subject: FDA request on NDA 21-976: Liver biopsy slides
Importance: High

Dear Dr. Goodman,

Please refer to the request we received from Division of Antiviral Products at FDA, in reference to NDA 21-976, to forward available liver biopsy slides for patient [REDACTED], CRF ID# C213-0688; DOB [REDACTED], enrolled in clinical trial TMC114-C213 to you for further review.

We have contacted [REDACTED] where the liver biopsy for this patient was performed. Dr. [REDACTED] contact is provided below for your reference:

[REDACTED]

[REDACTED]

In view of your availability in the upcoming week, we would like to facilitate the shipment of the original slides to you as soon as possible, [REDACTED] has indicated

that they can be ready for shipment tomorrow. Therefore, could you please advise the following:

1) In order to save on shipping time, we would like to suggest to ship directly from Switzerland to you at the following address, is this acceptable to you and is the mailing address correct?

Dr. Zachary Goodman
Director of Liver Histopathology Laboratory
Armed Forces Institute of Pathology
Walter Reed Army Medical Center
6825 16th Street NW
Washington, DC 20306-6000

2) Tibotec, Inc. will follow up with additional information as needed to facilitate your review of the slides, could you please advise what would be needed?

Thank you very much, and looking forward to receiving your feedback.

Jenny

Jenny Lin, Pharm.D.
Global Regulatory Affairs
Tibotec Inc.
1020 Stony Hill Rd. Suite 300
Yardley, PA 19067
Phone: (609) 730-7516
Fax: (609) 730-7501

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Thursday, May 11, 2006 2:16 PM
To: Thompson, Elizabeth
Subject: TMc114 revised bottle label
Attachments: 10101600_May 1 2006.pdf

Beth,

Please see attached revised bottle label.

Jenny

Revised Bottle Label
<<10101600_May 1 2006.pdf>>

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Friday, April 21, 2006 5:05 PM
To: Thompson, Elizabeth
Subject: Response to Clinical comment #3 received via April 6 FAX
Attachments: TMC114-C215-0303 skin biopsy & derm report Portuguese.pdf; TMC114-C215-0303 skin biopsy & derm report English translation.pdf; emfalert.txt

Hi Beth,

Please refer to the Clinical comments received via fax dated April 6, 2006. At this time we would like to provide the following response to comment #3 requesting additional clinical information on 3 subjects who discontinued study drug due to skin rash:

- 1) CRF ID #215-0303 (37 year-old **female**): Available digital pictures taken for this subject are provided on a CD-Rom being sent to you separately (for your receipt on Monday morning). In addition, the biopsy and dermatologic reports in Portuguese and English translation are attached with this email.
- 2) CRF ID #213-0681 (20 year-old male): Available digital pictures taken for this subject are provided on the CD-Rom being sent to you. Additional information (dermatologic report if available) has been requested however still pending.
- 3) CRF ID #202-1016 (45 year-old male): This event was initially reported as grade 1 by the investigator however Tibotec then requested the investigator to upgrade the event to be consistent with the ACTG grading scale. Given this reason, pictures or dermatologic reports are not available for this subject as they are not required per protocol rash management for grade 1 rash.

Please let me know if you have any questions regarding this response.

Jenny

Jenny Lin, Pharm.D.
Global Regulatory Affairs
Tibotec Inc.
1020 Stony Hill Rd. Suite 300
Yardley, PA 19067
Phone: (609) 730-7516
Fax: (609) 730-7501

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Friday, April 21, 2006 3:40 PM
To: Thompson, Elizabeth
Subject: RE: NDA 21976 -Hepatic Consult Darunavir (TMC114)

Beth,

Thank you for the below information. Our trial physician will further follow up with the hospital with this and I will contact Dr. Goodman once I hear back from them.

Jenny

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Friday, April 21, 2006 11:59 AM
To: Lin, Jenny [TIBUS]
Subject: NDA 21976 -Hepatic Consult Darunavir (TMC114)

Jenny,

After discussion with the medical reviewer and Dr. Goodman at AFIP, it is preferred that the glass slides, not CD Rom be sent and that he would be willing to send the slides back (however, he needs to keep a slide on file for their records at AFIP). It was suggested that you contact him directly to find out all the requirements. His contact info is:

Dr. Zachary Goodman
Director of Liver Histopathology Laboratory at the Armed Forces Institute of Pathology
Walter Reed Army Medical Center, Washington DC.
His telephone number is 202-782-1702 and email: goodman@afip.osd.mil

Dr. Goodman will be on leave from May 3rd to 17th.

Beth

Elizabeth Thompson, M.S.
LTJG, USPHS
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6317
Silver Spring, MD 20993
Phone (301) 796-0824
Fax (301) 796-9883
Email: Elizabeth.Thompson@fda.hhs.gov

From: Gibbs, Neville
Sent: Friday, April 21, 2006 11:53 AM
To: Thompson, Elizabeth
Subject: FW: NDA 21976 -Hepatic Consult Darunavir (TMC114)

Beth,

I spoke with Dr Goodman. He would prefer the glass slides not a CD ROM.....After reading the slides he would be willing to send them back BUT he needs to keep one slide on file for their records at the AFIP. Can you please give them this information and ask them to contact him directly ?

From: Senior, John R
Sent: Thursday, April 20, 2006 3:35 PM
To: Gibbs, Neville
Subject: RE: NDA 21976 -Hepatic Consult Darunavir (TMC114)

Neville,

I've been downtown at the FDA Science Forum all day Tuesday and Wednesday and half-day this morning, so missed your message. I Think they should get in touch with

John

From: Gibbs, Neville
Sent: Wednesday, April 19, 2006 11:33 AM
To: Senior, John R
Cc: Thompson, Elizabeth; Marcus, Kendall
Subject: NDA 21976 -Hepatic Consult Darunavir (TMC114)

Hello John,

I just stopped by your office.

I wish to chat with you about the logistics of arranging the 2nd opinion on the liver biopsy by Dr Zachary Goodman.

The Swiss, through the Sponsor (Tibtec Inc) wish to know whether they can submit the histology on a CD ROM, and if they send the original glass slides, whether they will be receiving their glass slides back after Dr Goodman has completed his work on the histology specimen.

Please give me a call whenever you are in house again.

Thanks,

Neville

301-796-0718

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Thursday, April 20, 2006 2:46 PM
To: Thompson, Elizabeth
Subject: RE: phone call

Hi Beth,

Further to our phone call yesterday, if this is of interest to Dr. Gibbs and Dr. Marcus: In addition to US, at this time the

Jenny

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Wednesday, April 19, 2006 2:41 PM
To: Lin, Jenny [TIBUS]
Subject: re: phone call

Jenny,

I mentioned earlier on the phone that another query was coming from Dr. Gibbs (re: worldwide approvals). I spoke with him and the team leader about this query and we felt that it did not need to be sent. I informed them that there are no tentative worldwide approvals of darunavir before US approval. If this changes, please inform FDA.

Beth

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Monday, April 17, 2006 4:21 PM
To: Thompson, Elizabeth
Subject: RE: Clinical comment for NDA 21-976 received 4/6

Beth,

The [REDACTED] has requested Tibotec to send a written request in regards to the liver biopsy slides for subject 213-0688.

Is it possible that you can assist in this process by confirming:

- 1) If the original microscopic slides are to be requested, whether they will be returned once review is complete by AFIP.
- 2) If a copy is available, eg, via a CD-Rom, whether that would be sufficient to be forwarded for review by AFIP.

Thanks very much for your help.

Jenny

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

From: Lin, Jenny [TIBUS]
Sent: Wednesday, April 12, 2006 3:44 PM
To: 'Thompson, Elizabeth'
Subject: Clinical comment for NDA 21-976 received 4/6

Hi Beth,

Please refer to the fax received on April 6 requesting liver biopsy slides (subject CRF ID 213-0688, Switzerland) to be sent to Dr. Zachary Goodman at the AFIP for further review.

We have contacted the investigator regarding this request and the feedback is pending. In order to obtain the biopsy slides, they will contact the pathology department as well as obtain the patient's consent. In addition, they would like to know whether the slides will be returned after evaluation.

In an attempt to answer the question above, I have searched on the AFIP website to see if there is a consultation process that we will need to go through. Could you please also take a look at the attached consultation form and advise whether it's applicable to us?

Additional insight you can provide to facilitate this process would be greatly appreciated.

Jenny

<http://www.afip.org/consult/ConsultationRequestForm.pdf>

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
ent: Tuesday, April 11, 2006 2:56 PM
ro: Thompson, Elizabeth
Subject: RE: Response to Chemistry comments for NDA 21-976

Attachments: 20060221&0327request_Chemistry.pdf; emfalert.txt



20060221&0327req emfalert.txt (1 KB)
uest_Chemistry...

Hi Beth,

Please find attached our responses to the Chemistry comments received via Filing Communication letter (2/21/2006) and email (3/27/2006).

Any feedback on this response would be greatly appreciated.

Thanks in advance.

Jenny

Jenny Lin, Pharm.D.
Global Regulatory Affairs
Tibotec Inc.
1020 Stony Hill Rd. Suite 300
Yardley, PA 19067
Phone: (609) 730-7516
Fax: (609) 730-7501

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Monday, March 27, 2006 10:57 AM
To: jlin10@tibus.jnj.com
Subject: FW: Response to Chemistry comments for NDA 21-976

Jenny,

Please see the attached Chemistry response to you email dated March 21, 2006 that references the teleconference between [redacted] and Tibotec for clarification of the filing meeting comments. Please let me know if you cannot open the attachment or if you have any questions.

Beth

Elizabeth Thompson, M.S.
LTJG, USPHS
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6317
Silver Spring, MD 20993
Phone (301) 796-0824
Fax (301) 796-9883
Email: Elizabeth.Thompson@fda.hhs.gov

RE: Response to Chemistry comments for NDA 21-976

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Monday, March 27, 2006 3:30 PM
To: Thompson, Elizabeth
Subject: RE: Response to Chemistry comments for NDA 21-976

Thank you Beth.

Our assumption was that the chemistry reviewer was aware of the USAN structure for darunavir, but in case we had missed it, FYI, here is the link to the approved USAN for darunavir published in 2005-2006 (as conveyed during the March 10 teleconference, the presentation of the Chemical name, Structural formula and Molecular formula in the original application was based on the approved USAN, which was without the ethanolate):

<http://www.ama-assn.org/ama1/pub/upload/mm/365/darunavir.pdf>

Jenny

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Monday, March 27, 2006 2:13 PM
To: Lin, Jenny [TIBUS]
Subject: FW: Response to Chemistry comments for NDA 21-976

Jenny,

Here is the response from the chemistry reviewer to your inquiry about the USAN structure that we discussed this morning:

"Presently, USAN book doesn't have any structure for darunavir. Yes they can simply add C₂H₅OH to the USAN structure. The structure I provided was copied from the NDA (Module 2.6.1 Introduction, page 4) but I added C₂H₅OH to it."

Hope this clarifies.

Beth

Elizabeth Thompson, M.S.
LTJG, USPHS
Regulatory Project Manager
FDA/CDER/OND/OAP
Division of Antiviral Products
10903 New Hampshire Ave., Bldg. 22, Room 6317
Silver Spring, MD 20993
Phone (301) 796-0824
Fax (301) 796-9883
Email: Elizabeth.Thompson@fda.hhs.gov

6/13/2006

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
ent: Tuesday, March 21, 2006 6:28 PM
fo: Thompson, Elizabeth
Subject: General correspondence

Attachments: emfalert.txt



emfalert.txt (1 KB)

Beth,

As discussed, in view of the ongoing review for NDA 21-976, we would like to provide our continued support in facilitating the Division's review. This includes timely responses to the FDA requests received during the NDA review, as well as the submission of a planned NDA safety update at the end of March 2006, providing safety data from the open label safety study TMC114-C209 (with clinical cut-off of December 1, 2005) and updated reports on death/SAEs in ongoing trials up to January 13, 2006 cut-off.

To date, no specific hepatic signals have been identified during our Phase IIb & III development program for TMC114; however, we recognize that hepatic adverse events have been the AE of special interest to the reviewers, and continue to report routinely DSMB LFT events from Phase IIb trials per previous agreement with the Division since the EOPI meeting.

Please refer to the FDA Clinical Query #6 of February 14, 2006 requesting additional information on 8 hepatic SAEs reported from TMC114 trials, and the Tibotec response specific to that request provided via email on February 27, 2006.

If needed, the following information can be made available upon request (please allow two weeks turnaround time), to supplement those provided in our response, should this facilitate the reviewer to perform a substantive review (within the planned review timeline) in this particular area of interest :

* Prior to September 24, 2005 cut-off for NDA: Overview of the treatment emergent grade 3 or 4 AST/ALT related AEs and AST/ALT lab abnormalities reported in Phase IIb studies C202/C213/C215/C208. (This overview would provide integrated data of those already submitted in the NDA.)

* Post September 24, 2005: Overview of grade 3 or 4 AST/ALT lab abnormalities reported in the ongoing Phase IIb studies C202/C213/C215/C208 and Phase III study C214 up to February 28, 2006 cut-off. (This overview would provide additional information beyond those submitted in the NDA and NDA safety update.)

Thanks very much, and please let me know if you have any questions regarding this correspondence.

Jenny

Jenny Lin, Pharm.D.
Tibotec Inc.
1020 Stony Hill Rd. Suite 300
Yardley, PA 19067

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Tuesday, March 21, 2006 5:31 PM
To: Thompson, Elizabeth
Subject: RE: Response to Chemistry comments for NDA 21-976

Attachments: Response to Chemistry comments for NDA 21-976 .rtf; emfalert.txt



Response to emfalert.txt (1 KB)
hemistry comments.

Hi Beth,

Since the format was lost when I had to send the encrypt message below, I am resending the original message as an attachment, hope you will be able to open and view it.

Jenny

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

From: Lin, Jenny [TIBUS]
Sent: Tuesday, March 21, 2006 5:06 PM
To: Elizabeth. Thompson (E-mail)
Subject: Response to Chemistry comments for NDA 21-976

Beth,

lease refer to our teleconference of March 10 to clarify the Chemistry comment received on TMC114 NDA via the Filing Communication Letter. As discussed during the teleconference the TMC114 container label will remain unchanged and will mention "Tradename (darunavir) tablets 300 mg", as well as "Each tablet contains darunavir 300 mg (corresponding to darunavir ethanolate [REDACTED]).

The USAN and INN names will remain unchanged: Darunavir.

In addition, could you please confirm our understanding that the reviewer had advised us to make the following changes:

I) Drug Master File (DMF [REDACTED]):

Sections 2.3.S.1.2 and 3.2.S.1.2

- * Structural formula: Add .C2H5OH
- * Molecular formula: Add .C2H5OH
- * Molecular weight: Add 46.07 to obtain 593.73

Sections 2.3.S.1.1 and 3.2.S.1.1

- * Chemical name(s): add . Ethanolate

II) US Package Insert:

Description section of the draft US labeling text will incorporate the same changes to the chemical name, molecular formula, structural formula and molecular weight as specified above for the DMF. (Beth, is it acceptable to provide you an updated description section of the USPI only, instead of resubmitting the entire US labeling text?)

III) NDA 21-976:

No revisions are needed for the NDA as a result of the above changes.

Thank you very much in advance.

Jenny

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Monday, March 20, 2006 9:59 AM
To: Thompson, Elizabeth
Subject: RE: IND 62,477 SN 451: Week 24 resistance data from C215

Attachments: DOC019.PDF; emfalert.txt



DOC019.PDF (759 KB)
emfalert.txt (1 KB)

Hi Beth,

Resending..
Jenny

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Monday, March 20, 2006 9:34 AM
To: Lin, Jenny [TIBUS]
Subject: RE: IND 62,477 SN 451: Week 24 resistance data from C215

Jenny,

I could not open the pdf file. Could you try to send again?

Thanks,

.eth

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

From: Lin, Jenny [TIBUS] [mailto:JLin10@TIBUS.JNJ.COM]
Sent: Friday, March 17, 2006 3:21 PM
To: Thompson, Elizabeth
Subject: IND 62,477 SN 451: Week 24 resistance data from C215

Hi Beth,

I would like to inform you that the attached general correspondence letter was submitted today (SN 451).

Please refer to the request from the Microbiology reviewer at the pre-NDA meeting and the NDA submission of December 2005. This correspondence provides an update on the availability of the additional Week 24 resistance data from C215 since the NDA submission of December 2005. With this submission, we would like to consult with the Microbiology reviewers whether they feel that a submission of the additional data is warranted at this time considering that most of the Week 24 genotype data were submitted in the NDA.

Thank you very much in advance for your feedback on this correspondence.

Please let me know if you have any questions.

Jenny

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Monday, March 13, 2006 1:24 PM
To: Thompson, Elizabeth
Subject: TMC114 Filing communication: item 4 (statistics)

Attachments: dmad.xpt; emfalert.txt



dmad.xpt (232 KB) emfalert.txt (1 KB)

Beth,

Please refer to my email correspondences of last Wednesday (March 8) and Friday (March 10), where I provided a define.PDF file for the requested dataset for study C202 and an additional clarification question for Dr. Hammerstrom in response to his comments on NDA 21-976.

In addition to the define.PDF file provided, please find attached also to facilitate Dr. Hammerstrom's review, the requested dataset prepared for study C202 as SAS transport file. If there are no additional comments on the attached dataset, we will be providing those for study C213, and studies C215/C208 (pooled).

We would like to prepare an eCTD submission of these datasets as well as the requested PK datasets by next week, therefore would greatly appreciate receive feedback on the statistical comments as soon as possible.

Thanks very much in advance.

Jenny

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Friday, March 10, 2006 1:49 PM
To: Thompson, Elizabeth
Subject: RE: 74 day filing letter for TMC114: Telecon of March 10, 2006
Attachments: emfalert.txt

Hi Beth,

As discussed after the telecon from this morning, please find below additional clarification question regarding which studies the Statistical comment is in reference to, that we would like to receive confirmation from Dr. Hammerstrom:

In response to the Statistical comment received requesting demographics dataset including the baseline covariates indicated, we are proposing to submit the requested dataset as per the define.PDF file, for study C202, study C213, and for studies C215 pooled with C208. Is this approach acceptable?

We look forward to receiving feedback on the above question and the define.PDF file that we provided on the requested dataset, as well as the proposed date for the telecon to address the feedback if needed.

Thanks very much.

Jenny

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

From: Lin, Jenny [TIBUS]
Sent: Wednesday, March 08, 2006 3:33 PM
To: 'Thompson, Elizabeth'
Subject: RE: 74 day filing letter for TMC114: Telecon of March 10, 2006

Beth,

Please find below list of attendees for Friday's teleconference and the dial-in information.

Toll Free Dial In Number: (877)807-4596
PARTICIPANT CODE: 838898

Tibotec attendees:

Tony Vangeneugden, MSc - Biostatistics Leader, TMC114
Ben Van Baelen, MSc - Biostatistician, TMC114
Marc Vanstockem, PhD - Chem-Pharm Leader, TMC114
Luc Janssens, PhD - CMC Regulatory Affairs
Hilde Walgraeve, PhD - Regulatory Leader, TMC114
Jenny Lin, PharmD - Regulatory Liaison, TMC114

Attendees from J&J Pharmaceutical Research and Development (US Agent for the DMF  holder):

Wendy Mavroudakis - Regulatory Affairs, API Support Group
Thomas Schultz, PhD - CMC Regulatory Affairs

Regarding the filing comments received, I would like to leave the specific questions to be asked by our team members during the telecon. However, here are some initial information which I hope would

be helpful to the reviewers.

1) Chemistry comment #1: we would like to receive a better understanding of the comment from Dr. Kambhampati and additional feedback on details of the proposed revisions.

2) Statistical comment #4: we would like to clarify whether Dr. Hammerstrom is requesting one single dataset containing the baseline variables he had listed instead of datasets organized per domain. We have started to prepare the dataset based on our understanding of the request and attached is a Define.PDF file for study C202 which we would like to receive feedback during the telecon.

Thanks very much!

Jenny

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]

Sent: Tuesday, March 07, 2006 9:31 AM

To: 'Lin, Jenny [TIBUS]'

Subject: RE: 74 day filing letter for TMC114

Jenny,

Both Dr. Hammerstrom (statistics) and Dr. Kambhampati (chemistry) have accepted. I only have those two attending (schedules are really tight for team leaders). Let me know if you will have any specific questions to be addressed, or if we will just wait for the teleconference.

Beth

Elizabeth Thompson, M.S.
Regulatory Project Manager
Division of Antiviral Products
301-796-0824 (phone)
301-796-9883 (fax)
Elizabeth.Thompson@fda.hhs.gov

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

From: Lin, Jenny [TIBUS] [mailto:JLin10@TIBUS.JNJ.COM]

Sent: Thursday, March 02, 2006 12:32 PM

To: Thompson, Elizabeth

Subject: RE: 74 day filing letter for TMC114

Hi Beth,

We would like to accept the proposed date of March 10 (11am -12pm EST).

I will provide Tibotec list of attendees as well as dial-in information to you prior to that date.

Thanks very much.

Jenny

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]

Sent: Tuesday, February 28, 2006 2:28 PM
To: 'Lin, Jenny [TIBUS]'
Subject: RE: 74 day filing letter for TMC114

Jenny,

I have 2 dates that can be reserved. March 6 or March 10, both from 11-12.
FDA attendees will be:

Rao Kambhampati, Ph.D., Chemistry Reviewer
Steve Miller, Ph.D., Pharmaceutical Assessment Lead
Tom Hammerstrom, Ph.D., Statistics Reviewer
and myself

optional:

Norman Schmuft, Ph.D., Branch Chief, Chemistry
Greg Soon, Ph.D., Statistics Team Leader

Please let me know if any of the above dates work.

Beth

Elizabeth Thompson, M.S.
Regulatory Project Manager
Division of Antiviral Products
301-796-0824 (phone)
301-796-9883 (fax)
Elizabeth.Thompson@fda.hhs.gov

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

From: Lin, Jenny [TIBUS] [mailto:JLin10@TIBUS.JNJ.COM]
Sent: Tuesday, February 28, 2006 1:53 PM
To: Thompson, Elizabeth
Subject: RE: 74 day filing letter for TMC114

Thanks Beth,

I think a morning telecon would be preferred (prior to noon) given the 6 hours time difference with Belgium. If no morning availability, then in the afternoon prior to 3pm.

Can you give me couple time slots that would work for your team from which we can choose based on everyone's availability here. Thanks in advance.

Jenny

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Tuesday, February 28, 2006 10:33 AM
To: 'Lin, Jenny [TIBUS]'
Subject: RE: 74 day filing letter for TMC114

Jenny,

Yes, we can arrange for a telecon to discuss the Chemistry and Statistics comments in the filing letter. I will begin to look at the calendar for the end of this week or next week sometime. Is there a time preference?

Beth

Elizabeth Thompson, M.S.
Regulatory Project Manager
Division of Antiviral Products
301-796-0824 (phone)
301-796-9883 (fax)
Elizabeth.Thompson@fda.hhs.gov

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

From: Lin, Jenny [TIBUS] [mailto:JLin10@TIBUS.JNJ.COM]
Sent: Friday, February 24, 2006 2:32 PM
To: Thompson, Elizabeth
Subject: RE: 74 day filing letter for TMC114

Beth,

I just had a team meeting today to discuss the comments received via the filing letter and we felt that further clarification is needed for comment #1 (Chemistry) and #4 (Statistics).

Could you please advise whether it's possible to schedule a short telecon with the Chemistry and Statistical reviewers sometimes next week to clarify couple of things? either Thursday or Friday would be great.

Thanks very much.

Jenny

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

From: Thompson, Elizabeth
[mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Tuesday, February 21, 2006 9:47 AM
To: 'Lin, Jenny [TIBUS]'
Subject: RE: 74 day filing letter for TMC114

Yes. The PDUFA date is June 23, 2006 and you may communicate that with Tibotec. The letter will not change, however, I verified with Tom (stats reviewer) that his comment is directed at C202, C213 and any other trials large enough to be used as pivotal.

Beth

Elizabeth Thompson, M.S.
Regulatory Project Manager
FDA/CDER/OND/OAP/DAVP

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

From: Lin, Jenny [TIBUS]
[mailto:JLin10@TIBUS.JNJ.COM]
Sent: Tuesday, February 21, 2006 9:42 AM
To: Thompson, Elizabeth
Subject: RE: 74 day filing letter for TMC114

Thank you Beth,

Two clarifications:

- 1) There is no communication of action date in the letter? If that's the case, can I communicate within the company that it will be June 23, 2006?
- 2) I intend to communicate this letter prior to receiving the signed copy so would like to make sure it won't change?

Jenny

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

From: Thompson, Elizabeth
[mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Tuesday, February 21, 2006 9:27 AM
To: 'Lin, Jenny [TIBUS]'
Subject: 74 day filing letter for TMC114

Jenny,

Here is the filing letter. You should receive the signed copy by mail.

<<74dayfilingletter.doc>>

Regards,

Beth

Elizabeth Thompson, M.S.
Regulatory Project Manager
Division of Antiviral Products
301-796-0824 (phone)
301-796-9883 (fax)
Elizabeth.Thompson@fda.hhs.gov

RE: [REDACTED]

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Wednesday, March 08, 2006 3:44 PM
To: Thompson, Elizabeth
Subject: RE: [REDACTED]

Hi Beth,

Please refer to the [REDACTED] amendment submitted to [REDACTED] on January 27, 2006 (SN 006). The EAP journal ads have been updated to be consistent with this protocol amendment and reviewed by the Division per email below.

I would like to follow up on the status of the review for the protocol amendment and whether you have received any comments so far.

Thanks very much in advance.

Jenny

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Friday, February 03, 2006 4:34 PM
To: 'Lin, Jenny [TIBUS]'
Subject: RE: TMC114 EAP Journal Ads for Review

Jenny,

These look fine!

Beth

Elizabeth Thompson, M.S.
Regulatory Project Manager
FDA/CDER/OND/OAP/DAVP

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

From: Lin, Jenny [TIBUS] [mailto:JLin10@TIBUS.JNJ.COM]
Sent: Wednesday, February 01, 2006 10:43 AM
To: Thompson, Elizabeth
Subject: RE: TMC114 EAP Journal Ads for Review
Importance: High

Dear Beth,

Please refer to the email correspondence below requesting the Division's review of EAP journal ads.

6/13/2006

RE: _____

Please also refer to the TMC114-C226 protocol amendment submitted to IND _____ on January 27, 2006 (SN 006). The EAP journal ads have been updated to be consistent with this protocol amendment.

At this time we would like to submit for Division's review the updated EAP ads intended for physicians and patients. A formal submission to IND _____ will follow.

I assume that the review time will be similar this time (3-5 days), please let me know if this assumption is incorrect.

Thanks very much in advance.

Jenny

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

From: Thompson, Elizabeth [mailto:ThompsonE@cder.fda.gov]
Sent: Thursday, September 15, 2005 12:28 PM
To: 'Lin, Jenny [TIBUS]'
Subject: RE: TMC114 EAP Journal Ads for Review

The Division is fine with these ads!!! Start printing...

Beth

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

From: Lin, Jenny [TIBUS] [mailto:JLin10@TIBUS.JNJ.COM]
Sent: Monday, September 12, 2005 3:26 PM
To: ThompsonE (E-mail)
Subject: TMC114 EAP Journal Ads for Review
Importance: High

Dear Beth,

Please refer to your email correspondence dated July 8, 2005 regarding the submission of EAP journal ads to the Division for review.

At this time we would like to submit two EAP advertisements intended for physicians and patients. I will follow up with an official submission (GC) to IND, I assume 73,000, could you confirm?

I understand that review can take up to several days. thanks in advance for informing once you receive feedback.

Jenny

>

6/13/2006

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Wednesday, March 08, 2006 12:59 PM
To: Thompson, Elizabeth
Subject: RE: Submission in response to FDA fax received on proprietary name consultation

Hi Beth,

I have a question regarding the timing of the final proprietary name approval from DMETS, that normally it would occur 90 days before the NDA action date. I am wondering whether this would still apply in the case of priority review, or if the final approval is closer to the action date, eg. one month prior?

Thanks very much for your feedback.

Jenny

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

From: Lin, Jenny [TIBUS]
Sent: Tuesday, March 07, 2006 1:50 PM
To: 'Thompson, Elizabeth'
Subject: Submission in response to FDA fax received on proprietary name consultation

Hi Beth,

Please be informed that I will be submitting today (SN 444) our responses to the comments received (via fax on January 26, 2006) regarding proprietary name consultation.

In this submission, we would like to provide results from the [REDACTED] regulatory safety research which included an assessment of any perceived promotional claims for [REDACTED] as a proposed proprietary name for TMC114. The data and analyses contained in this report are derived from a multi-faceted and global research study conducted by [REDACTED] in April 2005 for Tibotec.

We respectfully request that the Division reconsider [REDACTED] as an appropriate proprietary name for TMC114, based on the data provided in this submission.

Please contact me if you have any questions.

Regards,
Jenny

Jenny Lin, Pharm.D.
Tibotec Inc.
1020 Stony Hill Rd. Suite 300
Yardley, PA 19067
Phone: (609) 730-7516
Fax: (609) 730-7501

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Tuesday, February 28, 2006 2:04 PM
To: Thompson, Elizabeth
Subject: RE: NDA safety update

Hi Beth,

Thank you very much for the feedback.

I would like to further clarify, that patient narratives for the deaths/SAEs included in the NDA safety update (from all ongoing studies) will be provided via the CIOMS report (those that are typically submitted for the IND safety reports).

Jenny

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Tuesday, February 28, 2006 9:33 AM
To: 'Lin, Jenny [TIBUS]'
Subject: RE: NDA safety update

Jenny,

The review team finds this approach acceptable, as long as patient narratives are included.

Thanks for the heads up!

Beth

Elizabeth Thompson, M.S.
Regulatory Project Manager
Division of Antiviral Products
301-796-0824 (phone)
301-796-9883 (fax)
Elizabeth.Thompson@fda.hhs.gov

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

From: Lin, Jenny [TIBUS] [mailto:JLin10@TIBUS.JNJ.COM]
Sent: Friday, February 24, 2006 3:07 PM
To: Thompson, Elizabeth
Subject: NDA safety update

Hi Beth,

Per agreement at the pre-NDA meeting, we are currently preparing for an NDA safety update submission at the end of March.

As agreed, we will be providing the following information in this submission:

- Safety data from the open label safety study TMC114-C209 with a cut-off of December 1, 2005.
- Updated reports on death/serious adverse events in all ongoing Phase II and III trials up to January 13, 2006 cut-off. These SAE reports will consist of CIOMS line listings and reports.

In addition, we would like to seek the review team's concurrence on the following:

- Case report forms will be provided for all deaths reported in the ongoing trials, and discontinuation due to AE in study C209 only (given the safety analysis being done for this trial). CRFs for other SAEs and discontinuations due to AE from other ongoing trials can be made available upon request during the review.

Please let me know if the above approach is acceptable?

Let me know if anything is unclear. Thanks very much in advance.

Jenny

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]

Sent: Thursday, February 23, 2006 9:38 AM

To: Thompson, Elizabeth

Subject: NDA amendment sequence 0005

Hi Beth,

I would like to inform you that we intend to submit next week (Feb 27) an amendment to NDA 21-976 providing the following information:

- Stability update
- Updated financial disclosure information
- Responses to the Microbiology Query #1, Clinical Query #1-5, and Comments on financial disclosure

Please let me know if you have any questions regarding this submission.

Jenny

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Thursday, February 09, 2006 3:54 PM
To: Thompson, Elizabeth
Subject: RE: Pediatric plan comments

Hi Beth,

Thank you for the clarification. We are currently in the process of finalizing the actual protocol, therefore if possible, we would like to receive these comments now, rather than waiting until after the protocol submission. This is to avoid another protocol revision right after the submission which may have an impact on the study initiation.

I understand that this will certainly depend on the type of the comments that the reviewer had in mind to evaluate the impact, but if the above can be taken into consideration, I would greatly appreciate it.

Jenny

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]
Sent: Thursday, February 09, 2006 1:34 PM
To: 'Lin, Jenny [TIBUS]'
Subject: RE: Pediatric plan comments

Jenny,

I just spoke with the medical reviewer for the peds plan (Anitra Denson) and she needs to confirm with the medical team leader if we are going to send out comments on the protocol summary or if we are going to wait until we receive the actual protocol. I hope to hear by Friday (people are out at CROI). I also wanted to let you know that I am waiting to send the final fax until I hear about this so that I can take that statement out if we are not going to send comments so as to not confuse anyone.

Beth

Elizabeth Thompson, M.S.
Regulatory Project Manager
FDA/CDER/OND/OAP/DAVP

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

From: Lin, Jenny [TIBUS] [mailto:JLin10@TIBUS.JNJ.COM]
Sent: Tuesday, February 07, 2006 11:04 AM
To: Thompson, Elizabeth
Subject: RE: Pediatric plan comments

Hi Beth,

In comment under Q4 you mentioned that there are specific comments regarding the submitted protocol summary which will be provided separately.

I assume that you are also awaiting signature for those?

Jenny

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

From: Thompson, Elizabeth [mailto:Elizabeth.Thompson@fda.hhs.gov]

Sent: Tuesday, February 07, 2006 8:05 AM

To: 'Lin, Jenny [TIBUS]'

Subject: Pediatric plan comments

Jenny,

Wanted to send comments by email. I will fax the document once I receive final sign off (comments should not change; there are reviewers out at a conference that I am waiting on for signature). Let me know if you have questions.

<<SN400.doc>>

Elizabeth Thompson, M.S.
Regulatory Project Manager
Division of Antiviral Products
301-796-0824 (phone)
301-796-9883 (fax)
Elizabeth.Thompson@fda.hhs.gov

Thompson, Elizabeth

From: Thompson, Elizabeth
Sent: Thursday, January 12, 2006 9:37 AM
To: 'Lin, Jenny [TIBUS]'
Subject: Queries for NDA 21-976

Jenny,

With the review under way for TMC114, I wanted to brief you on our format for any information that is needed by reviewers to aid in their review. The Division finds it easiest to email queries from the appropriate reviewer or discipline as they are received by myself, instead of faxing. You may respond to the query by email or fax, whichever is easiest. I will provide the type of query in the subject line which you can use for reference.

If you have any questions in reference to this, please let me know.

Thanks,

Beth

Elizabeth Thompson, M.S.
Regulatory Project Manager
FDA/CDER/OND/OAP

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Wednesday, December 21, 2005 3:20 PM
To: Thompson, Elizabeth
Subject: RE: SN 367: Request for propriatery name consultation
Attachments: emfalert.txt

Hi Beth,

Please refer to SN 367 submitted in September. I would like to follow up on the status of the tradename review for TMC114. Will you be expecting feedback from DMETS sometimes in January?

Thanks in advance.

Jenny

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

From: Lin, Jenny [TIBUS]
Sent: Friday, September 23, 2005 4:08 PM
To: 'Thompson, Elizabeth'
Subject: SN 367: Request for propriatery name consultation

Hi Beth,

I would like to inform you that today we submitted a request for the Division's review of the following propriatery names for TMC114 in the following prioritized order:

~~1. PREZISTA~~
2. PREZISTA

A copy of the cover letter is attached for your reference. We would really appreciate any comments and a prompt review of these proposed names.

Regards,
Jenny

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Wednesday, December 14, 2005 3:56 PM
To: Thompson, Elizabeth
Subject: RE: Briefing package: Pivotal BE study results

Hi Beth,

Thank you very much for following up, please find below response to the Clinical pharmacology reviewer's question:

Results from study C166, including the information obtained from doses other than TMC114/rtv 600/100, are intended for assessing the comparative bioavailability of the clinical trial versus commercial formulation as a follow-up to the non-bioequivalence finding observed in study C116. Study C166 is only designed to explore whether finding from C116 was potentially due to the effect of food or the effect of dose administered, given the fact that a previous study C144 had shown comparable exposure for the clinical trial and commercial formulations at a dose level of 400 mg in the fed state and in the presence of low-dose ritonavir.

Looking forward to receiving the reviewer's comments.

Jenny

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

From: Thompson, Elizabeth [mailto:ThompsonE@cder.fda.gov]
Sent: Wednesday, December 14, 2005 10:58 AM
To: 'Lin, Jenny [TIBUS]'
Subject: RE: Briefing package: Pivotal BE study results

Jenny,

The clinical pharmacology reviewer will have additional comments. However, she has provided me with a question that she would like answered before she provides her comments. In addition, she feels that a brief teleconference would be helpful in order to answer any questions about the protocol that will be started in January. I think 15-30 minutes will be sufficient. As soon as we receive a response to her question and she provides a comment (I will email) we can communicate a time that would be good for everyone (let's try before the end of the year).

Her question:

How do you plan to use the results of Study C166, in particular the information from doses other than TMC114/rtv 600/100? Does the objective go beyond defining the exposure difference between the commercial formulation and the clinical trial formulation used in C202 and C213?

Please contact me if you have any questions.

Beth

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

From: Lin, Jenny [TIBUS] [mailto:JLin10@TIBUS.JNJ.COM]
Sent: Thursday, December 08, 2005 1:23 PM

To: Thompson, Elizabeth
Subject: RE: Briefing package: Pivotal BE study results

Hi Beth,
Could you please let me know couple time slots (one hour for now) on Tuesday & Wednesday morning of next week that would work for your team?
thanks!
Jenny

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

From: Lin, Jenny [TIBUS]
Sent: Tuesday, November 29, 2005 12:58 PM
To: 'Thompson, Elizabeth'
Subject: RE: Briefing package: Pivotal BE study results

Thank you Beth.

I will look for everyone's availability and propose a date for telecon next week to discuss the design of TMC114-C166 (BA study). This week most of the team members are not available.

Please let me know in the event that there will be members from other review team joining.

In addition, as indicated in the cover letter of SN 379, I will be submitting this week a follow-up package with additional data that became available this month.

Jenny

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

From: Thompson, Elizabeth [mailto:ThompsonE@cder.fda.gov]
Sent: Tuesday, November 29, 2005 11:28 AM
To: 'Lin, Jenny [TIBUS]'
Subject: RE: Briefing package: Pivotal BE study results

Jenny,

Clinical Pharmacology has looked this over and feels that your proposal is acceptable. In the submission, Tibotec mentions a follow-up Bioavailability study in the fed state. The review team (Clinical Pharmacology) would like to discuss this study with you at your convenience (not urgent).

Beth

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

From: Lin, Jenny [TIBUS] [mailto:JLin10@TIBUS.JNJ.COM]
Sent: Wednesday, October 05, 2005 9:23 AM
To: 'Thompson, Elizabeth'
Subject: Briefing package: Pivotal BE study results

Dear Beth,

Reference is made to our submission of draft protocol summary (Serial No. 227) on the conduct and design of pivotal bioequivalence (BE) study TMC114-C116. Reference is also made to the FDA Clinical Pharmacology comments received on the draft protocol (dated April 8, 2005), and to the final protocol for

TMC114-C116 provided to the Division on May 27, 2005 (Serial No. 285).

PK data from TMC114-C116 has become available and showed unexpected results. In view of the ongoing TMC114 NDA submission activities, we would like to share with the Division the available data from TMC114-C116, as well as to obtain feedback from the Division on our action plans moving forward.

A briefing package will be submitted (with a desk copy to you) in the course of next week. I will follow up with you again after the submission has occurred.

Please feel free to contact me if you have any questions.

Regards,
Jenny

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
ent: Friday, November 04, 2005 9:58 AM
ro: Thompson, Elizabeth
Subject: [REDACTED] DMF# [REDACTED] - Darunavir Drug Substance submitted

Attachments: darunavir-dmf-cover-letter-dated.pdf; [REDACTED] dmf [REDACTED] drug substance 02-Nov-05 fti.pdf; emfalert.txt



darunavir-dmf-cove
r-letter-dat...



[REDACTED] dmf [REDACTED]
drug substan...



emfalert.txt (2 KB)

Dear Beth,

In case that you are not yet aware, I would like to inform you that the DMF [REDACTED] for Darunavir Drug Substance was submitted on November 2, 2005.

Please find attached the DMF cover letter as well as FedEx tracking information for your reference.

Just to clarify, the number R319064 in the cover letter is the compound number assigned for Darunavir by J&JPRD (US agent for the DMF holder).

Please let me know if you have any questions.

Jenny

>
>
>

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Wednesday, November 02, 2005 10:17 AM
To: Thompson, Elizabeth
Subject: RE: TMC114 Pediatric consultation package

Hi Beth,

Please refer to the email correspondence below (July 20) regarding the pediatric consultation package that we were planning to submit during 4Q2005. I would like to inform you that we are currently targeting the submission during the week of November 28 - December 2.

This package will contain Nonclinical, CMC, PK and Clinical information pertaining to the TMC114 pediatric development program to support the initiation of TMC114-C212, a PK/safety study in pediatric patients. A protocol summary for TMC114-C212 will also be included in the package for Division's review.

We are looking forward to receiving the Division's feedback on the package as early as possible in order to timely initiate the pediatric study. In view of the upcoming submissions of the sections of NDA (November 4th for CMC & Nonclinical, and end of December for Clinical) as well as the year end holiday period, I would like to consult with you (for planning purpose) the availabilities of the reviewers that will be involved during the month of December.

Thanks in advance and I look forward to your reply.

Jenny

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

From: Thompson, Elizabeth [mailto:ThompsonE@cder.fda.gov]
Sent: Tuesday, July 26, 2005 3:37 PM
To: 'Lin, Jenny [TIBUS]'
Subject: RE: TMC114 Pediatric consultation package

Jenny,

The request can come in with the NDA package. No need for anything earlier.
We address all of it in the approval letter.

Beth

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

From: Lin, Jenny [TIBUS] [mailto:JLin10@TIBUS.JNJ.COM]
Sent: Wednesday, July 20, 2005 6:08 PM
To: ThompsonE (E-mail)
Subject: TMC114 Pediatric consultation package

Dear Beth,

Please refer to the TMC114 pre-NDA meeting held with the Division on June 7, 2005 to discuss the proposed format and content of the NDA submission for TMC114 for the treatment of HIV infection.

At the meeting, the Division agreed with the proposed approach regarding TMC114 pediatric development program and the proposal for providing pediatric assessment as a post approval commitment.

As described in the briefing package and discussed during the meeting, Tibotec intended to initiate a PK/safety study (TMC114-C212) in pediatric patients (age 6 years and older) using the [REDACTED]

[REDACTED]
3Q2005, and a consultation package regarding the pediatric program would be provided to the Division for review in the summer of 2005.

Tibotec is currently collating the available data from preclinical, PK and clinical studies that will be included in the consultation package to support a feasible and optimal design for the pediatric development program of TMC114. Because of findings in an ongoing reproductive toxicity study warranting further investigation, and consequently our intention to provide a more comprehensive preclinical data to facilitate the consultation discussion, we plan to postpone the submission of this consultation package to 4Q2005.

Given that pediatric assessment will be provided as a post approval commitment, in accordance with 21 CFR 314.55, please advise the preferred process (e.g. submission of a formal request, if needed) for obtaining the deferral and/or waiver agreement with the Division prior to the NDA submission for TMC114.

Thanks in advance, and please let me know if you have any questions regarding this correspondence.

Regards,
Jenny

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]

Sent: Monday, October 24, 2005 3:19 PM

To: Thompson, Elizabeth

Subject: Financial Disclosure- covered clinical studies

Hi Beth,

To comply with the FDA financial disclosure requirements, we are in the process of preparing financial disclosure information to be included in the Module 1 of December submission. As per *FDA guidance- Financial Disclosure by Clinical Investigators*, the covered clinical studies are those the applicant or FDA relies on to establish that the product is effective. In support of the TMC114 NDA, we intend to include financial disclosure information from the following studies: TMC114-C202, C213 and C215.

Please let me know if this approach is acceptable to the Division.

Thanks in advance for your feedback.

Jenny

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Friday, October 21, 2005 11:49 AM
To: Thompson, Elizabeth
Subject: RE: NDA 21-976 September submission: SDS datasets

Beth,

I just wanted to double check- I will make reference to this email correspondence regarding the updates of the datasets in the three studies in the cover letter of November submission only, rather than submitting officially the attached clarification document in the November eCTD submission. Let me know if you are Ok with this approach?

Thanks!
Jenny

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

From: Thompson, Elizabeth [mailto:ThompsonE@cder.fda.gov]
Sent: Wednesday, October 19, 2005 2:17 PM
To: 'Lin, Jenny [TIBUS]'
Subject: RE: NDA 21-976 September submission: SDS datasets

Jenny,

The Division agrees with this approach (additional information submitted in November to update September Clinical section).

Regards,

Beth

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

From: Lin, Jenny [TIBUS] [mailto:JLin10@TIBUS.JNJ.COM]
Sent: Wednesday, October 19, 2005 1:30 PM
To: ThompsonE (E-mail)
Subject: NDA 21-976 September submission: SDS datasets

Dear Beth,

Please refer to the September Clinical section of NDA 21-976 submitted on September 23, 2005.

Upon a recent review of the SDS datasets provided for the studies included in the September submission, we felt that further clarification may be needed for some of the datasets submitted for studies TMC114-C101, 102 and 104 in order to facilitate an efficient review. As a result, we would like to propose to provide the updated SDS domains for these studies as soon as possible, therefore in the upcoming November CMC & Nonclinical section submission of the NDA, rather than waiting until December.

An explanation for this proposed update is attached.

As we are currently in preparation of the November eCTD submission, could you please let me know by this Friday if the Division has any objection to this approach? Greatly appreciate your help

and I sincerely apologize for the short notice.

Regards,
Jenny

<<Tibotec TMC114 NDA 21-976 Domain Update Clarification.doc>>

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
ent: Friday, October 07, 2005 5:22 PM
o: Thompson, Elizabeth
Subject: CDA: Integrated Clinical Systems

Attachments: CDA-Integrated Clinical Systems.pdf; emfalert.txt



CDA-Integrated emfalert.txt (2 KB)
Clinical System...

Dear Beth,

We refer to the request for authorization made via your email correspondence dated September 16, 2005, to disclose Tibotec confidential and proprietary information in relation to the compound TMC114 contained in the NDA 21-976, to members of the staff of Integrated Clinical Systems, Inc. involved in the training with respect to the software called Integrated Review™.

Please note that Tibotec is willing to provide such authorization subject to the execution by Integrated Clinical Systems, Inc. of the attached Confidential Disclosure Agreement. Moreover, access to the TMC114 data by FDA staff for training purposes should be limited to those members of the FDA staff who are or will be involved in the review of the TMC114 NDA.

We would appreciate if you could return to us at your earliest convenience, the attached Confidential Disclosure Agreement executed by Integrated Clinical Systems, Inc., in duplicate. Both copies will then be forwarded to Tibotec Pharmaceuticals, Ltd for signature. One fully executed copy will be returned to Integrated Clinical Systems, Inc.

Please let me know if you have any questions. A submission of this correspondence to the IND 62,477 will follow.

Regards,
Jenny

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Wednesday, October 05, 2005 9:23 AM
To: Thompson, Elizabeth
Subject: Briefing package: Pivotal BE study results
Attachments: emfalert.txt

Dear Beth,

Reference is made to our submission of draft protocol summary (Serial No. 227) on the conduct and design of pivotal bioequivalence (BE) study TMC114-C116. Reference is also made to the FDA Clinical Pharmacology comments received on the draft protocol (dated April 8, 2005), and to the final protocol for TMC114-C116 provided to the Division on May 27, 2005 (Serial No. 285).

PK data from TMC114-C116 has become available and showed unexpected results. In view of the ongoing TMC114 NDA submission activities, we would like to share with the Division the available data from TMC114-C116, as well as to obtain feedback from the Division on our action plans moving forward.

A briefing package will be submitted (with a desk copy to you) in the course of next week. I will follow up with you again after the submission has occurred.

Please feel free to contact me if you have any questions.

Regards,
Jenny

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Thursday, September 29, 2005 1:06 PM
To: Thompson, Elizabeth
Subject: RE: Question

Hi Beth,

Just wanted to provide an update on this:

- I did end up receiving the fax yesterday, thanks for providing the requested information.
- Currently I am awaiting the finalization of CDA by legal, once that is ready, I will forward to our submission group to prepare for the electronic submission
- I also further received confirmation that the electronic submission preparation will take about 4-5 days before I can send out the formal submission to FDA.

Taking the above into account, I hope to be able to send out the formal submission by the end of next week (if you like, I can provide the letter & CDA to you via email once finalized so that you can get the process moving from your end). If this timeline is still acceptable to you, I will move forward with submitting to the NDA as planned.

Regards,
Jenny

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

From: Thompson, Elizabeth [mailto:ThompsonE@cder.fda.gov]
Sent: Tuesday, September 27, 2005 2:34 PM
To: 'Lin, Jenny [TIBUS]'
Subject: RE: Question

Jenny,

For review purposes, would it be easier to submit the letter to the IND and reference the NDA. That way there will not be a long wait. Otherwise, you can submit to the NDA (please advise as to how soon you would do this; waiting until the second submission will not give the reviewers time for training/review of the submission). As for the 356h, you would code as other. In your cover letter you can put something like:

RE: NDA 21-976 General Correspondence: Confidential Disclosure Agreement

Beth

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

From: Lin, Jenny [TIBUS] [mailto:JLin10@TIBUS.JNJ.COM]
Sent: Thursday, September 22, 2005 1:12 PM
To: 'Thompson, Elizabeth'
Subject: RE: Question

Beth,

I would like to also go over with you couple logistic issues relating to this submission:

1) You had mentioned that the letter should be submitted to the NDA, which means that it will be submitted after the first rolling submission of September but before the second submission in November. Could you confirm that the 'type of submission' on 356H should be coded as 'other'?

2) Since this will be an electronic submission, and because currently Tibotec still contract out to a third party for preparation of electronic submissions, I would like to give you a heads-up that there will be couple of days turnaround for the submission to occur from the time when we are able to finalize the letter. This can be avoided if we don't submit the letter to the NDA but providing separately.

Jenny

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

From: Lin, Jenny [TIBUS]
Sent: Wednesday, September 21, 2005 5:36 PM
To: 'Thompson, Elizabeth'
Subject: RE: Question

Hi Beth,

Although Tibotec is using the same vendor for the software, they have not seen our data.

We would like to facilitate as much as possible the FDA review process therefore certainly the training of the review tool. However given that there hasn't been a confidential agreement in place with the vendor, Tibotec would like to obtain through the Division the formal approval and execution by vendor of a confidentiality agreement.

As discussed, we will be preparing a CDA (confidential disclosure agreement) and include it with the submission. For that reason, could you please provide the following information about the vendor:

- 1) vendor full name, entity, address (*Is it Integrated Clinical Systems, Inc.?*)
- 2) authorized representative from vendor for the CDA
- 3) names of the vendor trainers that will need access
- 4) exact name of the software (*Integrated Review(tm)?*)

I know we have also discussed this on the phone, could you also confirm that the FDA staffs that will be involved in the training therefore need access to the data are those member of the Division that will be involved in review of the TMC114 NDA, plus training staff from OIM?

Thanks in advance.

Jenny

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

From: Thompson, Elizabeth [mailto:ThompsonE@cder.fda.gov]
Sent: Friday, September 16, 2005 7:15 AM
To: 'Lin, Jenny [TIBUS]'
Subject: FW: Question

Jenny,

We just had our first I-Review training session and one of the biggest comments that came out of this training was that it would be easier if the I-Review staff could see the data in order to show specific tools and to answer specific questions (see emails below). If Tibotec agrees, could you send a letter granting I-Review staff access to data during training?

Thanks (hope you are feeling better!!)

Beth

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

From: Weiss, Fran (CDER)
Sent: Thursday, September 01, 2005 11:22 AM
To: Thompson, Elizabeth; Gibbs, Neville
Subject: FW: Question

Hi Beth,
We need to ask Tibotec to send us a letter to the NDA stating that Integrated Review staff can see their data while we are reviewing it (see email below). This will allow Integrated Review staff to assist our review team in using/learning the I-Review product.

Fran

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

From: Gensinger, Gary M
Sent: Thursday, September 01, 2005 11:21 AM
To: Weiss, Fran (CDER)
Subject: FW: Question

Fran,

Here's the answer.

Gary

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

From: Collier, Bronwyn E
Sent: Thursday, September 01, 2005 11:14 AM
To: Gensinger, Gary M
Subject: RE: Question

The sponsor can give permission to whomever they want to view their data. A letter to the NDA is perfect. The letter needs to be specific as to who can view and exactly what they can view (e.g., the vendor probably cannot view any DMF that may be referenced by the application).

Bronwyn

Bronwyn Collier
Associate Director for Regulatory Affairs
Office of Drug Evaluation III, CDER

(p)301-827-3143
(f)301-480-3761

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

From: Gensinger, Gary M
Sent: Thursday, September 01, 2005 11:09 AM
To: Collier, Bronwyn E
Subject: Question

Hi,

We're looking at a new tool for data analysis. We would like to be able to show the vendor the actual data. The vendor happens to be the vendor for the sponsor so he's already seen the data. Is it ok to ask the sponsor if they would be willing to authorize the vendor to see the submitted data so the vendor could provide the reviewers with more help? If yes, would a letter to the NDA be sufficient?

Gary

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
ent: Monday, September 26, 2005 4:57 PM
To: Thompson, Elizabeth
Subject: Followup to CDISC t-con: [AH] and [CM] recoding approach

Attachments: emfalert.txt



emfalert.txt (2 KB)

Hi Beth,

Please refer to the FDA fax received on August 5 providing reviewers' comments following our CDISC teleconference of July 28. Please also refer to the TMC114 eCTD submission of September 23.

At this time, we would like to inform the Division the approach that we have taken in regards to the coding of the [AH] and [CM] datasets (in response to comment #3 of the fax).

Please let me know if you have any questions regarding this correspondence.

Regards,
Jenny

> FDA Comments:
>
> "3. AH domain: Please use generic names for antiretrovirals and
> concomitant medications for consistency."
>
>
> Response from Tibotec:
>
> "Variable AHDECOD of dataset [AH] and variable CMDECOD of dataset [CM]
> hold the preferred term of the standard WHO Dictionary. To comply with
> the FDA's request for variables AHDECOD and CMDECOD to hold generic
> names the following SAS programs were developed by Tibotec:
> AHRECODE.SAS and CMRECODE.SAS.
>
> The SAS programs (AHRECODE.SAS and CMRECODE.SAS) have been filed in
> the eCTD in the folder "...\[study]\datasets\tabulations\programs\
> for trials TMC114-C201, TMC114-C207, TMC114-C202, TMC114-C213 and
> TMC114-C119.
>
> The SAS programs (AHRECODE.SAS and CMRECODE.SAS) have been eCTD tagged
> with the metadata attribute for STF as "analysis-program"
> (info-type=FDA, name=analysis-program).
>
> As these programs run against the corresponding tabulation datasets to
> convert the WHO drug preferred term coding to generic names the
> programs have been placed in the "programs" folder under the
> "tabulations" folder."
>
> The SAS programs (AHRECODE.SAS and CMRECODE.SAS) require no user
> manipulation except for filling in the path of the location of the
> [AH] and [CM] datasets in the SAS LIBNAME statement.
>

> Tibotec has followed this approach to avoid submitting two [AH] and
> two [CM] datasets (with one dataset holding the preferred term of the
> WHO dictionary, one dataset holding the generic names)."
>

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]

Sent: Thursday, September 22, 2005 12:26 PM

To: Thompson, Elizabeth

Subject: TMC114-C211 study

Hi Beth,

In response to your question regarding the status of TMC114-C211 study (protocol submitted on July 29, 2005, SN-331), that in the US:

- So far no patients have been screened & no sites have received medication
- IRB approval for C211 was received
- First site initiation visit is planned for end of this week/early next week, target to screen first patient next week

I understand from you that the formal comments won't be expected in a week or so, however if you could let me know as soon as possible the nature of the comments and whether the comments will be related to the trial design (eg. inclusion/exclusion criteria), it would really be appreciated.

Thanks in advance.

Jenny

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Tuesday, September 20, 2005 12:30 PM
To: Thompson, Elizabeth
Subject: RE: SN302 (GC regarding safety reporting)

Hi Beth,

We would like to acknowledge the Division's concern & precaution towards hepatic events and following discussions with the Division during our clinical development program, we have continued to monitor closely in our clinical trials. We will also continue to submit weekly to IND the DSMB LFT reports from the Phase IIB trials in response to the Division's request at the EOPII meeting.

Adopting a conventional approach would not affect the interpretation of "expected" since under the current conservative approach that Tibotec is following (reports Serious and Unexpected events regardless of 'associated' or not), we do not report expected events -those that are listed in the IB.

If the Division has any special SAE of interest, could we discuss an alternative way to address? e.g. adopting a conservative approach for specific SAE(s)? The volume of SAEs will increase dramatically with the start up of EAP (may result in up to 20 SAEs a day to be submitted to the IND) if we continue with our current approach.

Looking forward to your reply.

Jenny

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

From: Thompson, Elizabeth [mailto:ThompsonE@cder.fda.gov]
Sent: Monday, September 19, 2005 7:22 AM
To: 'Lin, Jenny [TIBUS]'
Subject: RE: SN302 (GC regarding safety reporting)

Jenny,

On Friday I said the Division was ok with Tibotec adopting "conventional" IND safety reporting; however, the team has reconsidered their position. They are concerned that we will not receive notification of potentially serious hepatotoxic events if Tibotec interprets them as "expected" because you saw that one case early on, or that the event is considered not related because of reasons such as co-infection. Given the serious nature of hepatic adverse events, Tibotec should continue reporting using a conservative approach.

I apologize for this change, however we are in the process of getting our new team leader up to speed with Tibotec's product.

Beth

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Tuesday, September 06, 2005 6:47 PM
To: Thompson, Elizabeth
Subject: TMC114 NDA September 2005 submission

Attachments: TMC114 September submission outline.pdf; emfalert.txt



TMC114 September emfalert.txt (2 KB)
submission ou...

Dear Beth,

Please refer to the pre-NDA briefing package submitted for TMC114 (SN 269), where the proposed NDA submission plan for rolling review was provided.

The proposed plan was discussed with the Division at the pre-NDA meeting and agreed upon. As we are approaching the first portion of NDA submission (target submission date: September 23, 2005), I would like to provide a high level update regarding this submission.

Please note the following major changes made to the previously proposed submission content for September included in the pre-NDA briefing package:

- * As requested by the Division, modules 2.7.3 (Summary of Clinical Efficacy) and 2.7.4 (Summary of Clinical Safety, including Phase I safety pooling) will NOT be included in September submission, both modules will be submitted in December 2005.
- * Two Phase I study reports TMC114-C117 & TMC114-C136 (excluding tabulation and analysis datasets) were added to September submission per email correspondence to you dated May 16, 2005.
- * Study TMC114-C153 (ECG study) will NOT be included in the September submission due to a delay in the study report finalization. The study report (as well as any summary information related to this study) will be submitted in December 2005.
- * Case Report Forms and Individual Patient Listings will be included per individual study report folder instead of under a separate module 5.3.7.

An updated outline of September submission per CTD module is attached for your reference.

Please let me know if you have any questions or if the above information needs to be provided in an official submission.

Regards,
Jenny

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Tuesday, August 23, 2005 1:53 PM
To: Thompson, Elizabeth
Subject: RE: Information needed for DSI
Attachments: TMC114-C202 list of investigators.pdf; TMC114-C213 list of investigators.pdf; emfalert.txt

Dear Beth,

Please find attached the list of investigators from studies TMC114-C202 and C213 as per request of Division of Scientific Investigations, providing the following information from each study:

- 1) Address of investigational site
- 2) Name of the principal investigator and sub-investigators (please note the term 'co-investigator' was used instead in the list) from each site
- 3) Number of patients screened, enrolled and discontinued as of July 25, 2005. (please note that both trials are ongoing, therefore there is no subject completed at this point)

I will also submit this information as a GC submission which you should receive tomorrow morning.

Please let me know if you have questions or DSI would like additional information.

Jenny

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

From: Thompson, Elizabeth
Sent: Tuesday, July 19, 2005 11:23 AM
To: 'Jenny Lin (jlin10@tibus.jnj.com)'
Subject: Information needed for DSI

The Division of Scientific Investigations is aware of your future NDA submissions and would like to request the following information be sent to me as desk copies:

For the pivotal studies (TMC114-C202 and C213) please provide a list of all site investigators (and address) with the number of subjects enrolled, discontinued, and completed at this point. Submit one copy officially (GC) and two desk copies to me.

Could you also send another desk copy of the PreNDA background package (SN269)?

I did not find any guidances covering this.

Beth

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Monday, August 01, 2005 4:22 PM
To: Thompson, Elizabeth
Subject: Follow-up to 7/28 CDISC telecon

Hi Beth,

I am passing along the following feedback from Tibotec data management group, intended to address some of the questions raised by the reviewers during the FDA teleconference last Thursday regarding the sample datasets submitted. Please let me know if anything is not clear and we will provide additional clarification. In view of the September submission, it's crucial that we resolve the outstanding issues as soon as possible to avoid delay. As discussed, we hope to discuss further via a second telecon this week. Please let me know the available date and time for the review team.

1. DM domain

(Please refer to the email correspondence to FDA dated July 19, 2005 informing the revised approach regarding USUBJID.) Following the FDA telecon, we rechecked the [DM] and there are no patients with same USUBJID and different race or sex (except one blank race where the investigator did not want to complete it when the subject was a screening failure first time round).

2. Difference between [TI] and [CA] dataset

[TI] Contains all the inclusion and exclusion criteria that were applied during the trial, but not at a subject level. However, the current version of CDISC does not provide a solution yet on how to deal with amended criteria. This means that we can list all criteria, but we can not include dates from when on the new amendment is valid. Simply adding a date would not resolve the issue, the amendments are not approved at all sites simultaneously.

We contacted CDISC for a solution, but they were unable to provide one at this point in time, therefore we created a table [CA] which lists - on a subject level - which criteria were valid at the time when the subject was screened (all criteria listed per subject).

The [IE] dataset contains the criteria that the subject did not meet, but there is no distinction here between screening failures and those subjects that did not meet all criteria, but were allowed to continue in the study (dataset derived from forms Inc and Exc of the blank CRF). The [EM] table contains the list of criteria which the subject did not meet, but for which the site contacted the sponsor to grant permission to enter the subject in the study (dataset derived from form Exemp of the blank CRF).

3. Comments domain

Coref contains the CRF page or parent record to which the comment refers. We will look into this and see if we can make the reference more self-explanatory, as we do realize that the link is not always straightforward.

IDVAR and IDVARVAL are only completed if there is a link with a parent record (e.g. in cases where on the CRF we specifically foresaw that comments could be written, such as on the 'LAB' form where there are several instances with "remarks, if any:....". Other remarks are floating comments, for which there is no link with a parent record, and therefore IDVAR and IDVARVAL are left blank, as specified in the CDISC implementation guide. However, in order to be able to link the comment to a certain timepoint, we used the Coref as a combination of the page name or page number and the visit number where the floating comment was found.

4. We are looking into the other outstanding issues, concerning coding and additions to the disposition dataset.

Regards,
Jenny

**Appears This Way
On Original**

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Wednesday, July 20, 2005 6:08 PM
To: Thompson, Elizabeth
Subject: TMC114 Pediatric consultation package

Attachments: mmsalert.txt



mmsalert.txt (1 KB)

Dear Beth,

Please refer to the TMC114 pre-NDA meeting held with the Division on June 7, 2005 to discuss the proposed format and content of the NDA submission for TMC114 for the treatment of HIV infection.

At the meeting, the Division agreed with the proposed approach regarding TMC114 pediatric development program and the proposal for providing pediatric assessment as a post approval commitment.

As described in the briefing package and discussed during the meeting, Tibotec intended to initiate a PK/safety study (TMC114-C212) in pediatric patients (age 6 years and older) using the [REDACTED] formulation in combination with the commercial RTV formulation in 3Q2005, and a consultation package regarding the pediatric program would be provided to the Division for review in the summer of 2005.

Tibotec is currently collating the available data from preclinical, PK and clinical studies that will be included in the consultation package to support a feasible and optimal design for the pediatric development program of TMC114. Because of findings in an ongoing reproductive toxicity study warranting further investigation, and consequently our intention to provide a more comprehensive preclinical data to facilitate the consultation discussion, we plan to postpone the submission of this consultation package to 4Q2005.

Given that pediatric assessment will be provided as a post approval commitment, in accordance with 21 CFR 314.55, please advise the preferred process (e.g. submission of a formal request, if needed) for obtaining the deferral and/or waiver agreement with the Division prior to the NDA submission for TMC114.

Thanks in advance, and please let me know if you have any questions regarding this correspondence.

Regards,
Jenny

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Wednesday, July 20, 2005 5:32 PM
To: Thompson, Elizabeth
Subject: RE: Follow up to voice mail
Attachments: mmsalert.txt

Beth,

We are currently using the SAS viewer version 8.2.1.0 and the I-Review tool (mostly for clinicians) for viewing the SDS datasets. Structural checks for compliance with the CDISC specifications have been done. For the annotated waveform data we are using the FDA viewer software.

Do you happen to know the viewer tool that the Division is using? I saw WebSdm and JMP in the past email correspondences, so just like to clarify.

The datasets submitted in the sample submission are real data but they were in pre-final draft, the final converted SDS data (from the clinical databases) will be part of the NDA eCTD submission.

Thanks for your help. Please let me know if you need additional information.

Regards,
Jenny

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

From: Thompson, Elizabeth [mailto:ThompsonE@cder.fda.gov]
Sent: Wednesday, July 20, 2005 1:54 PM
To: 'Jenny Lin (jlin10@tibus.jnj.com)'
Subject: Follow up to voice mail

Jenny,

The Division would like to know what viewer tool you use for CDISC. Also, the datasets that were sent, is this real data?

Call me if you have questions.

Beth

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Tuesday, July 19, 2005 2:48 PM
To: Thompson, Elizabeth
Subject: RE: about TMC114-C133 and TMC114-C202
Importance: High
Attachments: AN_SDS_TMC114-C133_CRF_2.0.zip; AN_SDS_TMC114-C202_CRF_2.0.zip; mmsalert.txt

Beth,

Please find attached blankcrf files for both studies (both in zip files).

In addition, the explanation for having more than one record for some patients is provided below:

The reason why there are some patients with the same USUBJID, but different CRFID's is that these subjects were rescreened per amended inclusion and exclusion criteria (i.e. subjects originally not eligible and defined as screening failures became eligible as per protocol amendments). CDISC defined the USUBJID as 'unique subject identifier within the submission'.

However, as this was causing an issue with defining unique keys, we have recently decided to revise the approach. In the field USUBJID we will enter the TRIAL ID + CRFID, and in the [SC] dataset we have added a record SCTESTCD = SCSUBJID, and the unique subject identifier will be stored in the SCORRES field in this record. This has in the meantime been adapted in the define.pdf document, therefore the issue that the OIM raised should be resolved in the NDA submission.

I hope this has addressed the request.

I intend to also follow up with a submission of these files to the IND, please keep me posted if there are additional requests.

Regards,
Jenny

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

From: Thompson, Elizabeth [mailto:ThompsonE@cder.fda.gov]
Sent: Tuesday, July 19, 2005 10:13 AM
To: Jenny Lin (jlin10@tibus.jnj.com)
Subject: FW: about TMC114-C133 and TMC114-C202

Jenny, see the email below from OIM regarding our CDISC training. There are other discussions still underway.

Beth

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

From: Huang, Zei Pao
Sent: Monday, July 18, 2005 4:56 PM
To: Thompson, Elizabeth
Cc: Weiss, Fran (CDER); Hohlen, Mina
Subject: about TMC114-C133 and TMC114-C202

Beth:

I need you to request sponsor to send in a copy of the Blank_CRF for both studies. This is an item listed on the guidance document (Providing regulatory Submissions in Electronic Format) item 11 on page 45.

Please also ask them why some patients (around 28 patients) has more than one record in DM domain (Demographic domain which is in the DM.XPT dataset). I have included the patients ID in the attached XLS sheet.

<<Dm_patients_have_more_than_one_records.XLS>>

If you have any questions, please contact me.

Zei-Pao

Message

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Monday, July 11, 2005 11:46 AM
To: Thompson, Elizabeth
Subject: RE: CDISC training - IND 62477 (HFD-530)

Beth,

We now have define files available for both trials. They will be submitted (SN 317) via CD-Rom for your receipt by Tuesday AM. Please advise the number of copies you like to receive.

In addition, we wish to provide an example annotated waveform xml file from the ECG trial TMC114-C153, which is intended for OIM to verify whether the xml file complies with the HL7 aECG Implementation Guide and to ensure that there will be no issues when the reviewer is viewing the annotated waveform data with the FDA XML-ECG viewer tool. I will include the example file with this submission as well, it would be great if this can also be addressed at the CDISC training.

Thanks again for your help. Please let me know if you have any questions.

Regards,
Jenny

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

From: Thompson, Elizabeth [mailto:ThompsonE@cder.fda.gov]
Sent: Monday, July 11, 2005 7:39 AM
To: 'Lin, Jenny [TIBUS]'
Subject: RE: CDISC training - IND 62477 (HFD-530)

Jenny,

Go ahead and send the sample for the one study that is available. Thanks.

Beth

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

From: Lin, Jenny [TIBUS] [mailto:JLin10@TIBUS.JNJ.COM]
Sent: Friday, July 08, 2005 4:00 PM
To: 'Thompson, Elizabeth'
Subject: RE: CDISC training - IND 62477 (HFD-530)

Hi Beth,

Per discussion with our data management group, we are aware of the CDISC standards as per FDA study data specifications guidance (version 1.1).

The define files were not yet available as PDF at the time of the sample dataset submission, however they are available now (one for each study). Please let me know if they are needed for the training next week, and I will provide them to you ASAP (you will receive by Tuesday AM the latest).

Regards,

Message

Jenny

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

From: Thompson, Elizabeth [mailto:ThompsonE@cder.fda.gov]
Sent: Friday, July 08, 2005 9:16 AM
To: Jenny Lin (jlin10@tibus.jnj.com)
Subject: FW: CDISC training - IND 62477 (HFD-530)

Jenny, please see the email trail below. If you have questions, please contact me. I am not familiar with CDISC but can find out answers to your questions if you have any. Thanks.

Beth

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

From: Weiss, Fran (CDER)
Sent: Thursday, July 07, 2005 4:24 PM
To: Thompson, Elizabeth
Subject: FW: CDISC training - IND 62477 (HFD-530)

Hi Beth,

We are having trouble loading the Tibotec data. Please see the emails below.

Fran

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

From: Huang, Zei Pao
Sent: Thursday, July 07, 2005 4:21 PM
To: Weiss, Fran (CDER)
Subject: FW: CDISC training - IND 62477 (HFD-530)

Fran:

Please advise the sponsor to check the CDISC site for how to create define.pdf. It is important to follow the rule. It is as important as the datasets itself. The WEBSDM use that file to do the validation check and load the datasets. Thanks!

Zei-Pao

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

From: Huang, Zei Pao
Sent: Thursday, July 07, 2005 4:18 PM
To: Weiss, Fran (CDER)
Subject: RE: CDISC training - IND 62477 (HFD-530)

Fran:

I was about to load the data sets and found the sponsor did not submit define.pdf or define.xml. They sent in one define.doc. Can you ask the PM to request in define.pdf format?

Thanks!

Zei-Pao

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Friday, July 08, 2005 3:39 PM
To: Thompson, Elizabeth
Subject: RE: IND 62,477 : Question related to large datasets in eCTD

Hi Beth,
Thank you very much for the follow up on this question with both OIM and the Micro review team, I will let you know if our team has more questions related to the splitting of datasets.
Regards,
Jenny

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

From: Thompson, Elizabeth [mailto:ThompsonE@cder.fda.gov]
Sent: Friday, July 08, 2005 12:36 PM
To: 'Medart, Frederique [TIBBE]'
Cc: Jenny Lin (jlin10@tibus.jnj.com)
Subject: RE: IND 62,477 : Question related to large datasets in eCTD

Please see responses below.

Response from OIM: Datasets should rarely be larger than 100MB. A 600MB dataset will be problematic for review mainly because of the limitations of JMP (which many medical officers use). A 600MB dataset can be submitted if the division knows it is coming and agrees that they can handle it (usually such a larger dataset must be analyzed with native SAS).

Response from Microbiology Review team: We do not have the experience with a dataset that is this large and we are concerned about our software being able to handle it. The sponsor should create separate datasets for individual trials or we could try the large dataset. In any case, the sponsor is encouraged to send the dataset(s) to us as far ahead as possible given the anticipated number and complexity of the resistance issues.

Please follow the comment from the micro review team (to create separate datasets) if possible. Keep us informed as to how they will come in.

Thanks,

Elizabeth Thompson
Regulatory Project Manager
FDA/CDER/DAVDP
9201 Corporate Blvd/Room N402
Rockville, MD 20850
301-827-2419

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

From: Medart, Frederique [TIBBE] [mailto:fmedart@tibbe.JNJ.com]
Sent: Friday, July 01, 2005 8:56 AM
To: Esub (E-mail); Kenneth EDMUNDS Jr. (E-mail)
Cc: Elizabeth Thompson (E-mail); Lin, Jenny [TIBUS]; Depaepe, Anne [TIBBE]

Subject: IND 62,477 : Question related to large datasets in eCTD

Dear,

Please refer to the TMC114 pre-NDA meeting held with DAVDP on June 7, 2005. The question of acceptability of datasets larger than 100Mb was raised and discussed. The representative from OIM at the meeting indicated that this would be further discussed internally and would get back to us.

For our phase II trials, we have file sizes of the datasets larger than 100Mb. The largest tabulation dataset (virology data) has a size of 629 Mb. Currently, define files have been prepared of these datasets and publishing is ongoing.

May we kindly ask you to let us know at your earliest convenience whether these larger files are acceptable in an eCTD NDA.

Thanks and best regards,

Frédérique Médart

Johnson & Johnson @ Tibotec-Virco

Gen De Wittelaan L11b3 2800 Mechelen - Belgium

Phone: +32 15 285 630

fax: +32 15 444 298

Mobile: +32 473 554 007

e-mail: fmedart@tibbe.jnj.com

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Thursday, July 07, 2005 12:03 AM
To: Thompson, Elizabeth
Subject: DDMAC requirements on EAP ads

Hi Beth,

As discussed earlier today, I would like to clarify with you regarding the requirement for submitting EAP advertising materials to either the DAVDP or DDMAC for review.

During the TMC114 pre-NDA meeting, we received feedback from the Division that advertising materials related to EAP should be submitted to DDMAC for review. However, when such matter was discussed with the DDMAC reviewer for HIV drugs, Lynn Panholzer, PharmD, she advised that EAP ads are not submitted to DDMAC given that TMC114 is under the IND regulation (21 CFR 312.7). Unlike approved drugs, when in IND stage, there is no established submission and review mechanism between DDMAC and the sponsor, therefore DDMAC reviews are only done upon request from the review division.

The IND regulation 21 CFR 312.7 states that a sponsor shall not promote an investigational drug product as safe or effective prior to approval, however it does not intend to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media.

I would like to therefore seek guidance from the Division regarding the requirement. If DAVDP would prefer to review the EAP ads, please advise the submission process and review timeline, as well as the type of advertising materials need to be submitted, e.g. would submission be required for advertisement that highlights scientific information only and makes no product promotional claims.

Thanks in advance for your feedback.

Jenny

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Tuesday, June 14, 2005 7:42 PM
To: Thompson, Elizabeth
Subject: Proprietary name review process

Beth,

I would like to start discussing with you the FDA proprietary name review/approval process.

I understand that currently there is a proprietary name review/approval process within the OND in consultation with other CDER offices/divisions (ODS/DMETS, DDMAC). The request for proprietary name consultation can begin as early as EOPII by submitting to the Review Division via Project Manager, and there is a preliminary review process during IND stage however the final DMETS review occurs within 90 days prior to NDA approval.

The proprietary name development for TMC114 is currently ongoing and in view of the projected timeline of availability I would like to ask for your advice on the following:

Is it acceptable that we submit the request for proprietary name consultation/review to the Division separately after our first rolling submission of September 2005, instead of providing it as part of the September submission?

Any additional information you can provide to further clarify the FDA proprietary name review process would be greatly appreciated!

Jenny

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Monday, May 16, 2005 1:35 PM
To: Thompson, Elizabeth
Subject: Revised proposal submitted SN 275 (f/u to FDA fax of April 7, 200 5)

Dear Beth,

A revised proposal for CTD module 5.3.7 was submitted on May 13, 2005 (SN 275), in follow-up to the FDA fax dated April 7, 2005.

The previous proposal (SN 225) was also updated to reflect the 2 clinical submissions in September and December 2005 for rolling review. The proposal for rolling review was accepted by the Division via FDA fax of April 5, 2005 and details of submission for rolling review were provided in the Pre-NDA briefing package submitted (SN 269).

As discussed, we would like to request a teleconference during the week of May 23- 27, as it would be extremely helpful if the revised proposal can be discussed prior to the Pre-NDA meeting in view of the amount of questions proposed for the meeting. Please let me know your thoughts and also thanks again for proposing to answer some of the questions in the Pre-NDA briefing package prior to the meeting.

In addition, I would like to bring to your attention two Phase I PK studies (TMC114-C117 and TMC114-C136) evaluating other formulations of TMC114, titles provided below:

TMC114-C117: The relative bioavailability of a single intake TMC114, boosted with a low dose of ritonavir with the experimental solid formulations TF042, TF043 and TF044 as compared to the [REDACTED] /PEG [REDACTED] oral solution.

TMC114-C136: The relative bioavailability of a single intake of TMC114, boosted with a low dose of ritonavir with the experimental solid formulations TF051 and TF052 under fasted conditions as compared to the [REDACTED] /PEG [REDACTED] oral solution under fasted conditions.

These studies were not included as part of the Pre-NDA package (Table 1 of Attachment 1) since they evaluated dose forms that will not be further developed. However, we had just reached an internal agreement that study reports (excluding tabulation and analysis datasets) for these two studies will be included as part of the accelerated approval NDA submission for TMC114, with safety data summarized in the Summary of Clinical Safety. Please let me know should the Division disagree with this approach.

Regards,
Jenny

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Thursday, April 28, 2005 4:11 PM
To: Thompson, Elizabeth
Subject: TMC114 Pre-NDA meeting logistics

Dear Beth,

I have two logistic questions regarding the upcoming Pre-NDA meeting:

- 1) Regarding the due date of May 8th for the meeting package: It falls on a Sunday, therefore please advise whether it is acceptable that we submit the total number of copies requested (to the Document control room as well as desk copies to you) on Friday, May 6th which will arrive on early Monday morning of May 9th?
- 2) Tibotec attendees at the meeting: Due to the topics covered at the meeting (clinical, PK, virology, nonclinical, CMC and eCTD), although we are trying to limit the number of representatives from each function, there is still a possibility that the final number of attendees will be up to 16. I am wondering whether that would be an issue? (I remember we had 15 Tibotec attendees last year during the November 3 meeting.)

Thanks in advance for your feedback.

Jenny

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]

Sent: Thursday, April 28, 2005 6:08 PM

To: Thompson, Elizabeth

Subject: RE: fax for SN 225, eCTD format

Dear Beth,

As discussed on Monday this week, we are planning to provide a revised proposal in response to the fax received. There were couple statements in the FDA responses that we would like to clarify first.

- 1) Response 1: "However, if the datasets are going to exceed 100MB, please contact OIM for help." Could you please advise on the method of contact and a contact name?
- 2) Response 5: "Reviewers may ask for traditional format if needed". Please clarify the meaning of "traditional format"?
- 3) Response 7: "Division feels that it is in the best interest of the sponsor to submit a sample of the datasets for each of the domains in order to ensure proper loading and acceptable viewing format for the reviewers". We intend to submit sample datasets in May, however as you know, we currently don't submit documents electronically, therefore would you suggest that these datasets be provided via CD-Rom as the same approach we used for the HIV resistance data?

Thanks!
Jenny

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

From: Thompson, Elizabeth [mailto:ThompsonE@cder.fda.gov]

Sent: Wednesday, April 06, 2005 3:36 PM

To: Jenny Lin (jlin10@tibus.jnj.com)

Subject: Re: fax for SN 225, eCTD format

Jenny,

I am still waiting on final signoff from the medical reviewer who is gone for the day; therefore the fax will not be sent today. I am providing the contents of the fax in this email, but will send the signed fax copy tomorrow. Disregard the first page, it is for our records.

<<040505SN225.doc>>

Beth

Thompson, Elizabeth

From: Lin, Jenny [TIBUS] [JLin10@TIBUS.JNJ.COM]
Sent: Wednesday, April 13, 2005 7:39 PM
To: Thompson, Elizabeth
Subject: RE: fax for SN 225, eCTD format

Hi Beth,

As discussed, I have checked internally with our Regulatory submission group regarding the TOC that was referred to in the first response below.

It was confirmed that for eCTD, there will be no TOC, which means the following sections (normally part of the CTD) will not be included in the eCTD submission:
Section 2.1 of Module 2 "Overall CTD Table of Contents of Modules 2, 3, 4, and 5"
Section 3.1 of Module 3 "Module 3 Table of Contents"
Section 4.1 of Module 4 "Module 4 Table of Contents"
Section 5.1 of Module 5 "Module 5 Table of Contents"

However, there will be Section 5.2 of Module 5 "Tabular Listings of All Clinical Studies", which will list the clinical study reports to be provided in Section 5.3 of Module 5 "Clinical Study Reports". Could you please clarify whether this tabular listing is what the Reviewers referring to?

Please let me know if there is any additional information that I can provide further for the clarification.

Regards,
Jenny

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

From: Thompson, Elizabeth [mailto:ThompsonE@cder.fda.gov]
Sent: Thursday, April 07, 2005 3:49 PM
To: 'Lin, Jenny [TIBUS]'
Subject: RE: fax for SN 225, eCTD format

Jenny, please see the responses to your questions below (they are in red).

Beth

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

From: Lin, Jenny [TIBUS] [mailto:JLin10@TIBUS.JNJ.COM]
Sent: Wednesday, April 06, 2005 5:06 PM
To: 'Thompson, Elizabeth'
Subject: RE: fax for SN 225, eCTD format

Hi Beth,

Thank you very much for the email. I can already distribute this information (without first page) to the team.

I would also like to thank the Microbiology team for providing the outline for Module 5.3.5.4, as the ICH CTD guidance is not very clear regarding the sections on Virology. As a related topic, I know the following could be addressed at the scheduled pre-NDA meeting, however if possible that feedback from the Microbiology Review team could be obtained prior to that, it would be extremely helpful!

As indicated in the rolling review proposal submitted (SN223) and the feedback received, the Division agreed to our proposal of providing a stand alone Microbiology summary (describing in vitro virology and clinical virology data) under Module 2.7 "Clinical Summary" and the virology reports (describing in vitro and clinical virology data) under Module 5. Specifically, these will be Module 2.7.2.4 "Special Studies", and Module 5.3.5.4 "Other Study Reports". There will be no virology data to be included under the nonclinical sections of the NDA (e.g. Modules 2.4 and 4). Is this acceptable?

This is acceptable, but we request that studies be clearly labeled in the Table of Contents.

In addition, when it comes to NDA submission, is there a general terminology used by the Microbiology Review team to describe the virology data (mixture of in vitro virology and clinical virology), eg. Virology, Viral Microbiology, Antiviral Microbiology. I recognize it's a term sponsor would need to decide upon internally however would like to hear if you are aware of any preferred terms used by the Division.

"Virology" is acceptable general terminology.

Thanks again!
Jenny

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

From: Thompson, Elizabeth [mailto:ThompsonE@cder.fda.gov]
Sent: Wednesday, April 06, 2005 3:36 PM
To: Jenny Lin (jlin10@tibus.jnj.com)
Subject: Re: fax for SN 225, eCTD format

Jenny,

I am still waiting on final signoff from the medical reviewer who is gone for the day; therefore the fax will not be sent today. I am providing the contents of the fax in this email, but will send the signed fax copy tomorrow. Disregard the first page, it is for our records.

<<040505SN225.doc>>

Beth