

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-081

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

22-081

NAME OF APPLICANT / NDA HOLDER

Gilead Sciences, 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)

LETAIRIS™

ACTIVE INGREDIENT(S)

Ambrisentan

STRENGTH(S)

5 mg; 10 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.

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

5,703,017

b. Issue Date of Patent

12/30/1997

c. Expiration Date of Patent

12/30/2014

d. Name of Patent Owner

ABBOTT GMBH & CO.KG

Address (of Patent Owner)

MAX-PLANCK-RING 2

City/State

WIESBADEN, Germany

ZIP Code

65025

FAX Number (if available)

Telephone Number

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.)

7575 West 103rd Ave., #102

City/State

Westminster, CO

ZIP Code

80021-5426

FAX Number (if available)

Telephone Number

303-410-6666

E-Mail Address (if available)

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

Yes

No

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

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

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

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 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? 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.)

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
12/13/2006

{See appended electronic signature page}

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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

Michael Gerber, MD, Senior Vice President, Clinical Research

Address

7575 West 103rd Avenue, #102

City/State

Westminster, CO

ZIP Code

80021

Telephone Number

303-464-3988

FAX Number (if available)

303-410-3354

E-Mail Address (if available)

mike.gerber@gilead.com

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Ambrisentan

STRENGTH(S)

5 mg; 10 mg

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1. GENERAL

a. United States Patent Number

5,840,722

b. Issue Date of Patent

11/24/1998

c. Expiration Date of Patent

11/24/2015

d. Name of Patent Owner

ABBOTT GMBH & CO.KG

Address (of Patent Owner)

MAX-PLANCK-RING 2

City/State

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

Yes

No

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

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? 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

4. Method of Use

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

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

4.2 Patent Claim Number (as listed in the patent) 1 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.) Method of inhibiting endothelin receptors by administering ambrisentan to treat pulmonary arterial hypertension in a patient.

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.

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Date Signed
12/13/2006

{See appended electronic signature page}

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NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Michael Gerber, MD, Senior Vice President, Clinical Research

Address

7575 West 103rd Avenue, #102

City/State

Westminster, CO

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Telephone Number

303-464-3988

FAX Number (if available)

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E-Mail Address (if available)

mike.gerber@gilead.com

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Ambrisentan

STRENGTH(S)

5 mg; 10 mg

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1. GENERAL

a. United States Patent Number

5,932,730

b. Issue Date of Patent

8/3/1999

c. Expiration Date of Patent

10/7/2015

d. Name of Patent Owner

ABBOTT GMBH & CO.KG

Address (of Patent Owner)

MAX-PLANCK-RING 2

City/State

WIESBADEN, Germany

ZIP Code

65025

FAX Number (if available)

Telephone Number

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.)

7575 West 103rd Ave., #102

City/State

Westminster, CO

ZIP Code

80021-5426

FAX Number (if available)

Telephone Number

303-410-6666

E-Mail Address (if available)

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

Yes

No

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

Yes

No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

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

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

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

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

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

2.6 Does the patent claim only an intermediate? Yes No

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

3. Drug Product (Composition/Formulation)

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

3.2 Does the patent claim only an intermediate? Yes No

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

4. Method of Use

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

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

4.2 Patent Claim Number (as listed in the patent) 1	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
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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

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NDA Applicant/Holder

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Patent Owner

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Name

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E-Mail Address (if available)

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a. United States Patent Number
7,109,205

b. Issue Date of Patent
9/19/2006

c. Expiration Date of Patent
10/7/2015

d. Name of Patent Owner
ABBOTT GMBH & CO.KG

Address (of Patent Owner)
MAX-PLANCK-RING 2

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

Yes

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

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- 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
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4. Method of Use

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- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 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? 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.)

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
12/13/2006

{See appended electronic signature page}

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

Michael Gerber, MD, Senior Vice President, Clinical Research

Address

7575 West 103rd Avenue, #102

City/State

Westminster, CO

ZIP Code

80021

Telephone Number

303-464-3988

FAX Number (if available)

303-410-3354

E-Mail Address (if available)

mike.gerber@gilead.com

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

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

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EXCLUSIVITY SUMMARY

NDA # 22-081

SUPPL #

HFD # 110

Trade Name Letairis

Generic Name ambrisentan

Applicant Name Gilead Sciences, Inc.

Approval Date, If Known

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:

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d) Did the applicant request exclusivity?

YES NO

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

7

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

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: Dan Brum

Title: RPM

Date: 5/25/07

Name of Office/Division Director signing form: Robert Temple, M.D.

Title: Office Director

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

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/s/

Dan Brum
6/18/2007 12:17:16 PM

Robert Temple
6/22/2007 06:39:41 PM

Claimed Exclusivity

13 December 2006

Pursuant to 21 U.S.C. §§ 355(c)(3)(E)(ii) and 355(j)(5)(F)(ii), and in accordance with 21 C.F.R § 314.50(j), Gilead Sciences, Inc. ("Gilead") claims five years of exclusivity under 21 C.F.R § 314.108(b)(2) for LETAIRIS™ (ambrisentan) Tablets, 5 mg and 10 mg, which contain the active moiety ambrisentan. Gilead asserts that to the best of the company's knowledge and belief, the Food and Drug Administration has not previously approved a drug product under 21 U.S.C. § 355(b) containing ambrisentan.

Gilead also claims, under 21 U.S.C. § 360cc, seven years of orphan drug marketing exclusivity for ambrisentan [LETAIRIS™ (ambrisentan) Tablets, 5 mg and 10 mg] for the treatment of Pulmonary Arterial Hypertension ("PAH"). The Food and Drug Administration's Office of Orphan Products Development designated ambrisentan for the treatment of PAH on July 16, 2004 (Designation Request #04-1836).

{See appended electronic signature page}

Michael Gerber, MD,
Senior Vice President, Clinical Research

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PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-081 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: 12/18/06 PDUFA Goal Date: 6/18/07

HFD-110 Trade and generic names/dosage form: Letairis (ambrisentan) Tablets

Applicant: Gilead Sciences, Inc. Therapeutic Class: _____

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next question.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise capacity, delay clinical worsening

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
 No. Please proceed to the next question.

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 (fill in applicable criteria below):

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

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

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

Reason(s) for deferral:

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

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

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

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

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.

NDA 22-081

Page 3

This page was completed by:

{See appended electronic signature page}

Melissa Robb
Regulatory Health Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Melissa Robb

2/21/2007 10:10:34 AM

Debarment Certification

13 December 2006

To Whom It May Concern,

Gilead Sciences, Inc. 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 [NDA 22-081: LETAIRIS™ (ambrisentan) Tablets, 5 mg and 10 mg].

Sincerely,

{See appended electronic signature page}

Michael Gerber, MD
Senior Vice President, Clinical Research

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**CERTIFICATION: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See the attached list for the investigators for the following studies:	
	AMB-320, AMB-321, AMB-220, AMB-220-E, AMB-222, AMB-320/321-E	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Michael Gerber, MD	TITLE Senior Vice President, Clinical Reserach
FIRM / ORGANIZATION Gilead Sciences, Inc.	
SIGNATURE	DATE 12/13/06

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated

Name of clinical investigator

as a clinical investigator in the submitted study _____

Name of

_____, is submitted in accordance with 21 CFR part 54. The

clinical study

named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Michael Gerber, MD	TITLE Senior Vice President, Clinical Reserach
FIRM / ORGANIZATION Gilead Sciences, Inc.	
SIGNATURE	DATE 12/13/06

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

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Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

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Name of clinical investigator

as a clinical investigator in the submitted study _____

Name of

_____, is submitted in accordance with 21 CFR part 54. The
clinical study
named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
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NAME Michael Gerber, MD	TITLE Senior Vice President, Clinical Research
FIRM / ORGANIZATION Gilead Sciences, Inc.	

SIGNATURE

DATE
12/13/06

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Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

FORM FDA 3455 (4/06)

PSC Graphics (301) 443-1090 EF

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**DISCLOSURE: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated

Name of clinical investigator

as a clinical investigator in the submitted study _____

Name of

_____, is submitted in accordance with 21 CFR part 54. The
clinical study
named individual has participated in financial arrangements or holds financial interests that are
required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME Michael Gerber, MD	TITLE Senior Vice President, Clinical Research
FIRM / ORGANIZATION Gilead Sciences, Inc.	

SIGNATURE

DATE
12/13/06

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Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

FORM FDA 3455 (4/06)

PSC Graphics: (301) 443-1090 EF

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Project Manager Overview
NDA 22-081
Letairis (ambrisentan) Tablets

Overview:

Gilead Sciences, Inc. submitted a New Drug Application (NDA) for Letairis (ambrisentan) 5 and 10 mg Tablets on December 18, 2006. The data submitted is to support an indication for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity, delay clinical worsening, [REDACTED]. The sponsor is proposing once daily dosing. The PDUFA goal date for this application, which received Orphan designation and a Priority review, is June 18, 2007. This application is being reviewed under Subpart H [21 CFR 314.520] with restrictions to assure safe use.

Original NDA Application Reviews

Office Director's Memo

Dr. Robert Temple; June 15, 2007

Dr. Temple's review highlights several items:

- There is little reason not to use the higher approved dose e.g. 10 mg vs. 5 mg except for risk of edema
- Walks were not carried out at trough; addressed in PMCs
- To "delay clinical worsening" is a supported claim
- Until post-marketing experience provides more information, liver monitoring similar to bosentan is needed
- More drug-drug interactions studies are needed; addressed in PMCs

Division Director's Memo

Dr. Norman Stockbridge; May 26, 2007

Dr. Stockbridge recommended "at least approvable, and quite possibly amenable to first-cycle approval" and disagrees with the following aspects of the primary reviews:

- Dr. Stockbridge notes a lack of evidence for a claim of reduced clinical worsening,
- He does not believe a renal impairment study is critical since renal excretion is not a major route of clearance, and
- He does not think a clinical pharmacology study that establishes bioequivalence of the clinical service and to-be-marketed formulations is required.

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Clinical and Statistical Review; May 16, 2007

Dr. Thomas Marciniak (Efficacy)

Dr. Maryann Gordon (Safety)

Dr. Ququan Liu (Statistics)

In their review, Drs. Marciniak, Gordon, and Liu recommend APPROVAL of ambrisentan for the treatment of WHO group 1 pulmonary arterial hypertension (PAH) to improve exercise capacity (subject to acceptable results from a pending audit of a clinical site). From a clinical perspective they also recommend approval to improve time to clinical worsening. They note that ambrisentan is an endothelin receptor antagonist (ERA), similar to the approved drug bosentan, evaluated for the treatment of PAH.

In terms of efficacy, the results of the two adequate and well-controlled studies, AMB-320 and AMB-321, for the common primary endpoint, change from baseline in six minute walk, provide substantial evidence that ambrisentan is effective in improving exercise capacity at least at peak drug levels. The results are reasonably convincing that ambrisentan also improves time to clinical worsening but are less compelling for the other secondary endpoints.

Regarding safety, ambrisentan has an adverse event profile similar to that of the bosentan. There are some unanswered questions regarding the optimal use of ambrisentan (dosing interval, maximal dose, characterization of metabolism) but the favorable results shown in the clinical studies justify approval now with the resolution of these secondary issues post-marketing.

Chemistry Review #2; June XX, 2007

Dr. Haripada Sarker

In his second review, Dr. Sarker recommended APPROVAL from a chemistry, manufacturing and controls standpoint. The office of compliance has provided an acceptable overall recommendation and an agreement has been reached with the company to resolve the remaining CMC issues. The CMC issues in the review cycle #2 include revision of acceptance criteria and control _____ as well as dissolution specification of drug product. Drug product shelf-lives of 24 months have been granted for ambrisentan tablets, 5 mg and 10 mg, packaged in _____ blisters, stored at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F).

Chemistry Review #1; May 16, 2007

Dr. Haripada Sarker

In his review, Dr. Sarker recommended APPROVABLE from a chemistry, manufacturing and controls standpoint. He notes that proposed shelf-lives of 24 months for ambrisentan tablets, 5 mg and 10 mg, packaged in _____ blisters, stored at 25°C (77°F) with excursions permitted to 15-30°C (59-86°F) cannot be granted due to absence of dissolution and relevant test data on stability samples based on proposed

22-081 Letairis (ambrisentan)

dissolution specification. An IR (information request at the end of the review) has been sent to the company, and they have responded, which will be reviewed as review #2.

EES: Pending, as of May 16, 2007

EA: Categorical Exclusion Acceptable, March 30, 2007

Clinical Pharmacology Review; May 7, 2007

Dr. Peter Hinderling (Clinical Pharmacology)

Drs. Yaning Wang & Christoffer Tornoe (Pharmacometrics)

In their review, Drs. Hinderling, Wang, and Tornoe note that the submission is deficient because the authenticity of the formulations used in the bioequivalence study is not assured.

The sponsor was advised of the below identified issues in a briefing that took place April, 27, 2007:

- Demonstrating bioequivalence of the 5 mg and 10 mg commercial and clinical service formulations
- Exploring the interaction potential of ambrisentan in humans when co-administered with drugs known to be strong inhibitors of OATP and P-gp such as cyclosporine A and rifampin. In vitro studies indicate that ambrisentan is a substrate of P-gp and a probable substrate of OATP.
- Exploring the interaction potential of ambrisentan in humans when co-administered with strong inhibitors of CYP3A (e.g. ketoconazole) and CYP 2C19 (e.g. omeprazole). The CYP 450 catalyzed metabolism of ambrisentan is likely to exceed 20% of the administered dose in humans.
- Testing an increased dose range of ambrisentan and determining the adequacy of the 24 h dose interval by comparing q 12 h and q 24 h dose regimens (Reviewer's assessment)
- Exploring the impact of hepatic impairment (Child-Pugh Criteria) on the exposure to ambrisentan
- Exploring of the impact of severe renal impairment on the exposure to ambrisentan
- Validating the ambrisentan assay by inclusion of dilution QC samples

Pharmacology Review; May 1, 2007; May 22, 2007

Dr. Tim Link (P/T)

Dr. Mohammad Rahman (Stats of Carcin. Studies)

In his review, Dr. Link noted the following: The pre-clinical development plan for ambrisentan demonstrates that the compound is a specific and selective antagonist of the endothelin ETA receptor. Ambrisentan was rapidly absorbed with high bioavailability. Distribution, metabolism and excretion were generally comparable among species examined, and consistent with clinical observations.

Safety pharmacology studies did not reveal a large potential for adverse side effects. The observed reductions in blood pressure are consistent with the compound's pharmacological effects.

The demonstrated effects on reproduction are of primary concern. Principally, the teratogenic effects present the greatest area of concern and have no safety margin identified. These effects are recognized for the entire class of these compounds and are adequately addressed in the labeling as well as the marketing plans.

The observed effects on testicular histopathology are more sporadic than those observed regarding teratogenicity. The data are consistent with those of other members of this class of compounds. It is difficult to define a No-Effect dose in this finding. Similarly, the effect appears to reduce fertility in some cases and is, therefore, biologically relevant despite the inconsistency of the observed histopathological observations. A No-Effect dose is easier to apply to the fertility findings, relative to the histopathology. However, the male rat is highly fertile, relative to humans, so any reduction in rat fertility is of concern to this reviewer. These findings, and the potential class effect, will need to be addressed in the proposed labeling. In the label specifically presents studies with significant and positive findings as negative studies.

There appears to be little evidence for hepatic injury potential with ambrisentan, based on animal studies. Histopathological findings were limited to hepatocellular hypertrophy, consistent with minimal enzyme induction, and there was no evidence of necrosis.

The positive findings of human chromosomal aberrations are observed in the context of moderate cell toxicity and at high concentrations relative to plasma concentrations of ambrisentan in patients. Based on a weight-of-evidence approach considering all genetic toxicology studies, there does not appear to be a large potential for genetic toxicity associated with clinical use of ambrisentan. Nevertheless, the findings should be mentioned in the labeling, if only in the interest of full disclosure.

The findings in the rat carcinogenicity study should also be addressed in labeling. The findings of benign fibroadenoma in males at the high dose are only seen in the context of lethal toxicity, and the basal cell lesions at the mid dose are only significant when the high dose is excluded from analysis. The Executive CAC opinion on the rat study was that both findings were at doses above a maximal tolerated dose and do not provide adequate evidence for positive tumorigenicity.

The findings of the nasal epithelium in rodents are of lesser concern to this reviewer. These appear to be a rodent-specific phenomena and would easily be detected in human patients should it occur. It appears that the majority of the toxic signs in rodents are related to the respiratory distress associated with their obligate nasal breathing and the obstructive nature of this toxicity.

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22-081 Letairis (ambrisentan)

DMETS Review

In a review dated April 18, 2007, DMETS stated that they had no objections to the use of the proprietary name, Letairis. DMETS included label and labeling revisions to minimize potential errors with the use of the product. It was also noted that DDMAC finds the proprietary name Letairis acceptable from a promotional perspective.

DSRCS Review

On June 4, 2007, the Division asked the sponsor to modify the formatting/style of the proposed Medication Guide to look like that of Tracleer (bosentan). In a review dated June 12, DSRCS provided comments on the proposed Medication Guide and the sponsor will resubmit the Medication Guide June 14, 2007.

RiskMAP Review; May 17, 2007

OSE provided extensive comments on the sponsor's proposed RiskMAP (Discipline Review letter issued 5/17/07). The sponsor is modifying their RiskMAP procedures and plans to resubmit the proposed materials by May 29, 2007. OSE reviewed the resubmission, provided comments to the sponsor, and performed a final review of the sponsor's resubmitted RiskMAP received June 14, 2007. The final approved RiskMAP will be appended to the Action letter as labeling in addition to the PI and Medication Guide.

DDMAC Review; April 26, 2007

DDMAC provided extensive comments on the sponsor's proposed package insert and MedGuide.

PREA

Application exempt due to orphan drug status.

DSI Report; June 11, 2007

CAPT Sharon Gershon; Dr. Leslie Ball

The final report includes assessments of three inspections, however, only one of the investigations led to the issuance of a 5-item FDA-483 (Dr. Nazzareno Galie, Bologna, ~~—~~). The primary efficacy endpoint – the change from baseline in the 6-minute walk distance at 12 weeks of therapy compared to placebo – did not appear to be compromised. Likewise, the secondary endpoint – Borg Dyspnea Index reading immediately following exercise, WHO Functional Class; and SF-36 Health Survey, or clinical worsening of PAH, as evidenced by death, lung transplantation, hospitalization for PAH, was not compromised by the inspectional findings, and was consistent with data listings. For these reasons, and based on preliminary data DSI received concerning the site, DSI believes that the data at this site is acceptable for the primary and secondary

22-081 Letairis (ambrisentan)

endpoints, and recommends the data be considered acceptable for approval of this NDA. Note that the final EIR is pending as of June 14, 2007.

DSI Audit Findings; May 31, 2007
Dr. Mark Saale

Dr. Saale investigated Dr. Galie in Bologna, Italy and noted several observations that call into question the integrity of the data at that site ["I am not very comfortable with the data at this site. Although I don't think there was a way to unblind the study and determine which subjects received which treatment, there were too many other issues that raised red flags for me"]. We are awaiting a final recommendation from DSI based on observations cited on the FDA-483 and in Dr. Saale's e-mail dated 6/4/07 1:18 p.m. Depending on DSI's recommendation, the Division will recommend at least approvable based on the US study which demonstrated improvement in 6MWT, however, the "delay in clinical worsening" portion of the proposed indication may be without merit.

DSI Audit Findings; April 12, 2007
Dr. Leslie Ball

The inspection, which covered Study AMB-320, appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the NDA.

Action:

An APPROVAL letter has been drafted.

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/s/

Dan Brum
6/27/2007 09:00:47 AM
CSO

Brum, Dan

From: Linnea Tanner [Linnea.Tanner@gilead.com]
Sent: Friday, June 15, 2007 12:16 PM
To: Brum, Dan; Fortney, Russell
Cc: Todd Marshall
Subject: Confirm Additional Language is Acceptable
Attachments: emfinfo.txt

Hi Dan and Russell,

Would you confirm that the following text would be acceptable:

To Authorized Dispenser:

Provide a copy of the Letairis medication guide included in this carton to each patient and at each refill.

Regards,

Linnea

Linnea Tanner, M.S., RAC
Assoc. Dir., Regulatory Affairs
Gilead Sciences
7575 W. 103rd Ave., Suite 102
Westminster, CO 80021-5426
Phone: 303-410-3243 Fax: 303-410-3354
linnea.tanner@gilead.com

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6/15/2007

Brum, Dan

From: Linnea Tanner [Linnea.Tanner@gilead.com]
Sent: Friday, June 15, 2007 2:03 PM
To: Brum, Dan
Cc: Fortney, Russell
Subject: RE: PMCs to which we need agreement by 12:00 p.m. EST Friday
Attachments: emfinfo.txt

Dan,

We agree to the post-approval commitments below.

Regards,
Linnea

Linnea Tanner, M.S., RAC
Assoc. Dir., Regulatory Affairs
Gilead Sciences
7575 W. 103rd Ave., Suite 102
Westminster, CO 80021-5426
Phone: 303-410-3243 Fax: 303-410-3354
linnea.tanner@gilead.com

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From: Brum, Dan [mailto:Dan.Brum@fda.hhs.gov]
Sent: Friday, June 15, 2007 11:22 AM
To: Linnea Tanner
Subject: RE: PMCs to which we need agreement by 12:00 p.m. EST Friday

Linnea,

We need to come to an agreement on the following PMC timelines, please let me know your thoughts ASAP.

1. Gilead agrees to conduct a study examining the effects of LETAIRIS on 6-minute walk distance at trough plasma concentrations, and further agrees to reach agreement on an appropriate study design with the Division.
Protocol Submission: by 01/2008
Study Start: by 08/2008
Final Report Submission: by 12/2009
2. Gilead agrees to submit the results of the Phase 1 ketoconazole drug interaction study that has

6/15/2007

already been completed.

Final Report Submission: by 10/2007

3. Gilead agrees to a post-approval commitment to explore the interaction potential of strong inhibitors of CYP2C19 (e.g. omeprazole) on ambrisentan pharmacokinetics in humans. Gilead further agrees to explore the interaction potential of cyclosporine A (strong inhibitor of OATP and P-gp) and rifampin (inhibitor of OATP and inducer of P-gp, CYPs 3A and 2C19) on ambrisentan pharmacokinetics in humans. This commitment might also be addressed by analysis of existing data.

Protocol Submission: by 01/2008

Study Start: by 06/2008

Final Report Submission: by 12/2008

4. With regard to the RiskMAP, Gilead agrees to submit to the FDA by July 15, 2007, the following documents:
 - i. The pregnancy exposure root cause analysis plan including the questionnaire that will be used in the analysis plan;
 - ii. The patient and prescriber knowledge, attitude, and behavior survey tools for the RiskMAP evaluation plan;
 - iii. The Pharmacy Standard Operating Procedures (SOPs);and
 - iv. The Pharmacy Audit Plan.

Thanks,
Dan

From: Linnea Tanner [mailto:Linnea.Tanner@gilead.com]
Sent: Thursday, June 14, 2007 9:15 PM
To: Brum, Dan
Subject: RE: PMCs to which we need agreement by 12:00 p.m. EST Friday

Dan,

Attached is our response to the FDA recommended post-approval commitments below. If the Division believes that there needs to be further discussion to finalize the language for these post-approval commitments, we would be open to a teleconference with the Division tomorrow morning. I will be in the office very early tomorrow (7:00 a.m. EDT) and can coordinate a teleconference with our team members very rapidly, preferably between 9:30 – 11:30 a.m. EDT. If you cannot reach me at my work phone number, feel free to call me on my cell phone at 720.201.1197.

Regards,
Linnea

Linnea Tanner, M.S., RAC
Assoc. Dir., Regulatory Affairs
Gilead Sciences
7575 W. 103rd Ave., Suite 102
Westminster, CO 80021-5426
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6/15/2007

Memo to File

To: File, NDA 22-081 Ambrisentan (Letairis, Gilead)
From: Robert Temple, MD
Date: June 15, 2007
Subject: Office Director's Summary; written on 6/15/07

Ambrisentan is an endothelin receptor antagonist (ERA) intended for the treatment of pulmonary artery hypertension (PAH). It is pharmacologically similar to bosentan, approved for the same use, and it needs a risk management program similar to that of bosentan because it is a clear animal teratogen and it is critical to prevent exposure of pregnant women. PAH is a predominately female disease and affects women of child-bearing potential. The ERAs also, as a class, have been hepatotoxic and we do not yet have enough information to know that ambrisentan is different in this respect, although there are intriguing possibilities (see below).

All reviewers support approval; the few areas of modest disagreement will be described below

1. Effectiveness

As described in the review by Dr. Marciniak and in Dr. Stockbridge's Divisional Memorandum, there are two well-controlled studies (320, 321, Aries 1 and 2), conducted world-wide, with reasonable representation in the US and Western Europe. Both studies were randomized, fixed dose, dose-response studies (the optimal dose-finding design according to ICH E4), and both showed clear dose-related effects on 6 minute walk, the usual test for such drugs.

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drug vs 3 or 4 or 2.5 and 5 mg. Dr. Stockbridge is concerned about inconsistent results but, by Dr. Marciniak's classification (7 placebo vs 2 drug in 320; 13 placebo vs 4 drug in 321) the results are proportionately quite similar. In any event I find the two studies supportive and one is statistically quite strong. The claim is included in the approved labeling. It is "indicated....to improve exercise capacity and delay clinical worsening."

Effects on WHO class and SF 36 (a QOL scale) were directionally favorable in both studies but statistically significant in only one; improvement on the Borg dyspnea scale was significant in both studies, but, as a secondary endpoint, this endpoint would not be reached because earlier in sequence endpoints were not significant.

II. Safety

A. Overall safety; hepatotoxicity

Safety evaluation found nothing of major concern, other than the expected strong animal evidence of teratogenicity characteristic of the ERA class. There was a mean 1g/100 ml fall in Hg, not really explained, a roughly 5mm Hg fall in blood pressure. Peripheral edema was more common on drug than placebo (17% vs 11%) but mainly in the over 65 population (29% vs 4% on placebo); in the under 65 patients, rates were similar on drug and placebo (13%-14%). Treatment DC for ADEs was similar in drug and placebo (2%) as were serious ADE; (5-7%).

In the controlled 12 week trials AT levels $> 3 \times \text{ULN}$ occurred at 0.8% on drug and 2.3% on placebo; values $> 8 \times \text{ULN}$ were 0.2% on drug and 0% on placebo. The 1 year rate of values $> 3 \times \text{ULN}$ was 3% on drug (no placebo data). There was one case of AT elevation accompanied by elevated bilirubin to $> 2 \times \text{ULN}$ and other cases in which AT elevation seemed related to ambrisentan. It remains to be seen how ambrisentan's hepatotoxic potential compares with bosentan's. One encouraging finding exists, however, and is noted in labeling [section 14.3: Use in Patients with Prior endothelin Receptor Antagonist (ERA) Related Liver Function Abnormalities.] Thirty-six patients who had D/C'd ERA (mainly bosentan) because of AT elevations $> 3 \times \text{ULN}$ (but 36% $> 5 \times \text{ULN}$ and 9 patients $> 8 \times \text{ULN}$) were given ambrisentan. Two of the 36 dropped out early, but of the 34, one had AT elevation on 5 mg that resolved on 2.5 mg and that did not recur with later dosing to 10 mg, while the rest had no elevation at all. Eight of the 36 patients had been rechallenged with bosentan or the investigational drug that caused AT elevation, and all 8 had had recurrent AT abnormalities. As labeling notes, without systematic rechallenge with the initial treatment we cannot know how ambrisentan and the original treatment compare, but these are very promising results. At present, and until post-marketing experience gives further information, we have

June 15, 2007

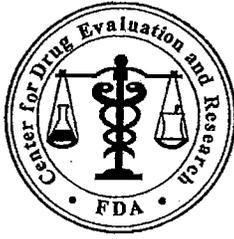
concluded that liver monitoring similar to what is done for bosentan is needed, but the full picture remains to be determined.

B. Drug-drug interactions

Ambrisentan does not interact with coumadin or sildenafil, two drugs commonly needed in PAH, which is an advance over bosentan. More interaction data are needed, however.

Ambrisentan is metabolized by CYP450 3A4 and 2C19 and other enzymes and carriers may be involved in its clearance. The sponsor has agreed to explore the interaction potential of strong inhibitors of CYP2C19 as well as the interaction potential of cyclosporine, a strong inhibitor of OATP and P-gp, and rifampin, an inducer of P-gp, and inhibitors and inducers of CYP3A4 and 2C19.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: June 12, 2007

To: Norman Stockbridge, M.D., Director
Division of Cardiovascular and Renal Products

Thru: Toni Piazza-Hepp, Pharm. D., Deputy Director
Division of Surveillance, Research and Communication Support

From: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist
Division of Surveillance, Research and Communication Support

Subject: Review of Patient Labeling (Medication Guide) for Letairis

Drug Name(s): Letairis (ambrisentan) 5 and 10 mg film-coated tablets

ApplicationType/Number: NDA #22-081

Applicant/sponsor: Gilead Sciences, Inc.

OSE RCM #: 2007-236

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INTRODUCTION

Gilead Sciences, Inc. submitted NDA #22-081 on December 13, 2006 for Letairis (ambrisentan) 5 and 10 mg tablets for the proposed indication: "...for the treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise capacity, delay clinical worsening ~~_____~~ ~~_____~~." The application has been classified as a priority review. Letairis (ambrisentan) is an Endothelin Receptor Antagonist. The need for a Medication Guide (MG) for this product is based on the identified serious and significant health concerns of teratogenicity and hepatotoxicity.

The Division of Cardiovascular and Renal Products has requested that the Division of Surveillance, Research and Communication Support review the sponsor's proposed draft MG submitted with the NDA.

MATERIAL REVIEWED

The sponsor submitted patient labeling in the form of a draft MG, appended to the proposed Professional Information as required in PLR format. Based on the identified safety issues, we requested that the sponsor revise the draft MG to include language similar to the language in the bosentan MG relating to the risks of being pregnant or becoming pregnant while taking Letairis (ambrisentan), as well as the risk of liver injury with Letairis (ambrisentan). For our review we used the review division's most current draft of the Professional Information and Medication Guide dated June 11, 2007 which includes the sponsor's revisions to the Professional Information and Medication Guide, dated June 7, 2007.

DISCUSSION

During the safety review of this application, it was concluded that "The safety issues associated with the use of ambrisentan appear to be not unlike those associated with the use of bosentan. The safety labeling for ambrisentan, therefore, should be similar to the labeling for bosentan." A RiskMap has been developed by the sponsor and reviewed by the OSE Ambrisentan RiskMap Review Team. A MG is part of the RiskMap to insure that patients are appropriately informed of the benefits and risks associated with Letairis (ambrisentan).

Comments to the review division are ***bolded, underlined and italicized*** in the attached document. We are providing to the review division a marked-up and clean copy of the revised PPI. We recommend using the clean copy as the working document.

CONCLUSIONS AND RECOMMENDATIONS

- See the attached document for our suggested revisions to the sponsor's revised draft MG. The sponsor's revised draft MG has a Flesch Kincaid Grade Level of 6.6 and a Flesch Reading Ease Score of 68.4. To enhance comprehension, patient materials should be written at a 6th to 8th grade reading level. The reading scores submitted by the sponsor are acceptable. We have reformatted the MG to a 2 page document for patient ease of use. We have made the MG consistent with the Professional Information, simplified the language where possible, removed unnecessary information, and put it in the format specified for Medication Guides in 21 CFR 208.20. These recommended changes are

consistent with current research to improve risk communication to a broad range of audiences of varying educational backgrounds including those with lower levels of literacy.

- Medication Guides should always be consistent with the prescribing information. All future relevant changes to the Professional Information should also be reflected in the MG.
- A statement should be added to section 17 Patient Counseling Information in the PI instructing doctors to review the Medication Guide with every patient as required by the RiskMap as part of the enrollment of prescribers, with written self-attestation.
- The sponsor should use the verbatim language from the Medication Guide to convey safety messages in the patient educational brochure that they are developing.
- The sponsor must follow the Medication Guide regulations and add the appropriate language to the label of each container or package according to 21 CFR 208.24 (d).

Please let us know if you have any questions.

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/s/

Sharon Mills
6/12/2007 04:41:06 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
6/12/2007 07:19:53 PM
DRUG SAFETY OFFICE REVIEWER



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: 6/12/2007
To: Norman Stockbridge, M.D., Ph.D., Director
Division of Cardiovascular and Renal Products (DCRP),
HFD-110
Thru: Ellis Unger, M.D., Acting Deputy Director
Office of Surveillance and Epidemiology
From: Ambrisentan RiskMAP Review Team
Subject: Review of Proposed RiskMAP
Drug Name(s): Ambrisentan (Letairis) Tablets
Application Type/Number: 22- 081
Applicant/sponsor: Gilead Sciences
OSE RCM #: 2007-265
Title OSE Safety Review

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EXECUTIVE SUMMARY

This is a review of the Sponsor's Risk Minimization Action Plan (RiskMAP) for ambrisentan (Letairis), a selective endothelin A receptor antagonist with a proposed indication to treat pulmonary arterial hypertension. The RiskMAP was proposed to minimize the risk of teratogenicity. The Sponsor has proposed a program similar to the Tracleer Access Program (TAP) for bosentan, another endothelin antagonist. The Sponsor proposes the use of performance-linked access, registration, attestation, and education of prescribers and patients, a limitation to a 30-day supply of ambrisentan with each refill, and a closed distribution system via Specialty Pharmacies to dispense ambrisentan.

The stated goals for the Letairis RiskMAP are:

- To promote informed benefit-risk decisions regarding the use of Letairis
- To minimize the risk of fetal exposure and adverse fetal outcomes in female patients of childbearing potential prescribed Letairis
 - Women who are pregnant must not be prescribed Letairis
 - Women taking Letairis must not become pregnant

We agree with the goals, tools, and structure of the RiskMAP. The Sponsor has responded to our previous comments by incorporating most of our suggestions into the RiskMAP. Issues remaining to be resolved to allow final approval of the RiskMAP include incorporation of LFT measurements into the RiskMAP, expedited reporting of cases of liver injury, agreement on the frequency of patient registration, submission of the pregnancy follow-up plan, development and submission of pharmacy SOPs, submission of the survey instruments, and minor wording changes for some of the RiskMAP materials.

1 BACKGROUND

1.1 INTRODUCTION

Ambrisentan (Letairis) is a selective endothelin A receptor antagonist with a proposed indication to treat pulmonary arterial hypertension (PAH) WHO Group I to improve exercise capacity, delay clinical worsening, and improve symptoms.

The Sponsor for Letairis, Gilead Sciences, has submitted a RiskMAP proposal to address teratogenicity. The Sponsor proposes the use of education of prescribers and patients, registration and attestation of prescribers and patients, a limitation to a 30-day supply of ambrisentan with each refill, and a closed distribution system for dispensing Letairis.

In addition to teratogenicity, the OND safety review identified hepatotoxicity as a serious safety concern. Dr. MaryAnn Gordon, the medical safety reviewer for the application, assessed the hepatotoxicity risk of ambrisentan to be similar to bosentan, a product for which hepatotoxicity is addressed in the product's RiskMAP.

1.2 REGULATORY HISTORY

To date, ambrisentan is an investigational product not approved for marketing in any jurisdiction. The Marketing Authorisation Application (MAA) for ambrisentan for the treatment of pulmonary arterial hypertension (PAH) was validated by the European Medicines Agency (EMA) in March 2007 following a review by the Committee for Medicinal Products for Human Use (CHMP). The next step for EMA authorization is formal review of the application by the CHMP.

Myogen, the previous sponsor for ambrisentan, requested orphan status from the FDA for ambrisentan for the treatment of PAH. The FDA granted orphan status in August 2004. Gilead Sciences acquired Myogen in 2006. The acquisition included in-process research and development for ambrisentan, a product for which phase III studies had been completed prior to the acquisition. Gilead submitted an NDA for ambrisentan in December 2006. In February 2007 the FDA granted the application priority review status with a PDUFA date of June 18, 2007.

2 METHODS AND MATERIALS

2.1 DATA AND INFORMATION SOURCES

The following documents were reviewed:

- Gilead Sciences Letairis Risk Management Plan, submitted to the NDA 1/12/2007, and 5/30/2007, available in EDR.
- Gilead Sciences amended Letairis Risk Management Plan, submitted to the NDA 5/30/2007, available in EDR.
- Letairis draft labeling, submitted to the NDA 12/18/2006, available in EDR.
- Maryann Gordon, MD; NDA 022081, Reviewing Division Medical Officer Safety Review, 4/30/2007. Available in DFS.
- Peter H. Hinderling, MD, Yaning Wang, Ph.D., Christoffer Tornøe, Ph.D., FDA Clinical Pharmacology Review, 5/7/07. Available in DFS.
- Letairis RiskMAP Educational and Enrollment materials, submitted to the NDA 1/12/2007 and 5/30/2007, available in EDR:
 - LEAP Prescriber Brochure
 - LEAP Patient Enrollment Guide (*For Starting Therapy with Letairis*)
 - LEAP Patient Education Guide (*Letairis Therapy: What You need to Know*)
 - LEAP Prescriber Enrollment Form
 - LEAP Patient Enrollment Form
 - LEAP Prescriber Enrollment and Agreement Form
 - LEAP Patient Enrollment and Consent Form

2.2 ANALYSIS TECHNIQUES

The Sponsor's submissions were reviewed for consistency with risk minimization measures in place for products with similar safety risks, especially bosentan, a member of the same class with a similar safety profile, for responsiveness to FDA comments on previous submissions, and for conformance with the concepts in the FDA Guidance for Industry, *Development and Use of Risk Minimization Action Plans (RiskMAPs)*.¹

3 RESULTS OF REVIEW

¹ Available at URL www.fda.gov/cder/guidance/6358fnl.pdf

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Mary Dempsey
6/12/2007 10:01:32 AM
DRUG SAFETY OFFICE REVIEWER

Ellis Unger
6/12/2007 02:44:33 PM
MEDICAL OFFICER

I. BACKGROUND:

Ambrisentan is an oral, endothelin receptor antagonist (ERA), intended to treat pulmonary arterial hypertension (PAH), a serious and life-threatening disease of the pulmonary vasculature. The proposed indication is the treatment of PAH to improve exercise capacity, delay clinical worsening, ~~_____~~

The progression of PAH is rapid without treatment, with a median survival time of 2.8 years, and survival rates of 68%, 48% and 34% at 1, 3, and 5 years, respectively. To date 5 products are approved in the US for treatment of PAH. These include prostacycline and prostacycline derivatives (epoprostenol, treprostinil, iloprost), a phosphodiesterase type 5 inhibitor (sildenafil), and a dual-selective ERA (bosentan). While current treatment options have substantially improved PAH symptoms, and in some case prolonged survival, there is still no cure. Ambrisentan has been designated an orphan drug (July 16, 2004), and was granted fast tract designation by FDA on 15 Feb 2006.

The ambrisentan clinical program consists of two pivotal randomized, placebo-controlled Phase 3 studies (AMB-320 and AMB-321). These two studies are identical except for the doses of ambrisentan and the geographic locations of investigative sites. The doses selected for AMB- 320 study are 5.0 and 10.0 mg per day, while Study AMB-321 is evaluating doses of 2.5 and 5.0 mg per day. The primary objective of this study is to determine the effect of ambrisentan on exercise capacity in subjects with PAH. Subjects must have a documented mean pulmonary arterial pressure (PAP) \geq 25 mmHg, pulmonary vascular resistance (PVR) $>$ 3 mmHg/L/min, and pulmonary capillary wedge pressure (PCWP) or left ventricle end diastolic pressure (LVEDP) of $<$ 15 mmHg.

These sites were selected because they enrolled large numbers of study subjects, and had high treatment responders.

II. RESULTS :

Clinical Investigator	Number of Subjects	Inspection Dates	Protocol No.	Field Classification	EIR Receipt Date
Site #126 Ronald J Oudiz Harbor-UCLA Medical Center 1124 W Carson St., Box 405 Torrance, CA 90502	13	February 26 – March 2, 2007	320	NAI	3/26/2007
Site #132 Fernando Torres Southwest Pulmonary Associates Suite 711 5939 Harry Hines Blvd Dallas, TX 75235	14	March 1 – 6, 2007	320	NAI	3/14/2007
Nazzareno Galie Insitute of Cardiology University of Bologna Via Massarenti, 9 40138 Bologna, Italy	23	May 24-May 29, 2007	321	OAI	pending

NAI = No deviation from regulations. Data acceptable
 VAI = Minor deviations(s) from regulations. Data acceptable
 VAIr= Deviation(s) form regulations, response requested. Data acceptable

OAI = Significant deviations for regulations. Data unreliable
Pending = Inspection not completed

A. Protocol #: #AMB-320 entitled "A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy Study of Ambrisentan in Subjects with Pulmonary Arterial Hypertension", sponsored by Gilead Sciences.

1. Dr. Fernando Torres, M.D., Southwest Pulmonary Associates, 5939 Harry Hines Blvd. Dallas, TX 75235

a. What was inspected? The inspection covered Study AMB-320. Dr. Torres screened 21 and enrolled 14 subjects between 3/22/2004 and 11/03/2005. Subject data was reviewed for 10 of the 14 subjects. Each subject chart was reviewed for documentation of informed consent; inclusion/exclusion criteria; adherence to protocol requirement for testing, evaluation and dosing. Efficacy data - including six minute walk test results, Borg dyspnea index and WHO functional classification - was audited, and found accurate. Adverse events, including all SAEs, were audited and found accurate. Test article accountability records were reviewed and found accurate. The inspection did not disclose deviations from federal regulations or study protocol.

b. Limitations: There were no limitations to this inspection.

c. General Observations: No FDA-483 was issued.

d. Assessment of Data Integrity: No Form FDA-483 was issued; the data at this site appear acceptable in support of safety and the efficacy endpoint for this NDA.

2. Dr. Ronald J. Oudiz, M.D. Harbor-UCLA Medical Center, Torrance, California 90502

a. What was inspected: Thirteen subjects were randomized and completed the study. Thirteen subject records were audited, for inclusion/exclusion criteria; protocol adherence; study drug compliance. Drug accountability was reviewed. Source documents were corroborated against case report forms, and data listings were corroborated with source records. 100% of the signed and dated consent forms were verified and there were no significant problems. The baseline and endpoint 6MWT results correlated with the data listings provided from the sponsor. All AEs were appropriately documented and correlated with the progress notes. Most all subjects met inclusion/exclusion criteria for enrollment.

b. Limitations: There were no limitations to this inspection.

c. General Observations: There was some brief discussions with management regarding: 1) Dr. Oudiz has an active research practice and there were no SOPs relating to research practice policies and procedures ; 2) there was no documented protocol training for Dr. Budoff, the sub-investigator for this study.

d. Assessment of Data Integrity: No Form-483 was issued at this site. No major deficiencies were noted, and the data appear acceptable in support of the safety and efficacy endpoint for this

NDA.

3. Nazzareno Galie, Insitute of Cardiology, University of Bologna, Via Massarenti, 9
40138 Bologna, Italy

a. What was inspected? 13 of 24 subject records were comprehensively reviewed, including informed consent documents for all subjects; all adverse events were audited. A 5-observational FDA-483 was issued to Dr. Galie for the following deficiencies: 1) failing to report to the IRB all adverse events involving risk to human subjects – Subject #207-002 was hospitalized for pneumonia and right heart failure on April 14, 2004, and the SAE report was not filled out until January 20, 2006; 2) failure to maintain adequate records concerning data pertinent to the investigation – some information in the clinic notes is crossed out obscuring the original data, and there is no indication who made the correction; mistakes are not crossed out, initialed or dated; white out was used to make corrections on the source records; entries on clinic notes were dated but not signed; dated entries did not always include a year, making it unclear when entries were made; 3) not all changes in research activity was approved by the IRB – Subject #207-014 had signed a 2nd version of an IC document on October 28, 2004, even though this version was not approved by the IRB until November 30, 2004 – one month later; 4) failure to obtain proper informed consent. For example, Subject #207-013 failed to sign an updated ICF during a visit; 5) investigation was not conducted according to plan – Subject #207-013 had no chest x-ray at screening, as per protocol requirements.

b. Limitations to the inspection: The Clinical Inspection Summary is based on discussions and notes from the field investigator; the EIR is pending. A translator was provided during this inspection.

c. General Observations: There were many issues that raised red flags to the field investigator at this site - a 5-observational FDA-483 was issued to Dr. Galie, relating to the following: 1) failure to report promptly to the IRB all unanticipated problems involving risks – subject #207-002 had an initial SAE on [REDACTED] and was hospitalized for pneumonia and right heart failure; this SAE report was not filled out until January 20, 2006, almost 2 years later; 2) failure to prepare or maintain case histories with respect to observations and data pertinent to the investigation – specifically, for subject #207-002, concomitant medication KCl-Retard is listed on the CRF for visit #3, however it is listed in the source records for this date and lined out; Subjects #207-020 and #207-010 had recordings for one of their 6-minute walk tests with 2 different dates (March 16 and March 17, 2004) and these same discrepancies existed with regards to dates on the case report forms; subject #207-022 had concomitant medications entered directly onto the case report forms and not recorded into the source records for the first 2 visits; subject #207-024 had vital signs at the screening visit that were entered directly onto the case report form and not into source records; 3) not all changes in research activity were approved by an IRB: Subject 207-014 signed 2 versions of the informed consent, even though one version was not IRB approved until a month later; 4) failure to obtain informed consent in accordance with 21 CFR Part 50: Subject #207-013 did not sign a second version of the ICF until Janaury 2005, even though the IRB approved it on November 30, 2004, and the subject attended study visit 4 on December 6, 2004; and 5) the investigational plan was not followed. Specifically Subject #207-013 had no chest x-ray at screening, as per protocol.

d. **Integrity of data:** A 5-item FDA-483 was issued at this site. The primary efficacy endpoint – the change from baseline in the 6-minute walk distance at 12 weeks of therapy compared to placebo – did not appear to be compromised. Likewise, the secondary endpoint –Borg Dyspnea Index reading immediately following exercise, WHO Functional Class; and SF-36 Health Survey, or clinical worsening of PAH, as evidenced by death, lung transplantation, hospitalization for PAH, was not compromised by the inspectional findings, and was consistent with data listings.

For these reasons, and based on preliminary data DSI received concerning the site, DSI recommends that the data at this site is acceptable for primary and secondary endpoint, and recommends the data be considered acceptable for approval of this NDA.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Note: Observations noted above are based on the Form FDA 483, preliminary EIR and communications from field investigator. An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

Follow-up action: none needed.

Sharon K. Gershon, Pharm.D.
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Sharon Gershon
6/12/2007 12:29:10 PM
CSO

Leslie Ball
6/12/2007 06:08:48 PM
MEDICAL OFFICER

Meeting Minutes

Date: May 25, 2007
Application: NDA 22-081
Drug: Letairis (ambrisentan)
Sponsor: Gilead Sciences, Inc.
Purpose: To discuss sponsor's proposed plan to study the interdosing interval
Meeting Type: C

FDA Attendees:

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products
Tom Marciniak, M.D.	Medical Team Leader
Mary Dempsey	Risk Management Program Coordinator, OSE
Joyce Weaver, Pharm.D., BCPS	Senior Drug Risk Management Analyst, OSE
Russell Fortney	Regulatory Health Project Manager
Dan Brum, Pharm.D., MBA	Regulatory Health Project Manager

*OSE = Office of Surveillance and Epidemiology

Gilead Attendees:

Norbert Bischofberger, Ph.D.	Executive Vice President, R & D and Chief Scientific Officer
Michael Gerber, M.D.	Sr. Vice President, Clinical Research
Tobias Peschel, M.D., Ph.D.	Vice President, Drug Safety and Public Health
Christopher Dufton, Ph.D.	Associate Director, Clinical Science
Rebecca Spence, Ph.D.	Sr. Clinical Research Scientist
Brian Wiens, Ph.D.	Director, Biometrics
Darrin Despain,	Manager, Biostatistics
Robert Roden, MS, MBA	Director, Project Management
Jennifer Stewart	Director, Professional Services
David Pizzuti, M.D.	Vice President, Regulatory Affairs
Linnea Tanner	Associate Director, Regulatory Affairs
Martine Krause	Director, Regulatory Affairs
Joyce Acbay	Associate Director, Regulatory Affairs

Background:

The purpose of this follow-up teleconference was to discuss the sponsor's updated proposal to assess the effect of maximum (peak) and minimum (trough) ambrisentan plasma concentrations on exercise capacity, as measured by 6-minute walk distance (6MWD). The proposal was previously discussed during a teleconference on April 16, 2007.

The preliminary response to the sponsor's submitted question was provided to the sponsor prior to the meeting (see Question 5). That response is copied below, and is followed by the discussion that took place during the meeting. The sponsor submitted some additional questions related to the proposed RiskMAP one hour prior to the teleconference (see Questions 1-4).

Meeting:

After introductions, the Agency made the following comment:

Measurement of LFTs and bilirubin (in a timeframe consistent with labeling) should be incorporated into the RiskMAP. We would expect testing for hepatotoxicity to be incorporated into all aspects of the RiskMAP (performance-linked access, attestations, education, RiskMAP evaluation, reporting to the Agency, etc). The sponsor should submit both a red-line version and clean version of their revised RiskMAP proposal.

The following questions from the sponsor were addressed:

1. Will the Agency be providing Gilead final comments on the RiskMAP and educational materials in conjunction with the forthcoming label review comments?
2. We acknowledge OSE and DDMAC's efforts in providing us initial comments on the RiskMAP. Because these RiskMAP materials (Prescriber Brochure, Patient Starting Therapy Brochure, Patient Education Guide, Prescriber Enrollment Form, and Patient Enrollment Form) need to be finalized and approved by OSE and DDMAC in order to make the product available to patients on the PDUFA date, we wish to confirm that OSE and the Review Division will plan to work with us (Gilead) to finalize the material during final label negotiations prior to the PDUFA date?

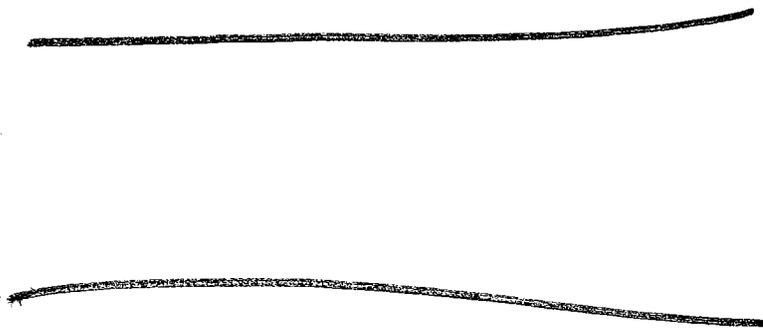
Discussion during meeting: Review of these materials is a priority but we cannot provide final comments on the proposed RiskMAP until labeling is finalized.

3. What suggestions does the Agency have that would facilitate the review of the final RiskMAP materials?

Discussion during meeting: We will review the revised RiskMAP materials and determine if a teleconference may be of value.

4. In the RiskMAP, under FDA Comment #10, the Agency asked the sponsor to submit survey instruments of prescribing physicians and patients prior to implementation. Would the Agency be amenable to submitting the survey instruments as a post-marketing commitment?

Discussion during meeting: Perhaps, but we will need to discuss the issue internally. Regardless, the sponsor should notify the Agency of the intended date of implementation (e.g., via email).





Minutes preparation: *{See appended electronic signature page}*
Dan Brum, Pharm.D.

Concurrence, Chair: *{See appended electronic signature page}*
Norman Stockbridge, M.D., Ph.D.

Drafted-5/30/07; Final-05/31/07

Reviewed: M. Dempsey – 05/31/07
T. Marciniak - 05/31/07
N.Stockbridge- 05/31/07

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Dan Brum
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Norman Stockbridge
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Preliminary Responses

Application: NDA 22-081
Sponsor: Gilead Sciences, Inc.
Drug: Letairis (ambrisentan) Tablets
Meeting Type: C
Purpose of Meeting: Guidance
Date of Internal Meeting: May 22, 2007
Date of Meeting with Sponsor: May 25, 2007
Briefing Package Received: May 15, 2007

List of Internal Meeting Participants:

Norman Stockbridge, M.D., Ph.D.	Director, Division of Cardiovascular and Renal Products
Thomas Marciniak, M.D.	Medical Team Leader
Maryann Gordon, M.D.	Medical Officer
Patrick Marroum, Ph.D.	Clinical Pharmacology Team Leader
Haripada Sarker, Ph.D.	Chemist
Cherry Liu, Ph.D.	Statistician
Edward Fromm	Chief Project Manager
Dan Brum	Regulatory Health Project Manager
Russell Fortney	Regulatory Health Project Manager

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for May 25, 2007, between Gilead Sciences and the Division of Cardiovascular and Renal Products. This material is shared to promote a collaborative and successful discussion at the meeting. If there is anything in it that you do not understand or with which you do not agree, we very much want you to communicate such questions and disagreements. The minutes of the meeting will reflect the discussion that takes place during the meeting and are not expected to be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the RPM), but this is advisable only if the issues involved are quite narrow. It is not our intent to have our preliminary responses serve as a substitute for the meeting. It is important to remember that some meetings, particularly milestone meetings, are valuable even if pre-meeting communications seem to have answered the principal questions. It is our experience that the discussion at meetings often raises important new issues. Please note that if there are any major changes to the purpose of the meeting (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting, but we will be glad to discuss them to the extent possible. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

v:

Signature, Chair: *{See appended electronic signature page}*
Norman Stockbridge, M.D., Ph.D.

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Norman Stockbridge
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 Deliberative Process

Withheld Track Number: Administrative-



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-081

INFORMATION REQUEST LETTER

Gilead Sciences, Inc.
Attention: Todd Marshall, RAC
Associate Director, Regulatory Affairs
7575 West 103rd Avenue, Suite #102
Westminster, CO 80021

Dear Mr. Marshall:

Please refer to your December 13, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Letairis (ambrisantan) tablet 5 and 10 mg.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA:

1.

3.

4. Justify your proposed acceptance criterion of NMT ~~_____~~ for drug substance based on the lots used during clinical studies and commercial batches showing acceptable bioequivalence and in vitro dissolution properties.
5. Clarify what stability data for dissolution was obtained using the proposed dissolution method and media (pH = 5.0). Please provide stability data from your on-going stability studies using the proposed dissolution method.
6. Justify your proposed dissolution acceptance criterion of Q ~~_____~~ based on the dissolution of clinical, commercial and stability batches including shelf-life stability data for the stability batches.
7. The first three commercial batches of the drug substance and the drug product in the post-approval stability commitment should also be placed under accelerated storage conditions along with the long-term storage conditions. Revise your drug substance and drug product post-approval stability commitments accordingly.
8. Tighten the acceptance criterion for total impurities in drug product release and stability specifications based on the observed levels. Also revise the drug product acceptance criterion for individual unknown impurity to NMT ~~_____~~ based on identification threshold as per ICH Q3B(R).

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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Ramesh Sood
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 Deliberative Process

Withheld Track Number: Administrative-

Executive CAC

Date of Meeting: April 17, 2007

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Lynnda Reid, Ph.D., DRUP, Alternate Member
Charles Resnick, Ph.D., DCRP, Team Leader, DCRP
William Link, Ph.D., DCRP, Presenting Reviewer

Authors of Draft: Charles Resnick & William Link

The committee met to discuss the results of rat and mouse carcinogenicity studies conducted with ambrisentan, an endothelin receptor antagonist proposed for the treatment of pulmonary hypertension.

NDA #22-081

Sponsor: Gilead Science, Inc.

The Rat Study

A 2-year, dietary administration study was conducted in Wistar rats at ExecCAC-recommended dose levels of 10, 30 and 60 mg/kg/day. There were 50 animals/sex/group including each of two control groups. An additional 12 rats/sex/group used for toxicokinetics were included in the analysis for tumorigenic effects.

Body weight gain and food consumption were dose-dependently reduced for both sexes at the mid and high dose levels ($p < 0.01$), and hunched posture, labored respiration, rales and emaciation were evident in these groups before the end of the first year of dosing. The high and mid-dose male and female groups had their doses lowered to 40 and 20 mg/kg/day, respectively, in week 51. The high dose males and females were taken off drug completely in weeks 69 and 93, respectively. Effects on survival of these groups became evident within the first 6 months. Only 13 (of the 50 main study) high dose males and 12 high dose females and 17 mid-dose males and 21 mid-dose females survived to scheduled termination (remaining animals of these groups died or were sacrificed in extremis) compared with at least 35/sex in each of the other (control and low dose) groups. The only evidence of ambrisentan-related carcinogenicity was a positive trend ($p < 0.025$) for the combined incidence of benign basal cell tumor and basal cell carcinoma of skin/subcutis in male rats when the high dose group was eliminated from the analysis (1 animal with each tumor at the mid-dose, none in any other group, $p < 0.025$) and the occurrence of mammary fibroadenomas in male rats of that same high dose group (4 animals with the tumor in that group, none in any other male group, $p < 0.05$, pairwise comparison with controls).

The Mouse Study

A 2-year, dietary administration study was conducted in CD-1 mice at ExecCAC-recommended dose levels of 50, 100 and 250 mg/kg/day. There were 60 animals/sex/group, including each of

two control groups. An additional 12 animals/sex/group used for toxicokinetics were included in the analysis for tumorigenic effects.

Increased incidences of hunched posture, emaciation and rales were observed in high and mid dose males and high dose females. The high dose male and female groups had their dose lowered to 150 mg/kg/day in week 39 and were taken off drug completely in week 96 (males) or week 76 (females). Effects on survival became evident within the first six months in males and females. Only 11 high dose males, compared with at least 25 in each of the other main study male control and treated groups, survived to scheduled sacrifice at 24 months. None of the main study high dose females survived to 24 months as all 9 surviving members of this group were sacrificed at 84 weeks. Only 14 mid-dose females and 18 low dose females survived to 24 months compared with at least 24 females in each of the concurrent control groups. Statistical analysis revealed no evidence of drug-related tumorigenesis, whether or not the high dose groups were included.

Committee Conclusions and Recommendations

The committee concluded that the rat study was adequate, noting the prior Exec CAC concurrence with dose selection. The committee further concluded that the limited evidence for drug-related tumorigenicity in rats was obtained at dose levels that were clearly above the MTD and, with the exception of the male mammary tumor finding, there were no significant differences between the incidences at those levels and the incidences in the concurrent control groups. Though the mammary fibroadenomas appeared to be treatment-related, occurring in males which had been treated for a maximum of only 69 weeks, the committee expressed only limited concern over a benign tumor that was observed only at levels producing a marked increase in unrelated lethality.

The committee concluded that the mouse study was adequate noting the prior Exec CAC concurrence with dose selection. The committee further concluded that there was no evidence of drug related tumorigenicity in the mouse.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\n
/Division File, DCRP
/CAResnick, DCRP
/WLink, DCRP
/RPM, DCRP
/ASeifried, OND IO

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/s/

Abby Jacobs
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NDA 22-081

DISCIPLINE REVIEW LETTER

Gilead Sciences, Inc.
Attention: Ms. Linnea Tanner
7575 West 103rd Ave., Suite #102
Westminster, CO 80021-5426

Dear Ms. Tanner:

Please refer to your December 13, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Letairis (ambrisentan) 5 and 10 mg Tablets.

We also refer to your submissions dated January 11 and February 28, 2007.

A review by the Office of Surveillance and Epidemiology's Division of Medication Errors and Technical Support (DMETS) is complete, and we have identified the following deficiencies:

In the review of the container labels, carton, blister and insert labeling for Letairis, DMETS has focused on safety issues relating to medication errors. DMETS has identified the following areas of improvement in the interest of patient safety that may minimize potential user error.

1. Relocate the net quantity statement ("30 tablets") away from the product strength. Postmarketing reporting has shown that the net quantity and strength can be confused when they are in close proximity to each other.
2. Differentiate the presentation of strength on the container and blister labels and the carton labeling. The current presentation and use does not sufficiently differentiate these strengths in order to decrease the potential of selection errors. This may be achieved by color blocking.
3. In the medication guide, under "How should I take Letairis", you note "Do not split, crush, or chew your tablets." However, this information is not present in the Dosage and Administration or the Patient Counseling Information sub-sections of the labeling. If this statement is true of this film-coated tablet, please repeat this statement in both sections of the insert labeling, container labels, and carton/blister labeling.
4. In the Medication Guide, there is a notation to maintain Letairis in its original packaging. However, there is no corresponding statement in the insert labeling to substantiate the requirement. Please revise.

In light of the proposed controlled distribution plan, DMETS has no objections to the use of the proprietary name, Letairis. Additionally, the Division of Drug Marketing, Advertising, and Communications finds the proprietary name of Letairis acceptable from a promotional perspective.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your

application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, please call Melissa Robb, Regulatory Health Project Manager, at (301) 796-1138.

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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Edward Fromm
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MEMORANDUM**Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
WO 22, Mailstop 4447, HFD-420
Center for Drug Evaluation and Research**

To: Norman Stockbridge, MD
Director, Division of Cardiovascular and Renal Products, HFD-110

Through: Denise Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Errors and Technical Support, HFD-420

From: Kimberly Pedersen, RPh, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: February 8, 2007

Subject: OSE Review 2007-70
Proprietary Name: Letairis (Ambrisentan Tablets)
Strengths: 5 mg and 10 mg
Sponsor: Gilead Sciences
NDA #: 22-081

This memorandum is in response to a January 10, 2007 request from your Division for a re-review of the proposed name "Letairis." DMETS reviewed this proposed name in 2005 and found it unacceptable due to the potential for confusion with Lotensin, Ventavis, Librium, ██████████^{***}. At the time of the initial name review, the sponsor referred to a controlled distribution program; however, specifics of the plan were not provided at that time.

Since this review, the sponsor has submitted details on the controlled distribution plan and also submitted a Risk Management Plan (including insert labeling and medication guide). Comments in regards to the Risk Management Plan will be forwarded under a separate cover from the Office of Surveillance and Epidemiology Risk Management Team.

- A. The sponsor submitted details of their controlled distribution plan, which included statements that an order for Letairis will never be "scripted" or "called in via telephone." The sponsor will achieve this by a three step method of ordering. In order to enroll in the RiskMAP and receive drug product, the physician must completely fill-out an enrollment form. The Letairis order will be part of this enrollment form. This form will be faxed by the physician to the RiskMAP coordinating center. This center will assure the form has been completed correctly and the information will be forwarded to the specialty pharmacy of the patient's choice. The specialty pharmacy will send the medication to the physician or patient as indicated on the order.

The sponsor also clarified how refill or repeat orders will be handled. The specialty pharmacy can call the prescriber to receive authorization to renew the order or provide a facsimile of a typed refill authorization form to the prescriber. This form will be created by the respective specialty pharmacies. Thus, Letairis prescriptions will not be written by the physician for the patient to take to their neighborhood pharmacies. Additionally, patients who are hospitalized will either take their medication with them or the medication will be discontinued during the hospitalization. No medication will be sent to hospitals from the specialty pharmacy. This distribution system will limit the possibility of errors arising from misinterpretation of verbal prescriptions and those that are poorly scripted.

*** Proprietary and Confidential information not to be released to the public.

Since the previous review, six additional names were identified [Ultragris (discontinued), Ultravist, Liotrix, Cetirizine, Lantus, and Levitra] as having the potential to look or sound similar to Letairis. However, after reviewing the controlled distribution plan, DMETS believes there is minimal risk of orthographic/phonetic confusion between the newly identified names and those identified in the initial review of the name. Thus, DMETS has no objections to the use of the proposed name, Letairis.

- B. In the review of the container labels, carton, blister and insert labeling for Letairis, DMETS has focused on safety issues relating to medication errors. DMETS has identified the following areas of improvement in the interest of patient safety that may minimize potential user error.
1. Relocate the net quantity statement (“30 tablets”) away from the product strength. Postmarketing reporting has shown that the net quantity and strength can be confused when they are in close proximity to each other.
 2. Differentiate the presentation of strength on the container and blister labels and the carton labeling. The current presentation and use of does not sufficiently differentiate these strengths in order to decrease the potential of selection errors. This may be achieved by color blocking.
 3. In the medication guide, under “How should I take Letairis”, the sponsor notes “Do not split, crush, or chew your tablets.” However, this information is not present in the Dosage and Administration or the Patient Counseling Information sub-sections of the labeling. If this statement is true of this film-coated tablet, please repeat this statement in both sections of the insert labeling, container labels, and carton/blister labeling.
 4. In the Medication Guide, there is a notation to maintain Letairis in its original packaging. However, there is no corresponding statement in the insert labeling to substantiate the requirement. Please revise.

In summary, in light of the proposed controlled distribution plan, DMETS has no objections to the use of the proprietary name, Letairis. DMETS recommends implementation of the proposed label and labeling changes. Additionally, Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the proprietary name of Letairis acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any communication to the sponsor with regard to this review. If you have further questions or need clarifications, please contact Diane Smith, Project Manager, at 301-796-0538.

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Kimberly Culley-Pedersen
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DRUG SAFETY OFFICE REVIEWER

Denise Toyer
4/18/2007 11:49:48 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
4/18/2007 02:27:27 PM
DRUG SAFETY OFFICE REVIEWER

Minutes of a Teleconference

Application Number: NDA 22-081
Sponsor: Gilead Sciences, Inc.
Drug: Letairis (ambrisentan) Tablets

Type of Meeting: 90-Day Conference
Classification: B

Teleconference Date: March 29, 2007
Preliminary Responses Sent: March 28, 2007

FDA Participants:

Division of Cardiovascular and Renal Products

Thomas Marciniak, M.D.	Team Leader, Clinical
Tim Link, Ph.D.	Pharmacologist
Melissa Robb	Regulatory Health Project Manager
Edward Fromm	Chief, Project Management Staff

Office of New Drug Quality Assessment

Haripada Sarker, Ph.D.	Chemist
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Office of Clinical Pharmacology

Peter Hinderling, M.D.	Senior Advisor
Yaning Wang, Ph.D.	Pharmacometrics

Office of Biostatistics

Cherry Liu, M.D., M.S	Statistician
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Office of Surveillance and Epidemiology (OSE)

Mary Ross Southworth, Pharm.D.	Safety Evaluator, Division of Drug Risk Evaluation
Kim Pederson, RPh	Safety Evaluator, Division of Medication Errors and Technical Support
Joyce Weaver, Pharm.D., BCPS	Risk Management Analyst, OSE Immediate Office
Claudia Karwoski, Pharm.D.	Risk Management Team Leader, OSE Immediate Office
Suzanne Berkman, Pharm.D.	Risk Management Analyst, OSE Immediate Office

Division of Drug Marketing and Communications

Lisa Hubbard	Senior Regulatory Review Officer
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Gilead Participants

Norbert Bischofberger, Ph.D.	Executive Vice President, Research and Development and Chief Scientific Officer
Michael Gerber, M.D.	Sr. Vice President, Clinical Research
Christopher Dufton, Ph.D.	Associate Director, Clinical Science
Tobias Peschel, M.D., Ph.D.	Vice President, Drug Safety and Public Health
Richard Gorczynski, Ph.D.	Sr. Vice President, Research
Laurie Wiedl, Ph.D.	Associate Director, Drug Safety Evaluation
Arun Mandagere, Ph.D.	Associate Director, Drug Metabolism
Brian Wiens, Ph.D.	Director, Biometrics
Darrin Despain	Manager, Biostatistics
Jennifer Stewart	Director, Professional Services

Gwyn Wold
Robert Roden
Monique Plamondon
Linnea Tanner
Todd Marshall

Director, Project Management
Director, Project Management
Director, Quality Assurance
Associate Director, Regulatory Affairs
Associate Director, Regulatory Affairs – CMC

Background:

Ambrisentan is a non-sulfonamide, propanoic acid-class, endothelin receptor antagonist. A New Drug Application was received on December 18, 2006 for the use of this NME for the treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise capacity, delay clinical worsening ~~_____~~. This application was granted a Priority review and the PDUFA goal date is June 18, 2007. The sponsor requested this meeting to confirm the current status of the review and discuss the next steps in the review process.

Questions:

1. *Does the Division anticipate that there will be any additional, significant questions or issues to which Gilead should be prepared to respond?*

Pre-Meeting Response

We can not anticipate whether there will be further questions. The outstanding clinical issue is whether you have provided adequate justification for your interdosing interval. Please also advise when the 120-day safety update will be received.

Discussion at Teleconference

Elimination of ambrisentan from the body is mainly by non-renal processes. The respective contributions of biliary excretion and metabolism to the elimination of ambrisentan are unknown. The individual radioactivities assignable to major circulating moieties in plasma were only determined by a semi-quantitative method. The individual radioactivities assignable to the major moieties in feces and urine have not been determined and the existence of unidentified metabolites cannot be excluded. The relative contributions of the metabolism by CYPs and UGTs are unknown. CYP2C19 and UGTs are subject to pharmacogenetic polymorphism and the contribution of polymorphism to the variability of the oral clearance of ambrisentan is unknown. The inhibitory impact of ambrisentan on CYPs and UGTs in vitro was negligible at concentrations attained after administration of 10 mg qd to patients. However, in these experiments ambrisentan was not pre-incubated. In vitro data indicate that ambrisentan is a substrate of P-gp and OATP. In conclusion, the interaction liability of ambrisentan when co-administered with strong CYP3A and 2C19 inhibitors and inducers or strong P-gP and OATP inhibitors or inducers is unknown. . The Agency and sponsor agreed that this issue could be discussed further at a follow-up teleconference with the clinical pharmacologist.

The sponsor stated that data to support once-daily dosing was submitted with the original NDA and in a follow-up submission in response to the Division's 74-day filing letter. The sponsor believes the effect seen on WHO classification and time to clinical worsening support the proposed dosing regimen. The sponsor stated that they have submitted an amendment (#176) to their IND to collect 6-minute walk data at peak and trough during their open-label extension study. They plan to conduct this testing at weeks 12 and 24 and collect plasma levels. This data would be submitted for review as part of a post-marketing commitment. The Agency stated that this data would likely not be very useful as it is unblinded and not placebo-controlled. The Agency believes this type of assessment is easily influenced by bias. The sponsor stated that they plan to account for potential variability in walk times by having the walks conducted at peak and trough done within

one hour of each other. The Agency and the sponsor agreed that this issue could be discussed further at a follow-up teleconference with the clinical review team.

The Agency noted that the issues of metabolite characterization and interdosing interval may not preclude approval, but would be incorporated in the approved labeling.

The sponsor stated that they plan to submit the 120-day safety updated by April 18, 2007. The sponsor confirmed that it will be consistent with the previous guidance on this submission given by the Division.

2. *Reference is made to Amendment No. 1 to NDA 22-081 in which Gilead responded to comments by the Division of Medication Errors and Technical Supports (DMETS) in the Office of Surveillance and Epidemiology regarding the proposed proprietary name of Letairis. What is the status of review by DMETS regarding the acceptability of the proprietary name of Letairis?*

Pre-Meeting Response

The proprietary name Letairis is still under review by DMETS. Please clarify how a second order prescription will be handled by the prescriber and the Specialty Distributor. It is likely that DMETS will have additional comments within the next month.

Discussion at Teleconference

The sponsor clarified that when a new patient is prescribed Letairis, a patient enrollment form will be completed by the physician. This form will be faxed to the RiskMAP coordinating center where the patient and prescriber will be enrolled in the program. At this time the database will be updated. The patient enrollment form will then be forwarded to the specialty distributor according to state procedures. If a new order is needed, the specialty distributor will either call the prescriber to get a new order or fax a typed refill authorization form for approval by the prescriber. The specialty distributor will be responsible for creating the refill authorization form.

3. *At which additional clinical investigational sites and contract manufacturing sites does the Agency plan to inspect prior to the Prescription Drug User Fee (PDUFA) date of June 18, 2007?*

Pre-Meeting Response

The Division of Scientific Investigations is currently in the process of completing all requested investigations of clinical and analytical sites.

All manufacturing sites have been submitted to the Office of Compliance for inspection request. The Office of Compliance will determine which sites will be inspected. However, all sites should be prepared for a GMP inspection if deemed necessary.

Discussion at Teleconference

This issue was not discussed.

4. *Does the Agency anticipate that there will be any questions or issues regarding the Quality (chemistry, manufacturing, and controls) technical sections to which Gilead should be prepared to respond?*

Pre-Meeting Response

We can not anticipate whether there will be further questions. However, at this time, there are none.

Discussion at Teleconference

This issue was not discussed.

5. *A comprehensive Data Analysis Plan (DAP) for the combined analysis of the two pivotal Phase 3 clinical studies AMB-320 and AMB-321 (ARIES-C) was submitted on November 28, 2005 to IND 64,915 (Serial No. 100) prior to unblinding of these studies. Gilead did not receive feedback on this DAP from the Division, yet the Clinical Summaries (m2.7.3 and m2.7.4) focused on this combined analysis to provide an integrated presentation of the Phase 3 safety and efficacy data. Would the Division confirm that the ARIES-C DAP provides a statistically appropriate analysis of the integrated Phase 3 data to support labeling?*

Pre-Meeting Response

We judge that the most appropriate analyses of the two studies AMB-320 and AMB-321 are the individual analyses of each study, as we typically do for all drug approvals. There is evidence of substantial heterogeneity between the two studies such that the interpretation of simple pooled analyses is hazardous. We will discuss with you during labeling negotiations how the results of both studies should be reflected in the label if, after completion of all reviews, we decide to approve.

Discussion at Teleconference

6.

Pre-Meeting Response

Discussion at Teleconference

The sponsor was instructed to submit this request to the IND.

7. *The Filing Communication dated February 16, 2007 indicates that the application will be reviewed under the provisions of 21 CFR 314.520 (Subpart H - Approval with restrictions to assure safe use). We are aware that under the provisions of Subpart H, Gilead is required unless otherwise informed by the Agency to submit for consideration preapproval copies of all promotional materials, including promotional labeling as well as advertisements, to be used within the first 120 days after approval (21 CFR 314.550). We are also aware that under the provisions, the company is required to submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement unless otherwise informed by the Agency. Would the Division please advise as to whether the referenced provisions apply to the NDA for ambrisentan and, if so, whether the Division would be amenable to -- following the first 120 days after approval of the product -- Gilead submitting all promotional materials at the time of initial dissemination (under FDA Form 2253) only?*

Pre-Meeting Response

The application will be reviewed under the provisions of 21 CFR 314.520 (Subpart H - Approval with restrictions to assure safe use.) Therefore, the application is subject to 21 CFR 314.550. You would be required to submit for consideration preapproval copies of all promotional materials, including promotional labeling as well as advertisements, to be used within the first 120 days after approval. You also are required to submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement. The requirement will not be waived.

Discussion at Teleconference

This issue was not discussed.

8. *What is the anticipated timing for initial Agency feedback regarding the proposed ambrisentan prescribing information, medication guide, and risk management plan (RiskMAP), including associated RiskMAP materials?*

Pre-Meeting Response

The Agency plans to provide feedback approximately one month prior to the PDUFA goal date.

Discussion at Teleconference

The Agency stated that the comments on the RiskMAP should be completed soon. Although these comments are not final as the review of the NDA is not yet complete, the Agency will try to provide comments as soon as possible, especially on the forms. However, the RiskMAP content is influenced by the agreed-upon labeling.

9. *The following documents, which are provided as attachments to this cover letter and were provided in the risk management plan (RiskMap) as Appendices 2 and 3 in Amendment No. 1 to NDA 22-081, will be needed for use in the communications with physicians and patients immediately upon approval/availability of the product:*
 - *Prescriber Educational Brochures*
 - o *Prescriber Enrollment and Agreement Form*
 - o *Prescriber Information*
 - *Patient Educational Brochures*
 - o *RiskMAP Patient Enrollment and Consent Form*
 - o *Patient Enrollment Guide*
 - o *LETAIRIS™ Therapy – What You Need to Know*

Would the Division please advise as to its process for review of the RiskMap and associated documents and how we will be able to work with the Division towards availability of those documents in their final form at the time of approval. Additionally, will any documents associated with the RiskMAP, which were submitted in the original NDA, also need to be submitted to the Division of Drug Marketing, Advertising, and Communications (DDMAC) prior to approval?

Pre-Meeting Response

The RiskMAP is being reviewed by this Division with consultation from the Office of Surveillance and Epidemiology and DDMAC. We will provide comments to you as soon as possible on these documents. All documents associated with the RiskMAP which were submitted in the original NDA have been reviewed by DDMAC, and therefore, do not need to be submitted to DDMAC prior to approval.

Discussion at Teleconference

This issue was not discussed.

Recorder: *{See appended electronic signature page}*

Chair Concurrence: *{See appended electronic signature page}*

Drafted: 4/5/07 Finalled: 4/16/07

RD:	
Marciniak	4/13/07
Link	4/12/07
Fromm	4/12/07
Sarker	4/12/07
Hinderling	4/11/07
Wang	4/9/07
Liu	4/9/07
Southworth	4/6/07
Pederson	4/5/07
Weaver	4/5/07
Karwoski	4/9/07
Berkman	4/5/07
Hubbard	4/5/07

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/s/

Melissa Robb
4/16/2007 11:31:00 AM

Thomas Marciniak
4/17/2007 03:23:38 PM

MEMORANDUM

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

DATE: March 29, 2007

FROM: Sriram Subramaniam, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations

SUBJECT: Review of EIRs Covering NDA 22-081, Letairis™
(ambrisentan) Tablets, Sponsored by Gilead Sciences,
Inc.

TO: Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products (DCRP)

At the request of DCRP, the Division of Scientific Investigations (DSI) conducted audits of the clinical and analytical portions of the following bioequivalence study:

Study AMB-103: "A Phase 1, Open-label, Randomized, Crossover Study to Compare Ambrisentan Formulations for Bioequivalence at Multiple Drug Doses in Healthy Adult Volunteers"

The study involved comparison of research and to-be-marketed tablets for 3 dosage strengths (2.5, 5 and 10 mg). There were 3 groups: Groups 1, 2, and 3 compared formulations of dosage strengths 2.5 mg, 5 mg, and 10 mg, respectively. The clinical portion of the study was conducted at _____ and the analytical portion was performed at _____

Following the inspection at _____ (3/20-28/07) and at _____ (3/19-28/07), Form 483s were issued. DSI's evaluation of the inspectional findings follows:

Clinical Site: _____

1. Failure to maintain reserve drug samples.

Contrary to regulatory requirement for retention of bioavailability and bioequivalence reserve samples (21 CFR 320.38 and 320.63), the clinical site failed to randomly

select and retain reserve drug samples from the study drugs that were shipped to the site. The Final Rule* for retention of reserve samples states that the **testing facility** should randomly select and retain reserve samples to assure that the reserves are representative of the study drugs administered to the subjects. Instead, reserve samples were preselected and retained by the study drug packager,

Therefore, the authenticity of the drugs used in Study AMB 103 cannot be assured.

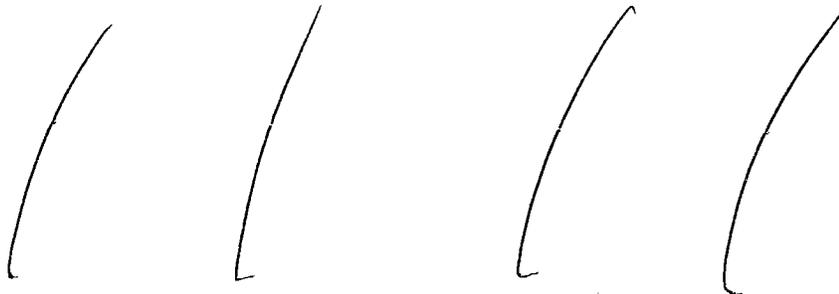
Analytical Site:

2. Failure to reject inaccurate (of nominal concentration) quality controls (QC) in analytical runs 9 and 40R.

QC acceptance criterion requires rejecting QCs of their nominal. Although both low QCs ($\mu\text{g/mL}$) had error > ng/mL in each of the analytical runs 9 and 40R, rejected only one low QC and accepted the other low QC as the QC was failing only by a narrow margin (Exhibit 1).

should have rejected both low QCs in the runs. Since, the rejection of both low QCs results in failure of Runs 9 and 40R to meet run acceptance criterion, the accuracy of ambrisentan concentrations for Period 2 samples from Subjects 105, 107, 108, 109, 211, 214, 215 and 216 analyzed in Runs 9 and 40R was not demonstrated.

3. Dilution integrity was not demonstrated for study subjects.



† Subject, hour, period

The calibration range for the ambrisentan assay was ng/mL . The inspection found that 16% and 33% of subject samples in the Cmax range in Groups 2 and 3, respectively, were diluted (5x) and reanalyzed in Runs 27-33, as their

* Retention of Bioavailability and Bioequivalence Testing Samples, Federal Register Vol. 58, No. 80, Pages 25918-25928 (1993).

original concentrations were estimated by extrapolation from the standard curve. Review of data of subject samples before and after dilution indicated a consistent and significant difference in response. For example, 16% of samples for Group 2 subjects had undiluted concentrations > 1000 ng/mL (above the limit of quantitation), whereas majority of their concentrations (corrected for dilution) estimated after dilution were between 250-400 ng/mL (see examples in Table 1a). Also, a similar trend was observed for subject samples that were diluted and reassayed although their original concentrations < 1000 ng/mL (see examples in Table 1b). ~~_____~~ could not explain this difference during the inspection. The inspection also confirmed that ~~_____~~ did not validate dilution integrity, either prior to or during the study. Therefore, the accuracy of ambrisentan concentrations of the diluted plasma samples for Group 2 and 3 subjects was not demonstrated. Table 2 provides the list of diluted subject samples (note that none of the samples from Group 1 subjects were diluted).

Conclusions:

Based on the above findings, DSI concludes the following:

- a. The authenticity of the drugs used in Study AMB-103 cannot be assured as the clinical sites failed to randomly select the reserve samples (Item 1 above). Therefore, Study AMB-103 fails to meet the regulatory requirements for the retention of reserve samples for bioequivalence studies [21 CFR 320.38 and 63].
- b. The accuracy of Period 2 ambrisentan concentrations for Group 1 Subjects 105, 107, 108, 109, and Group 2 Subjects 211, 214, 215 and 216 cannot be assured as the accuracy of analytical runs 9 and 40R was not demonstrated (Item 2).
- c. The accuracy of ambrisentan concentrations was not demonstrated for samples subjected to dilution for Group 2 and Group 3 subjects (listed in Table 2), as dilution accuracy was not demonstrated (Item 3).

After you have reviewed this memo, please append it to the original NDA submission.

Sriram Subramaniam, Ph.D.

1 Page(s) Withheld

 0 Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-

Final Classifications:

VAI: _____

VAI: _____

CC:

HFD-45/RF

HFD-48/Himaya/Subramaniam(2)/CF

HFD-860/Hinderling/Marroum

OND1/DCRP/Robb/NDA 22-081

HFR-SW250/Aiken

HFR-SW150/Waldron

Draft: SS 3/26/07

Edit: MKY 3/29/07

DSI:5749;O:\BE\eircover\22081gil.amb.doc

FACTS ID 800652

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 Draft Labeling

 Deliberative Process

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/s/

Sriram Subramaniam

4/2/2007 04:46:21 PM

PHARMACOLOGIST/TOXICOLOGIST

Dr. Viswanathan signed the paper copy on 4/2/07.

NDA 22-081
Letairis (ambrisentan) Tablets
Gilead Sciences, Inc.
90-Day Conference
Preliminary Responses

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for March 29, 2007 at 1:00 pm between Gilead Sciences, Inc. and the Division of Cardiovascular and Renal Products. This material is shared to promote a collaborative and successful discussion at the teleconference. If there is anything in it that you do not understand or with which you do not agree, we very much want you to communicate such questions and disagreements. The minutes of the teleconference will reflect the discussion that takes place during the teleconference and are not expected to be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the teleconference (contact the RPM), but this is advisable only if the issues involved are quite narrow. It is not our intent to have our preliminary responses serve as a substitute for the teleconference. It is important to remember that some meetings, particularly milestone meetings, are valuable even if pre-meeting communications seem to have answered the principle questions. It is our experience that the discussion at meetings often raises important new issues. Please note that if there are any major changes to your development plan, the purpose of the teleconference, and/or to the questions (based on our responses herein), we may not be able to reach agreement on such changes at the teleconference, but we will be glad to discuss them to the extent possible. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the teleconference, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the teleconference.

Questions:

1. *Does the Division anticipate that there will be any additional, significant questions or issues to which Gilead should be prepared to respond?*

We can not anticipate whether there will be further questions. The outstanding clinical issue is whether you have provided adequate justification for your interdosing interval. Please also advise when the 120-day safety update will be received.

2. *Reference is made to Amendment No. 1 to NDA 22-081 in which Gilead responded to comments by the Division of Medication Errors and Technical Supports (DMETS) in the Office of Surveillance and Epidemiology regarding the proposed proprietary name of Letairis. What is the status of review by DMETS regarding the acceptability of the proprietary name of Letairis?*

The proprietary name Letairis is still under review by DMETS. Please clarify how a second order prescription will be handled by the prescriber and the Specialty Distributor. It is likely that DMETS will have additional comments within the next month.

3. *At which additional clinical investigational sites and contract manufacturing sites does the Agency plan to inspect prior to the Prescription Drug User Fee (PDUFA) date of June 18, 2007?*

The Division of Scientific Investigations is currently in the process of completing all requested investigations of clinical and analytical sites.

All manufacturing sites have been submitted to the Office of Compliance for inspection request. The Office of Compliance will determine which sites will be inspected. However, all sites should be prepared for a GMP inspection if deemed necessary.

4. *Does the Agency anticipate that there will be any questions or issues regarding the Quality (chemistry, manufacturing, and controls) technical sections to which Gilead should be prepared to respond?*

We can not anticipate whether there will be further questions. However, at this time, there are none.

5. *A comprehensive Data Analysis Plan (DAP) for the combined analysis of the two pivotal Phase 3 clinical studies AMB-320 and AMB-321 (ARIES-C) was submitted on November 28, 2005 to IND 64,915 (Serial No. 100) prior to unblinding of these studies. Gilead did not receive feedback on this DAP from the Division, yet the Clinical Summaries (m2.7.3 and m2.7.4) focused on this combined analysis to provide an integrated presentation of the Phase 3 safety and efficacy data. Would the Division confirm that the ARIES-C DAP provides a statistically appropriate analysis of the integrated Phase 3 data to support labeling?*

We judge that the most appropriate analyses of the two studies AMB-320 and AMB-321 are the individual analyses of each study, as we typically do for all drug approvals. There is evidence of substantial heterogeneity between the two studies such that the interpretation of simple pooled analyses is hazardous. We will discuss with you during labeling negotiations how the results of both studies should be reflected in the

6.

The target date of June 1, 2007, for submitting a pediatric study request is acceptable.

7. *The Filing Communication dated February 16, 2007 indicates that the application will be reviewed under the provisions of 21 CFR 314.520 (Subpart H - Approval with restrictions to assure safe use). We are aware that under the provisions of Subpart H, Gilead is required unless otherwise informed by the Agency to submit for consideration preapproval copies of all promotional materials, including promotional labeling as well as advertisements, to be used within the first 120 days after approval (21 CFR 314.550). We are also aware that under the provisions, the company is required to submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement unless otherwise informed by the Agency. Would the Division please advise as to whether the referenced provisions apply to the NDA for ambrisentan and, if so, whether the Division would be amenable to -- following the first 120 days after approval of the product -- Gilead submitting all promotional materials at the time of initial dissemination (under FDA Form 2253) only?*

The application will be reviewed under the provisions of 21 CFR 314.520 (Subpart H - Approval with restrictions to assure safe use.) Therefore, the application is subject to 21 CFR 314.550. You would be required to submit for consideration preapproval copies of all promotional materials, including promotional labeling as well as advertisements, to be used within the first 120 days after approval. You also are required to submit promotional materials at least 30 days prior to the intended time of initial dissemination of the labeling or initial publication of the advertisement. The requirement will not be waived.

8. *What is the anticipated timing for initial Agency feedback regarding the proposed ambrisentan prescribing information, medication guide, and risk management plan (RiskMAP), including associated RiskMAP materials?*

The Agency plans to provide feedback approximately one month prior to the PDUFA goal date.

9. *The following documents, which are provided as attachments to this cover letter and were provided in the risk management plan (RiskMap) as Appendices 2 and 3 in Amendment No. 1 to NDA 22-081, will be needed for use in the communications with physicians and patients immediately upon approval/availability of the product:*

- *Prescriber Educational Brochures*
 - o *Prescriber Enrollment and Agreement Form*
 - o *Prescriber Information*
- *Patient Educational Brochures*
 - o *RiskMAP Patient Enrollment and Consent Form*
 - o *Patient Enrollment Guide*
 - o *LETAIRIS™ Therapy – What You Need to Know*

Would the Division please advise as to its process for review of the RiskMap and associated documents and how we will be able to work with the Division towards availability of those documents in their final form at the time of approval. Additionally, will any documents associated with the RiskMAP, which were submitted in the original NDA, also need to be submitted to the Division of Drug Marketing, Advertising, and Communications (DDMAC) prior to approval?

The RiskMAP is being reviewed by this Division with consultation from the Office of Surveillance and Epidemiology and DDMAC. We will provide comments to you as soon as possible on these documents. All documents associated with the RiskMAP which were submitted in the original NDA have been reviewed by DDMAC, and therefore, do not need to be submitted to DDMAC prior to approval.

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

/s/

Thomas Marciniak
3/28/2007 07:42:07 AM

Confirmation of a Teleconference

Drug: Letairis (ambrisentan) Tablets
NDA: 22-081
Sponsor: Gilead Sciences, Inc.

Date Requested: March 6, 2006
Date Confirmation Faxed: March 8, 2007

Type: Ninety-Day Conference
Classification: B

Teleconference Date: March 29, 2007
Teleconference Time: 1:00 PM EST

FDA Participants:

Division of Cardiovascular and Renal Products

Thomas Marciniak, M.D.	Team Leader, Clinical
Maryann Gordon, M.D.	Medical Officer
Tim Link, Ph.D.	Pharmacologist
Melissa Robb	Regulatory Health Project Manager

Office of New Drug Quality Assessment

Kasturi Srinivasachar, Ph.D.	Pharmaceutical Assessment Lead
Haripada Sarker, Ph.D.	Chemist

Office of Clinical Pharmacology

Patrick Marroum, Ph.D.	Team Leader
Peter Hinderling, M.D.	Senior Advisor
Yaning Wang, Ph.D.	Pharmacometrics

Office of Biostatistics

Cherry Liu, M.D., M.S	Statistician
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Office of Surveillance and Epidemiology

Mary Dempsey	Risk Management Program Coordinator
Joyce Weaver, Pharm.D.	Senior Drug Risk Management Analyst
Jodi Duckhorn, M.A.	Social Science Research Analyst, Team Leader, Patient Information and Research
Claudia Karwoski, Pharm.D.	Team Leader, Risk Management Team
Suzanne Berkman, Pharm.D	Acting Senior Risk Management Analyst

- **PLEASE PROVIDE ME WITH A LIST PARTICIPANTS AND A CALL-IN NUMBER BY E-MAIL NO LATER THAN ONE DAY BEFORE THE MEETING.**

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-081

Gilead Sciences, Inc.
Attention: Dr. Michael Gerber
7575 West 103rd Avenue, Suite #102
Westminster, CO 80021-5426

Dear Dr. Gerber:

Please refer to your December 13, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Letairis (ambrisentan) 5 and 10 mg Tablets.

We also refer to your submissions dated January 11 and 26, 2007.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on February 16, 2007 in accordance with 21 CFR 314.101(a). This application has been classified as a priority review and the user fee goal date will be June 18, 2007.

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

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

Metabolites

Ambrisentan is eliminated from the body by non-renal pathways. Quantitative methods for the determination of the metabolites in biological fluids (plasma, urine and feces) measuring radiolabeled or nonlabeled species were not developed. The plasma concentrations of the metabolites were determined with a semi-quantitative method. The respective recoveries of total radioactivity assignable to the individual metabolites in urine and feces were not determined. The existence of unidentified metabolites in addition to the 3 identified metabolites cannot be excluded. In vitro experiments examining whether intestinal contents can metabolize ambrisentan were not performed. Absolute bioavailability of ambrisentan is not known. Therefore, the relative contributions of metabolism and biliary excretion to the elimination of ambrisentan from the body are unknown. It can be estimated that 22 to 88% of an administered dose of ambrisentan could be metabolized. Thus, clinically relevant metabolic interactions caused by metabolic inhibitors and inducers of ambrisentan cannot be ruled out. The main metabolite in plasma appears to be 4-hydroxymethyl ambrisentan. Involvement of CYP3A and possibly other CYPs based on the results of in vitro studies is probable. In vivo interaction studies exploring the impact of CYP inhibitors and inducers have not been conducted.

Transporters

Ambrisentan has been shown to be a substrate of P-gp in vitro. In vivo studies examining the impact of inhibitors and inducers of P-gp have not been conducted.

Adequacy of the qd Dose Regimen

The time interval between drug intake and performance of the 6-minute walk test and the Borg dyspnea index was not pre-specified in the clinical study protocols. The trough concentrations of the drug are about 6-7% of the peak concentrations. Performance of these tests at trough concentrations of the drug could have demonstrated that the qd dose regimen is appropriate for ambrisentan.

In our preliminary review of your application we have been unable to find any data or discussion regarding the time course of pharmacodynamic effects, particularly 6-minute walk, over the interdosing interval. At the pre-NDA meeting on May 19, 2006, you were advised to provide data and arguments justifying the dosing interval: "Another application for this indication was approved with scant data on the dosing interval. However, if we were to approve ambrisentan without such information, the lack of data on duration of effect would likely be incorporated in the labeling. The Division suggested the sponsor include some argument in their NDA that ambrisentan has an effect on some measure of disease progression or demonstrates an important clinical benefit and therefore, these data are not essential. The Division stated that the sponsor needs to have some rationale for the dosing interval." Our minutes from that meeting also record the following: "The sponsor believes that they will not have data at trough or late in the evening, but will be able to provide a good sample of walks at times from 8 AM-6 PM." We note that the case report forms did not capture times of day of the walks and we do not find times of day of the walks in the SAS data sets. Please provide the times of day of "a good sample of walks at times from 8 AM-6 PM" as discussed and data and arguments justifying the dosing interval.

Significant Treatment related Decrease in Alkaline Phosphatase, Bilirubin and GGT

In vitro studies indicate that ambrisentan does not inhibit the transport of probe substrates of NTCP, OATP, or BSEP. However a decrease of the serum concentrations of bilirubin, alkaline phosphatases and GGT was observed in the clinical studies. What is the mechanism explaining the observed decrease in the bilirubin -alkaline phosphatase-, and GGT- values and what is the clinical significance?

Enantiomer Inversion

Ambrisentan is an enantiomer. Data demonstrating absence of enantiomeric inversion of ambrisentan and its metabolites in vivo have not been submitted.

Assays

The reports on the long-term effects of storage of samples in the freezer on the stability of sildenafil, and N-desmethylsildenafil (Study report AMB-105) and S- and R-warfarin (Study Report AMB-106) could not be found in the submitted material.

In study AMB-220, ambrisentan was measured in a subset of patients with PAH. The report does not indicate the laboratory measuring the plasma concentrations and the method used. The report was completed in 2006 and contains an assay report "Determination of BSF 208075 in Human Plasma and Urine: Method Validation" completed in 2001 ~~_____~~. Please provide the respective information.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that

may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

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

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

If you have any questions, please call Ms. Melissa Robb, Regulatory Health Project Manager, at (301) 796-1138

Sincerely,

(See appended electronic signature page)

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-081

DISCIPLINE REVIEW LETTER

Gilead Sciences, Inc.
Attention: Dr. Michael Gerber
7575 West 103rd Avenue, Suite #102
Westminster, CO 80021-5426

Dear Dr. Gerber:

Please refer to your December 13, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Letairis (ambrisentan) 5 and 10 mg Tablets.

We also refer to the teleconference between Dr. Thomas Marciniak of this Division and yourself on January 9, 2007. We remind you of the discussion and agreements made at that teleconference:

1. The case report forms (CRFs) in the NDA submission did not include the SAE Reports. You were advised that CRFs should include all documents containing clinical information, regardless of whether they are labeled a "form." You agreed to submit a complete set of CRFs, including the missing SAE Reports and any other CRFs that were omitted from the original submission. As discussed, please get back to us regarding when you will submit the complete CRFs, keeping in mind that they should be submitted prior to the filing date.
2. Some of the CRFs are illegible. You agreed to resubmit the legible CRFs for the two cases (156-007 and 126-008) in Study 320 that were discussed. It was also agreed that it was acceptable for the Agency to request legible copies of any illegible CRFs (they are uncommon) during the review process if you would commit to supplying the legible copies within one week of request. Additionally, you may submit annotated CRFs that you believe include legible copies of all information.

If you have any questions, please call Melissa Robb, Regulatory Health Project Manager, at (301) 796-1138.

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-081

Gilead Colorado, Inc.
Attention: Ms. Linnea Tanner
Director, Regulatory Affairs
7575 West 103rd Ave., #102
Westminster, CO 80021-5426

Dear Ms. Tanner:

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

Name of Drug Product: Letairis (ambrisentan) 5 and 10 mg Tablets

Date of Application: December 13, 2006

Date of Receipt: December 18, 2006

Our Reference Number: NDA 22-081

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 16, 2007 in accordance with 21 CFR 314.101(a).

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact:

Ms. Melissa Robb
Regulatory Health Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
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Advancing Therapeutics.
Improving Lives.

Linnea Tanner
Director, Regulatory Affairs

13 December 2006

Norman L. Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Food and Drug Administration
Center for Drug Evaluation & Research
Central Document Room
5901-B Ammendale Rd.
Beltsville, MD 20705-1266

Subject: **NDA 22-081 (022081-0000)**
LETAIRIS™ (ambrisentan) Tablets

NEW DRUG APPLICATION
Original Submission

Dear Dr. Stockbridge:

Pursuant to the Paragraph 505(b)(1) of the Federal Food, Drug and Cosmetic Act (the ACT) and 21 CFR 314.50, Gilead Sciences, Inc. (Gilead) hereby submits a New Drug Application (NDA) for LETAIRIS (ambrisentan) Tablets, 5 and 10 mg. Ambrisentan is a non-sulfonamide, propanoic acid-class, endothelin receptor antagonist (ERA) that is selective for the endothelin type A (ET_A) receptor. LETAIRIS is indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise capacity, delay clinical worsening

Myogen, Inc. was acquired by Gilead Sciences, Inc. and became a wholly owned subsidiary known as Gilead Colorado, Inc., effective November 17, 2006. Thus, the NDA applicant is Gilead Sciences, Inc., which assumes all the responsibilities and obligations of the NDA. However, the name Myogen, Inc. is used throughout the NDA for historical reasons and because of the timing of acquisition.

Request for Priority Review

Ambrisentan was granted Fast Track designation for the treatment of pulmonary arterial hypertension (PAH) on February 15, 2006; therefore, we request that this application be given priority review. PAH is a rare, serious and life-threatening disease for which there is no cure. Although there are other therapies currently approved for this disease, there still is an unmet medical need for the treatment of PAH. LETAIRIS is an alternative, therapeutic option for these patients that has the potential to provide significant benefit over currently authorized therapies for the following reasons:

Confidentiality Statement

The confidential information contained in this document is the property of Gilead Sciences, Inc. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from Gilead Sciences, Inc.

- Improved effects on exercise capacity, an efficacy measure that has been shown to correlate with and be prognostic of long-term survival
- Significant delay of the clinical worsening of PAH, an efficacy measure of disease progression in this ultimately fatal disease
- Improved effects on symptoms associated with PAH (WHO functional class, Borg dyspnea index, and SF-36[®] physical function scale)
- Low incidence of liver function test (LFT) abnormalities, a serious toxicity that can lead to discontinuation of treatment with other ERA therapies
- Potential to provide benefit to PAH patients who have previously discontinued ERA therapy due to LFT abnormalities
- No clinically significant cytochrome P450 (CYP) enzyme-related interactions with several drugs that are currently contraindicated, less effective, or associated with significant safety issues when co-administered with other PAH therapies

Orphan Drug Designation

Ambrisentan was granted orphan drug designation (Designation Request #04-1836) for the treatment of PAH and, therefore, qualifies for seven (7) years of exclusive marketing rights pursuant to Section 527 of the ACT (21 U.S.C. 360 cc). A letter dated December 07, 2006 was submitted to the Office of Orphan Drug Products Development to transfer the orphan designation from Myogen, Inc. to Gilead Sciences, Inc.

Application Fee

Under Section 736(a)(1)(E) of the ACT, this NDA is not subject to an application fee because LETAIRIS (ambrisentan) Tablets, 5 and 10 mg, is indicated for the treatment of a rare disease or condition designated under Section 526 of the ACT (orphan drug designation).

Pediatric Data

Since ambrisentan was granted orphan designation for PAH under Section 526 of the ACT (21 U.S.C. 360bb), no pediatric data is submitted in the original NDA 22-081. Pediatric data is not required for applications to market the product for the orphan-designated indications and a waiver is not needed [21 CFR 314.55(d) for NDAs and 601.27(d) for BLAs].

Proposed Proprietary Name

The proposed proprietary name of LETAIRIS was submitted for review on November 4, 2005 in Serial No. 094 of IND 64,915.

Application Format

The archive copy of NDA 22-081 (eCTD 022081-0000) is provided in its entirety as an electronic submission using the electronic Common Technical Document (eCTD) format in accordance with the guidance *M2: eCTD: Electronic Common Technical Document Specification* and as agreed in the Pre-NDA meeting on May 19, 2006. Gilead has notified the FDA Denver District office about the NDA submission in the eCTD format. A copy of the field copy certification is provided in Section m1.3.2.

Please refer to an attachment (Summary of FDA Interactions and Commitments for Ambrisentan Development Plan) to this cover letter for any other agreements of the format and content of the NDA, including the electronic datasets.

Required Regulatory Forms applicable to this submission have been included in the electronic submission and are signed electronically. Pursuant to 21 CFR 11.100, Gilead certifies that all electronic signatures executed by our employees, agents, or representatives, located anywhere in the world, are the legally binding equivalent of traditional handwritten signatures.

This submission is provided on a DVD-ROM and is approximately 4.2 GB. Gilead certifies that the submission is virus free as defined by the 11 December 2006 version of the McAfee[®] VirusScan[®] Enterprise-program, Version 8.0.0, Scan Engine 5100, with 4916 virus definitions.

Annotated ECG Waveform Data

In accordance with the instructions available on the CDER Electronic Regulatory Submissions and Review website, and confirmation with the Office of Business Process Support (OBPS), Gilead has submitted annotated ECG waveform data in XML format to the E-Scribe ECG Warehouse. These files are representative of data collected in a Phase 1 QTc study (AMB-104), and the two pivotal Phase 3 studies (AMB-320 and AMB-321). These data files are now available for your review through E-Scribe ECG Warehouse.

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Contact Information

Regulatory Contact:

Linnea Tanner
Director, Regulatory Affairs
Gilead Colorado, Inc.
7575 West 103rd Ave., #102
Westminster, CO 80021-5426
Phone (direct): 303-410-3243
Facsimile: 303-410-3354
e-mail: linnea.tanner@gilead.com

Regulatory Contact - CMC:

Todd Marshall
Associate Director, CMC Regulatory
Gilead Colorado, Inc.
7575 West 103rd Ave., #102
Westminster, CO 80021-5426
Phone (direct): 303-464-3958
Facsimile: 303-410-3354
e-mail: todd.marshall@gilead.com

Technical Contact for the eCTD:

Liam Curran
Senior Manager, Regulatory Operations
Gilead Colorado, Inc.
7575 West 103rd Ave., #102
Westminster, CO 80021-5426
Phone (direct): 303-410-3206
Facsimile: 303-410-3354
e-mail: liam.curran@gilead.com

Please do not hesitate to contact me with any questions.

Sincerely,

{See appended electronic signature page}

Linnea Tanner
Director, Regulatory Affairs
Phone: 303-410-3243
Fax: 303-410-3354

Attachment: Summary of FDA Interactions and Commitments for Ambrisentan Development Plan

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0 Trade Secret / Confidential

 Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative-

13 December 2006

Linnea Tanner
Director, Regulatory Affairs

Belinda Collins
District Director
FDA Denver District Office
P.O. Box 25087
Denver, CO 80225-0087

Subject: **NDA 22-081 (022081-0000)**
LETAIRIS™ (ambrisentan) Tablets

FIELD COPY CERTIFICATION
New Drug Application

Dear Ms. Collins:

Pursuant to Paragraph 505(b)(1) of the Federal, Food, Drug and Cosmetic Act and 21 CFR 314.50, Gilead Sciences, Inc. submitted a New Drug Application (NDA) for LETAIRIS™ (ambrisentan) Tablets, 5 and 10 mg, to the Division of Cardiovascular and Renal Products. In accordance with 21 CFR 314.50 (l)(3), the purpose of this letter is to notify the Denver District Office that the NDA was submitted in the electronic Common Technical Document (eCTD) format.

The proposed indication for LETAIRIS™ (ambrisentan) is as follows:
LETAIRIS™ is indicated for the treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise capacity, delay clinical worsening ~~_____~~
~~_____~~

Please do not hesitate to contact me with any questions.

Sincerely,

{See appended electronic signature page}

Linnea Tanner
Director, Regulatory Affairs
Phone: 303-410-3243
Fax: 303-410-3354

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MEMORANDUM OF MEETING MINUTES

MEETING DATE: July 26, 2006
TIME: 2:30 pm - 4:00 pm
LOCATION: Food and Drug Administration, White Oak Campus
APPLICATION: IND 64,915
SPONSOR: Myogen, Inc.
DRUG NAME: BSF 208075 Ambrisentan
TYPE OF MEETING: CMC Type B
MEETING CHAIR: Ramesh Sood, Ph.D.
Branch Chief, DPMA I
MEETING RECORDER: Scott N. Goldie, Ph.D.
Regulatory Health Project Manager for Quality, DPMA I

FDA ATTENDEES:

CENTER OF DRUG EVALUATION AND RESEARCH

Office of New Drug Quality Assessment

Division of Pre-Marketing Assessment I

Ramesh Sood, Ph.D., Branch Chief

Kasturi Srinivasachar, Ph.D., Pharmaceutical Assessment Lead

Ramsharan D. Mittal, Ph.D., Review Chemist

Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality

Division of Pre-Marketing Assessment III & Manufacturing Science

Terrance Ocheltree, Ph.D. R.Ph., Review Chemist

Division of Clinical Pharmacology I

Robert O. Kumi, Ph.D., Pharmacologist

MYOGEN ATTENDEES:

Gwyn Evans Wold, Director, Ambrisentan Program

Rick Gorczynski, Ph.D., Senior Vice President, Research and Development

Michael Hui, Ph.D., Director, Analytical Chemistry

Arun Mandagere, Ph.D., Research Fellow, ADME

Todd Marshall, Associate Director, CMC Liaison, Regulatory Affairs

Larry Melvin, Ph.D., Vice President, Drug Discovery

Praful Shah, Ph.D., Director, Product Development

Linnea Tanner, Director, Regulatory Affairs

BACKGROUND:

Myogen, Inc., (Myogen) is developing BSF 208075, proposed for the treatment of pulmonary arterial hypertension. Myogen requested a Chemistry, Manufacturing and Controls (CMC) type B pre-NDA meeting on May 17, 2006, received May 18, 2006, to discuss Chemistry, Manufacturing and Controls issues associated with electronic CTD submission, including proposed timing, format and content of the data package. Myogen submitted a pre-meeting CMC briefing document dated June 28, 2006, received June 29, 2006, providing additional information on discussion topics and questions. FDA provided written responses to all questions outlined in the briefing document on July 25, 2006, via email from Scott N. Goldie, Ph.D., (ONDQA) to Todd Marshall, (Myogen). These preliminary draft responses were archived in the administrative file. Myogen and FDA discussed the responses at the face to face meeting on July 26, 2006. FDA supplied written revisions to the preliminary responses to questions 4 and 8 at the meeting, and are included in these meeting minutes.

MEETING DISCUSSION:

The questions from the Myogen meeting packages are related verbatim. The pre-meeting responses submitted by FDA to Myogen are included. Where additional discussion or clarification occurred during the meeting, a summary is recorded below. The revised responses to questions 4 and 8 that were distributed to Myogen by FDA are included below.

Drug Substance

FDA Preliminary Response: Your proposed starting materials as presented in the meeting package are acceptable.

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 Draft Labeling

 Deliberative Process

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/s/

Ramesh Sood
8/23/2006 10:40:50 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 64,915

Myogen, Inc.
Attention: Todd Marshall, RAC
Associate Director, Regulatory Affairs
7575 West 103rd Avenue, Suite #102
Westminster, CO 80021

Dear Mr. Marshall:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BSF 208075, (Ambrisentan).

We also refer to the meeting between representatives of your firm and the FDA on July 26, 2006. The purpose of the meeting was to discuss Chemistry, Manufacturing and Controls issues associated with electronic CTD submission, including proposed timing, format and content of the data package for BSF 208075, Ambrisentan.

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

If you have any questions, please call me at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure

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Meeting Minutes
May 19, 2006

Drug: ambrisentan
IND: 64,915
Sponsor: Myogen, Inc.

Internal Pre-Meeting: May 11, 2006
Pre-Meeting Comments sent to sponsor: May 17, 2006

Type: Pre-NDA
Classification: B

FDA Participants:

Norman Stockbridge, M.D., Ph.D.	Director Division of Cardiovascular and Renal Products
Thomas Marciniak, M.D.	Team Leader, Clinical Division of Cardiovascular and Renal Products
Tim Link, Ph.D.	Pharmacologist Division of Cardiovascular and Renal Products
Lydia Velazquez, Pharm.D.	Clinical Pharmacologist Division of Clinical Pharmacology 1
Cherry Liu, Ph.D.	Statistician Division of Biometrics 1
Edward Fromm	Chief, Project Management Staff Division of Cardiovascular and Renal Products
Melissa Robb	Regulatory Health Project Manager Division of Cardiovascular and Renal Products
Mary Ross Southworth, Pharm.D.	Safety Reviewer Division of Drug Risk Evaluation, Office of Surveillance and Epidemiology
Mary Dempsey	Project Management Officer Office of Surveillance and Epidemiology -IO
Cheryle Milburn	Regulatory Health Project Manager Office of Surveillance and Epidemiology -IO

Myogen Participants:

Michael Gerber, M.D.	Senior Vice President, Clinical Development and Regulatory Affairs
Richard Gorczynski, Ph.D.	Senior Vice President, Research and Development
Gwyn Evans	Director, Ambrisentan Program Management
Craig Hartman, Ph.D.	Director, Development
Laurie Wiedl, Ph.D.	Senior Scientist, Toxicology
Christopher Dufton, Ph.D.	Associate Director, Clinical Science
Brian Wiens, Ph.D.	Director, Biometrics and Data Management
Darrin Despain	Principal Statistician, Biometrics and Data Management
Linnea Tanner	Director, Regulatory Affairs
Liam Curran	Senior Manger, Regulatory Operations

Background:

Ambrisentan is a propanoic acid class endothelin receptor antagonist, selective for the endothelin type-A receptor being developed for the treatment of pulmonary arterial hypertension (PAH) in WHO Group 1 patients to improve exercise capacity, delay clinical worsening, ~~_____~~. The sponsor requested this meeting to confirm that the content, format, and analysis plans for the clinical and nonclinical data packages meet the expectations of the Agency and to clarify any remaining questions the Agency has regarding these data. The sponsor is planning to submit a New Drug Application (NDA) in the electronic Common Technical Document format in October 2006.

Questions:

1. *Myogen believes that the clinical data package consisting of 2 pivotal randomized, placebo-controlled Phase 3 studies (AMB-320 [ARIES-1] and AMB-321 [ARIES-2]), two Phase 2 studies (AMB-220 and AMB-222), 2 long-term safety and efficacy studies (AMB-220-E and AMB-320/321-E) and seven Phase 1 studies to support clinical pharmacology and pharmacology is an adequate basis to submit the NDA and support marketing approval. Does the Division agree?*

Preliminary Response

The Division agrees. However, you should also include data to support once daily dosing. An example of such data would be 6-minute walk at trough or late afternoon or evening.

Discussion during Face to Face Meeting

The sponsor stated that ambrisentan's terminal half-life is very long according to data collected during pivotal Phase 3 studies. The Division clarified that the sponsor should be evaluating the effective half-life or EC50. However, this may not be as important if the sponsor believes that at a small fraction of peak, ambrisentan has saturated all receptors. But, in that case, this would result in no dose-response being seen. The sponsor stated that there is a dose-response seen. The Division believes that the sponsor will need to address this issue in their NDA application. The sponsor could provide data to support that dose does not matter as the receptors are saturated early or submit other data to support once daily dosing.

The Division believes it is important to have data to describe the duration of a symptomatic treatment. The Office may have a different opinion of what data is needed at trough to support approval.

The sponsor stated that besides the symptomatic benefit (improvement in 6-minute walk distance) evaluated, other endpoints that were significant included time to clinical worsening, change in WHO functional class, and improvement in quality of life. The Division stated that showing significance in these types of outcomes may make it less worrisome that duration of effect data are not available. However, as the fixed benefit outcome becomes less meaningful, it will become more difficult for the sponsor to argue that these data are not important. The Division noted that it is possible that better outcomes would have been seen if a BID regimen would have been studied.

The sponsor stated that patients were instructed to take their medications in the AM. However, patients performed exercise testing at any time throughout the day. The sponsor believes that they will not have data at trough or late in the evening, but will be able to provide a good sample of walks at times from 8 AM-6 PM. The Division inquired if there was information available from patients on the time they took their medication. The sponsor stated that that information was not collected. The sponsor added that this information may not be useful as many would argue that endothelin receptor antagonists do not have direct vasodilator properties.

The Division stated that this is not an issue that would result in the NDA not being filed. In addition, the application could get approved without these data. In the past, an application was approved for this

indication with a post-marketing commitment to evaluate dose further. Another application for this indication was approved with scant data on the dosing interval. However, if we were to approve ambrisentan without such information, the lack of data on duration of effect would likely be incorporated in the labeling. The Division suggested the sponsor include some argument in their NDA that ambrisentan has an effect on some measure of disease progression or demonstrates an important clinical benefit and therefore, these data are not essential. The Division stated that the sponsor needs to have some rationale for the dosing interval.

2. *Myogen believes the pre-specified analysis plans summarized in Section 12.0 for the individual pivotal Phase 3 studies (AMB-320 and AMB-321), integrated (combined) analysis of the pivotal Phase 3 studies (AMB-320 and AMB-321), and the long-term Phase 3 extension study (AMB-320/321-E) are adequate to evaluate the efficacy and safety of ambrisentan. Does the Division agree?*

Preliminary Response

The Division agrees, but we will also evaluate the data using other analyses.

Discussion during Face to Face Meeting

The sponsor noted the Division's preliminary response and stated that they will provide datasets so the Division can conduct other analyses.

3. *Representative tables and figures are discussed in Section 12.0 and are provided in Appendices 20.3-20.5. Does the Division agree that presentation of data is appropriate?*

Preliminary Response

Your planned presentation of data is appropriate; however, for data that are not normally distributed, please present the data as median (with 25th and 75th percentiles), in addition to mean (\pm standard deviation).

Discussion during Face to Face Meeting

The sponsor stated that most of the presented data includes median data, without the 25th and 75th percentiles. The sponsor would like to follow-up in writing with their proposed plan for data presentation and get concurrence from the Division. The Division agreed.

4. *The target submission date for the ambrisentan NDA is October 2006 and Myogen has selected a data cut-off date of 16 February 2006 for the database lock for all ongoing long-term studies. Myogen will also provide a tabulated summary of all SAEs that occurred from the data cut-off date of 16 February 2006 up to 90 days prior to submission of the NDA. Finally, Myogen will provide a 120-day safety update with a data cut-off date of approximately 30 days after the submission of the NDA (90 days prior to the submission of the 120-day safety update). Does the Division agree that this plan is acceptable?*

Preliminary Response

The Division agrees but would like an integrated safety dataset submitted for review.

Discussion during Face to Face Meeting

The sponsor stated they plan to integrate data from the pivotal trials together and data from the long-term trials together. The Division agreed with this plan.

5. *Ambrisentan has been granted Orphan Drug Designation and is therefore exempt from providing pediatric use information (21 CFR 314.55) in the original NDA. Myogen does not plan to submit data to support the use of ambrisentan in pediatric patients in the NDA submission.* _____

2

Preliminary Response

The Division agrees.

Discussion during Face to Face Meeting

This question was not discussed at the meeting any further.

6. *At the End-of-Phase 2 (EOP2) meeting held on 27 August 2003, the Division agreed that it would be acceptable to submit data for the mouse and rat carcinogenicity studies as appropriately formatted electronic datasets for analysis during the NDA review cycle. Myogen plans to submit a complete study report for the rat carcinogenicity study and appropriately formatted electronic datasets for the mouse carcinogenicity study at the time of the original submission of the NDA. Does the Division agree that the format for the electronic datasets (as described in Section 16.0) for the mouse carcinogenicity study is appropriate for review by the Division?*

Preliminary Response

Please clarify what you plan to submit and when in the review cycle it will be submitted.

Discussion during Face to Face Meeting

The sponsor stated that a full report and datasets for the rat and datasets for the mouse will be submitted with the NDA submission. The sponsor will submit the full report on the mouse shortly after the NDA is submitted. The Division stated that this plan is acceptable provided the full study report is submitted within 45 days of the application being received by the Agency. The Division stated that all study data should be submitted with the application, including parameters such as body weight, food consumption, and clinical chemistry in addition to tumor incidence. The sponsor agreed.

7. *Myogen is developing a Risk Minimization Action Plan (RiskMAP) to assure that the potential safety risks associated with ambrisentan are minimized while preserving the benefits. Ambrisentan will likely be prescribed through an access program in a closed distribution network. Does the Division anticipate that ambrisentan may be approved under Subpart H (21 CFR 314.520) with restrictions to assure safe use?*

Preliminary Response

The Division agrees.

Discussion during Face to Face Meeting

The sponsor clarified that they are trying to determine if they develop a RiskMAP for use with ambrisentan, will the NDA have to be approved under Subpart H or would the Division consider granting it an unrestricted

approval. The Division stated that even if ambrisentan is less hepatotoxic than other endothelin receptor antagonist, it likely has the same teratogenicity associated with the drug class. Therefore, the Division is unsure if a potent teratogen should be available unrestricted. It is likely that even a little evidence of hepatotoxicity would result in the drug being approved under Subpart H (restricted distribution).

8. *As part of the Risk Minimization Action Plan (RiskMAP), Myogen will develop educational materials for prescribers and patients. Myogen proposes _____ in Module 1 of the original NDA submission, but all other materials will be submitted during the review of the NDA based upon mutually agreed timelines. Does Division agree that this plan is acceptable?*

Preliminary Response

- It would be valuable to the review process to submit all RiskMAP materials at the time of the original NDA submission, and such materials should be clearly marked.
- When the RiskMAP is submitted, you are encouraged to include a background section that outlines the teratogenicity, testicular toxicity, and hepatotoxicity safety risks that are the basis for the program. Additionally, we request that the submission provide the overall goals and objectives of the risk management program, identify which elements of the program would be implemented to achieve those goals and objectives, and explain how they would achieve them. A rationale for each element of the proposed limited distribution program should be included. The submission should also include a plan to evaluate the effectiveness of the proposed RiskMAP.
- You propose to submit _____ in your NDA submission. Products that are required to have a Medication Guide _____ . The Medication Guide would be the only allowable approved patient labeling.
- For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:

Premarketing Risk Assessment: <http://www.fda.gov/cder/guidance/6357fml.htm>

Development and Use of Risk Minimization Action Plans:

<http://www.fda.gov/cder/guidance/6358fml.htm>

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:

<http://www.fda.gov/cder/guidance/6359OCC.htm>

- If there is any information on product medication errors from the premarketing clinical experience, ODS requests that this information be submitted with the NDA application.
- You are encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.

Discussion during Face to Face Meeting

The sponsor stated they plan to submit their RiskMAP for review prior to the NDA submission. The Agency stated that it is difficult to review this prior to a clinical review outlining areas of concern has been completed. The sponsor therefore plans to submit their RiskMAP with the NDA application.

The sponsor noted that they have already submitted their proposed proprietary name for review and plans to submit all labeling for review with the NDA. The Division noted that the sponsor's proposed proprietary name is currently under review by the Office of Surveillance & Epidemiology. However, proprietary names submitted under INDs have a lower priority for review than those submitted with a new NDA.

9. *Myogen will provide all references cited in Module 2 of the CTD at the time of the original NDA submission, except for references that are dated prior to 1980. References in the other Modules will be available upon request. Does Division agree that this plan is acceptable?*

Preliminary Response

The Division agrees.

Discussion during Face to Face Meeting

This question was not discussed at the meeting any further.

Additional Comments:

Preliminary Response

Please submit the following datasets to support the population pharmacokinetic analysis:

- All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
- A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Discussion during Face to Face Meeting

The sponsor stated that they have provided the information the Division included in their pre-meeting comments to their population PK vendor and will contact the Division for further discussion if needed regarding this issue.

The sponsor requested to discuss an additional question submitted to the Division in serial #127, dated March 15, 2006, and the answer provided by the Division in a letter dated April 20, 2006, as follows:

Myogen will submit an integrated analysis of the pivotal Phase 3 studies, AMB-320 and AMB-321, which will provide a robust comparison of safety for 3 doses of ambrisentan to placebo for a 12-week period. In addition, a separate long-term integrated analysis of AMB-320, AMB-321, and AMB-320/321-E will provide a broad evaluation of safety for 3 blinded doses of ambrisentan for periods of more than 2 years, including

blinded fixed doses for at least 24 weeks. Myogen believes these integrated analyses, which will be provided as two additional clinical study reports, supplemented with key animal and pharmacokinetic data, and summarized in the CTD Summary of Safety, will satisfy the requirement for the Integrated Summary of Safety. Does the Division agree?

The Division agrees. However, since only approximately 400 subjects were exposed in these studies, the Division believes this number of exposures is inadequate to evaluate the safety of this drug. You should note that the Division will be reviewing the accumulated safety data to ensure it provides sufficient support for relevant doses.

Based on the different design and significant difference of adverse events between Phase 2 and Phase 3 studies, the Division agrees that the analysis of safety for the two Phase 2 studies (AMB-220 and AMB-222) should be presented separately from the Phase 3 studies. In addition, a study of evaluation of QTc should be provided with the application.

The sponsor clarified that 400 patients is the number of patients enrolled in the 2 pivotal trials. This number does not include patients enrolled in Phase 1 and 2 trials. The sponsor stated they have at least 720 patients exposed, including long-term data. The Division stated that this is a review issue, and that the application would be filable with this amount of data.

Signature, minutes preparer: *{See appended electronic signature page}*

Concurrence Chair: *{See appended electronic signature page}*

Drafted: 5/23/06 Finaled: 5/26/06

RD:

Stockbridge	5/25/06
Marciniak	5/24/06
Link	5/24/06
Velazquez	5/23/06
Liu	5/23/06
Fromm	5/25/06
Southworth	5/23/06
Dempsey	5/23/06
Milburn	5/23/06

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/s/

Melissa Robb
5/26/2006 07:39:41 AM

Norman Stockbridge
5/30/2006 08:56:19 AM

Dec. 17, 2004

Re: IND 64,915, Submission No. 064

Memorandum of telephone communication

The above submission reported excessive mortality observed at the high dose level in both the rat and mice carcinogenicity studies which are currently ongoing. This reviewer forwarded their findings and proposed reduction of the dosing to the Executive Carcinogenicity Assessment Committee on 12/15 for evaluation. Concurrence with the proposed dose reduction was received from Dr. Jacobsen-Kram and Dr. Jacobs on the same day. For further details regarding the doses employed and the proposed reduction, please refer to the original submission (064).

The agreement on dose reduction was communicated to the Sponsor's representative, Dr. Lynne Weissberger by telephone (message on voice mail) at approximately 12:30 p.m. on 12/17/04.

William T. Link

Pharm/Tox Reviewer for IND 64,915

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/s/

William Link
12/20/04 11:07:46 AM
PHARMACOLOGIST

Minutes of a Meeting
August 27, 2003

Drug: BSF 208075 (ambrisentan)
IND: 64,915
Sponsor: Myogen, Inc.

Date Requested: May 16, 2003
Date Confirmation Faxed: May 23, 2003
Date Reschedule Requested per Quintiles: July 3, 2003
Date Reschedule Confirmation Faxed: July 8, 2003
Briefing Package Received: August 6, 2003

Type: End of Phase 2
Classification: B

FDA Participants:

Robert Temple, M.D.	Director, ODE I, HFD-101
Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Juan Carlos Pelayo, M.D.	Medical Officer, HFD-110
Katharine Lillie, M.D.	Medical Officer, HFD-110
Monica Cooper, Ph.D.	Chemist, HFD-810
Angelica Dorantes, Ph.D.	Pharmacokineticist, HFD-860
William T. Link, Ph.D.	Pharmacologist, HFD-110
John Lawrence, Ph.D.	Statistician, HFD-710
Jasmine Choi, Ph.D.	Statistician, HFD-710
Melissa Robb	Regulatory Health Project Manager, HFD-110

Sponsor Participants:

Michael J. Gerber, M.D.	Sr. Vice President, Clinical Development and Regulatory Affairs, Myogen, Inc.
Richard J. Gorczynski, Ph.D.	Vice President, Research and Development, Myogen, Inc.
Rosemary Evans, M.D., M.P.H.	Senior Director, Clinical Development, Myogen, Inc.
Robert L. Roden, M.S., MBA	Director, Ambrisentan Program, Myogen, Inc.
Christopher Dufton, Ph.D.	Clinical Scientist, Ambrisentan Program, Myogen, Inc.

Background:

Ambrisentan is being developed for the treatment of patients with pulmonary arterial hypertension (PAH). The sponsor requested a meeting to seek concurrence from the Agency on the design of the Phase 3 clinical development program and the Phase 3 clinical studies. Additionally, the sponsor would like to reach agreement on the total number of subjects and length of exposure that would be required to demonstrate safety in this patient population.

Meeting:

The Agency then noted their concern with dose selection for the proposed Phase 3 trial. The Agency was unsure if the Phase 2 results showed that ambrisentan was effective at any of the doses studied because there was no placebo group and all doses looked the same. The sponsor stated that they chose to conduct a study without a placebo-control because they had been advised that with the approval of bosentan, a placebo-control group was considered inappropriate. Therefore, the sponsor studied four dose groups, 1, 2.5, 5 and 10 mg. The sponsor acknowledged that no dose response was seen, but believes that a drug effect was shown. The sponsor believes the fact that there was improvement noted in patients studied past week 12, which is often not seen in placebo groups, is evidence of effectiveness. The sponsor also points out that a hemodynamic effect was seen at week 12, further evidence of effectiveness. The Agency suggested that the sponsor might perform a smaller, placebo-controlled study, with rising doses, before investing the resources needed for the proposed Phase 3 trial. The Agency believes this will aid in proper dose selection. The Agency stated that the doses chosen for the Phase 3 trial differ only marginally and they believe the trial has a high likelihood of failure. The sponsor supported their choice of 2.5 and 5 mg by stating they believed the results of their Phase 2 trial revealed that the 1 mg dose may not be adequate to sustain effectiveness over a 24 hour period. Meanwhile, the sponsor believed the 10 mg dose did not show much superiority to the 5 mg dose.

The Agency then began answering the sponsor's specific questions:

1. Myogen believes the Clinical Development Plan to conduct two randomized, placebo-controlled Phase 3 studies is sufficient to establish the safety and efficacy of ambrisentan for the treatment of patients with PAH and is therefore acceptable for NDA submission. Does the Agency agree?

The Agency agreed, but suggested an alternative to the sponsor's proposed open-label extension study. The Agency strongly recommended that rather than unblinding the patients and putting all patients on a 2.5 mg dose, allowing investigators to titrate to 1 or 5 mg as indicated, the sponsor should centrally unblind the treatment allocation, and keep all patients on their current dose of ambrisentan, if tolerated. The patients assigned to the placebo group in the initial trial should be rerandomized to either 2.5 or 5 mg of ambrisentan (again, keeping the investigator blinded to dose). This study design would allow for collection of more long-term, comparative data that would be more supportive for safety at the various doses. The Agency believes the only negative aspect of this trial design will be to make its administration slightly more complicated, but sees strong potential benefits for this course. The sponsor will consider this option and submit a revised protocol.

The Agency requested a copy of the Informed Consent and Investigator's Brochure to review to see whether the toxicity warnings were adequately presented. The Agency also requested a longer follow-up for testicular injury. The sponsor stated they plan to follow all patients in the study every 3 months. The Agency agreed that monitoring every 3 months was adequate but said that longer-term evaluation is essential, and should continue in males for as long as they are exposed to drug in the trials. The sponsor inquired about the collection of neurohormones. The sponsor has stated that they have not seen any utility in this data and wanted to know if the Agency believed it to be useful. The Agency stated as these were recommendations made by the Division of Reproductive and Urologic Drug Products (DRUDP), they were unable to comment at this time. The Agency encouraged the sponsor to submit a written argument outlining why they believe these data are not needed. This could be then consulted to DRUDP for comment and advice. The sponsor agreed.

2. Myogen believes that a statistically significant and clinically meaningful increase in placebo-corrected six-minute walk distance is an approvable primary efficacy endpoint for this indication. Does the Agency agree?

The Agency agreed. The Agency commented that the key to this question is a statistically significant increase.

3. Enrollment into the pivotal Phase 3 study will be based on six-minute walk distance and hemodynamic criteria, rather than specified WHO Functional Classification. We believe that if an appropriate proportion of subjects with WHO Functional Class II or III are enrolled in the pivotal Phase 3, then the product labeling should include both of these Classes. Does the Agency agree?

The Agency agreed. The Agency commented that the Clinical Trials section of the labeling always describes the population used in the trial. Meanwhile, the Indications section is data driven. Therefore, the information should appear in at least one of those sections.

4. Myogen believes that a safety database of approximately 400 subjects with a duration of exposure outlined in the Clinical Development Plan would be acceptable for NDA submission. Does the Agency agree?

The Agency believes this number of exposures is on the low side even for this patient population. The Agency cautioned the sponsor that if anything unexpected were to occur, they would not have the power to put anything in context. The sponsor acknowledged this risk.

5. Myogen believes that the pivotal Phase 3 study protocol (draft ARIES-1 protocol in Appendix 1) is suitable for initiation of the Phase 3 program. Does the Agency agree?

The Agency agreed.

6. Does the Agency agree with the proposed statistical considerations and plan?

The Agency said the sponsor would need to have a clear plan for evaluation of the secondary endpoints. In general, we would look at secondary endpoints only if the sponsor has shown an effect on the primary endpoint. The overall (family-wise) error rate for all secondary endpoints should be controlled at $\alpha = 0.05$. The Agency encouraged the sponsor to use a sequential test procedure. In other words, prospectively rank the secondary endpoints and test each endpoint sequentially at $\alpha = 0.05$. Stop testing when a non-significant result is found. It made sense to have endpoints that have a high correlation to the primary endpoint early in the sequence. The sponsor agreed and plans to submit a formal statistical analysis plan for review.

7. Does the Agency agree with the proposed handling of missing efficacy values?

The Agency agrees that the plan proposed by the sponsor to deal with premature discontinuation seems acceptable. The sponsor plans to assign drop outs due to death or clinical worsening the worst rank. Meanwhile, patients who discontinue for other reasons will have their last observation carried forward. The Agency suggested the sponsor include a narrative section for participants to document why they are discontinuing. The Agency believes this may help reviewers determine whether premature discontinuation was due to the drug.

The Agency was also concerned about the handling of early escapes as listed on page 136 of the briefing document. The Agency believes that patients who meet the early escape criteria and are removed from the study may be people that would have been captured in the study as clinically worsening. The Agency suggested following the early escape patients after removal from the study. The sponsor stated they plan to follow all patients as long as they have not withdrawn consent. The sponsor added that they had reviewed this issue of early escapes previously, but will revisit it and submit a new plan for the Agency to review.

8. Myogen believes the Phase 2 safety results indicate that liver function tests (LFTs) may be safely assessed on a monthly basis in the pivotal Phase 3 and all other future studies. In addition, we have proposed several changes to the Dose Adjustment and Monitoring algorithm for aminotransferase elevations. Does the Agency agree with these changes?

The Agency agreed.

9. Myogen believes that evaluation of QTc can be conducted in the Phase 3 studies using the recently proposed Preliminary Concept Paper guidelines, November 15, 2002. Does the Agency agree?

The sponsor stated after reviewing the Preliminary Concept Paper and discussing it with consultants, they believe the best plan was to monitor random ECGs in the target population. The sponsor was concerned with administering a drug from this classification to a healthy population. The Agency commented that with this drug class, they believe an eight day trial using a healthy population is acceptable. The Agency stated that the Preliminary Concept Paper does not require that the trial be conducted using healthy patients, although it may be easier. The Agency stated that the random collection of ECGs is not an acceptable plan. The sponsor stated they believed collection of QTc data may not be indicated for this drug in this population as they already are a very ill population. The Agency believes that this information is clearly still useful, even in a 'sick' population, as it may reveal an easy preventative measure that could be followed. Based on this need, the sponsor is expected to provide adequate assessment of the effects of the compound on repolarization. While the Agency acknowledged that what constitutes adequate QT assessment is an issue in evolution and agreed that the sponsor can submit a formal written argument outlining why they believe that a trial evaluating QTc data is not needed for ambrisentan, the Preliminary Concept Paper describes current expectations.

10. Myogen believes that the Phase 3 studies (planned initiation October 2003) can proceed prior to completion of the ongoing 9-month chronic toxicity study in dogs (initiated April 2003). Does the Agency agree?

The Agency agreed. The Agency stated that animal exposure should stay ahead of human exposure.

11. Myogen plans to initiate rat and mouse carcinogenicity studies in the first half of 2004. Myogen believes that marketing approval of ambrisentan will not be withheld pending the completion of carcinogenicity studies. Does the Agency agree?

The Agency did not agree. The Agency acknowledged that the sponsor is developing this drug for a serious illness, but also noted that there are currently three approved therapies for this condition, one of which is in the same drug class. The Agency noted that there are alternative carcinogenicity studies that can be done in the mouse that require shorter exposure times. Unfortunately, there are no shorter exposure studies for rats. The Agency added that it would be acceptable to submit the data during the review time. The sponsor stated they plan to have the final report available 10 months after filing and the data sets available 6 months after filing. The Agency stated that the sponsor could submit appropriately formatted datasets for analysis during the review cycle.

The sponsor noted that they have a concern with conducting the rat carcinogenicity studies. Due to the effects noted in the nasal cavity of rats in the toxicity studies, the sponsor is concerned about how they will be able to conduct the rat carcinogenicity studies. The sponsor is planning on submitting a Special Carcinogenicity Protocol Assessment for review in the next couple weeks. The Agency suggested using other dose selection methods, perhaps a 25 fold AUC exposure. The sponsor commented that even at lower doses they still have concerns. The Agency stated this issue should be addressed by the CAC committee. It was noted that possibly another species rather than rat could be studied.

12. Section 13 of this information package provides current information regarding the CMC development status and plans. Myogen believes that the actions taken to date are appropriate and that the development plan will meet FDA requirements for NDA approval. Does the Agency have any comments at this time?

The Agency noted that they have no comments at this time, but will discuss the issue of starting materials in the future.

The sponsor wanted to address two clinical issues that were not previously discussed. The first issue concerned the length of the trial. The sponsor has written the protocol as a 16 week trial, but wanted to know whether the Agency believed a 12 week trial was sufficient to show efficacy. The Agency agreed that twelve weeks is sufficient for efficacy. Safety long term can be addressed through the blinded follow-on trial, as discussed above.

The other issue the sponsor wanted to discuss was the assignment of a more stringent alpha in one of their trials. The sponsor acknowledged that it is hard to predict effect and outcome in a population never studied, patients currently on Flolan. However, they are confident they will be able to meet this outcome. The sponsor wanted to know if they were unable to achieve this, would they still be able to gain approval. The Agency acknowledged that other factors are considered, such as how close the trial comes to not failing, when making decisions. The Agency added that although this is a small trial, sometimes small trials become very important when evaluating all data, such as the case with bosentan. The Agency also believed it would be hard to understand why this population would have results that differed greatly from what was expected.

The Agency then addressed Clinical Pharmacology issues. The Agency stated it was unclear what data the sponsor has already collected. Therefore, the Agency asked for an update of the clinical pharmacology and biopharmaceutics development program for their product. The Agency noted that both a single dose and multiple dose trial were performed in healthy individuals. The sponsor stated they had done a study on a subpopulation in their Phase 2 trial, collecting data up to hour 6 and at hour 24. They plan to do this again in their Phase 3 trial. The Agency stated that as the drug's half-life after multiple dosing is about 15 hours, the collection time should be extended to at least 72 hours. The Agency also encouraged sparse sampling within the clinical trials as a better method for data collection. The sponsor stated they plan to submit a PK-sparse sampling plan for review.

The Agency inquired whether the sponsor is planning on submitting the protocol for Special Protocol Assessment (SPA). The sponsor is unsure at this time, but will discuss this issue further internally and get back with the Agency. The Agency stated that a SPA allows the sponsor to determine if the changes suggested by the Agency were adequately carried out and will also allow comment on their sparse sampling plan.

Signature, minutes preparer: _____

Concurrence Chair: _____

Drafted: 8/28/03 Finalized: 9/8/03

RD:

Temple	9/8/03
Throckmorton	9/5/03
Stockbridge	9/5/03
Pelayo	9/5/03
Lillie	9/5/03
Cooper	9/4/03
Dorantes	9/4/03

Link	9/4/03
Lawrence	9/2/03
Choi	9/2/03

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/s/

Melissa Robb

9/9/03 11:12:04 AM

Signed by Dr. Temple and Faxed to Sponsor 9/9/03

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain: N/A

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- 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)]? 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? N/A YES NO

- Does the submission contain an accurate comprehensive index? YES NO
If no, explain: N/A

- 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: N/A

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES

2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

Does the eNDA, follow the guidance? (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

- 3. This application is an eCTD NDA. YES
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments: N/A

- Patent information submitted on form FDA 3542a? YES NO

- Exclusivity requested? YES, 7 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 . . ."

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?

N/A Orphan Designation

YES NO

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)?

N/A

YES NO

- Is this submission a partial or complete response to a pediatric Written Request? YES NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 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) YES NO

- PDUFA and Action Goal dates correct in tracking system? 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? YES

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: 64,915

- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) August 27, 2003 NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) May 26, 2006 and August 23, 2006 NO
(CMC)
- Any SPA agreements? Date(s) Only Carcinogenicity NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request: N/A
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application:

N/A

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? 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 | <input checked="" type="checkbox"/> | NO | <input type="checkbox"/> |
| • If no, did applicant submit a complete environmental assessment? | N/A | YES | NO | <input type="checkbox"/> |
| • If EA submitted, consulted to EA officer, OPS? | N/A | YES | NO | <input type="checkbox"/> |

- | | | | | |
|---|-----|-------------------------------------|----|--------------------------|
| • Establishment Evaluation Request (EER) submitted to DMPQ? | YES | <input checked="" type="checkbox"/> | NO | <input type="checkbox"/> |
|---|-----|-------------------------------------|----|--------------------------|

- | | | | | | |
|--|-----|-----|--------------------------|----|--------------------------|
| • If a parenteral product, consulted to Microbiology Team? | N/A | YES | <input type="checkbox"/> | NO | <input type="checkbox"/> |
|--|-----|-----|--------------------------|----|--------------------------|

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ATTACHMENT

MEMO OF FILING MEETING

DATE: February 6, 2007

NDA #: 22-081

DRUG NAMES: Letairis (ambrisentan) 5 and 10 mg Tablets

APPLICANT: Gilead Sciences, Inc.

BACKGROUND: Ambrisentan is a non-sulfonamide, propanoic acid-class, endothelin receptor antagonist. A New Drug Application was received on December 18, 2006 for the use of this NME for the treatment of pulmonary arterial hypertension (WHO Group 1) to improve exercise capacity, delay clinical worsening

ATTENDEES:

Division of Cardiovascular and Renal Products

Norman Stockbridge, M.D., Ph.D.	Director
Thomas Marciniak, M.D.	Team Leader, Clinical
Tim Link, Ph.D.	Pharmacologist
Melissa Robb	Regulatory Health Project Manager
Edward Fromm	Chief, Project Management Staff

Office of New Drug Quality Assessment

Kasturi Srinivasachar, Ph.D.	Pharmaceutical Assessment Lead
Haripada Sarker, Ph.D.	Chemist

Office of Clinical Pharmacology

Patrick Marroum, Ph.D.	Team Leader
Peter Hinderling, M.D.	Senior Advisor
Yaning Wang, Ph.D.	Pharmacometrics

Office of Biostatistics

Cherry Liu, M.D., M.S	Statistician
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Office of Surveillance and Epidemiology

Mary Dempsey	Risk Management Program Coordinator
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ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>	<u>Review Due in DFS</u>
Medical (Efficacy):	Tom Marciniak, M.D.	May 1, 2007
Medical (Safety):	Maryann Gordon, M.D.	May 1, 2007
Secondary Medical:	Norman Stockbridge, M.D., Ph.D.	May 21, 2007
Statistical:	Cherry Liu, M.D., M.S	May 1, 2007
Pharmacology:	Tim Link, Ph.D.	May 1, 2007
Statistical Pharmacology:	None yet assigned, to be determined by Dr. Link	
Chemistry:	Haripada Sarker, Ph.D	April 18, 2007
Biopharmaceutical:	Peter Hinderling, M.D.	May 1, 2007
Pharmacometrics:	Yaning Wang, Ph.D	April 1, 2007

Regulatory Project Management: Melissa Robb

Per reviewers, are all parts in English or English translation? YES NO
 If no, explain: N/A

CLINICAL FILE REFUSE TO FILE
 • Clinical site audit(s) needed? YES NO
 If no, explain:
 • 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. study site audits(s) needed? YES NO

PHARMACOLOGY/TOX N/A FILE REFUSE TO FILE

• GLP audit needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

• Establishment(s) ready for inspection? YES NO

• Sterile product? YES NO

If yes, was microbiology consulted for validation of sterilization? N/A

YES NO

ELECTRONIC SUBMISSION:

Any comments: Yes eCTD

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):

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. 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.
4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. Convey document filing issues/no filing issues to applicant by Day 74.

Melissa Robb
Regulatory Project Manager

**Appears This Way
On Original**

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

/s/

Melissa Robb
2/21/2007 08:46:18 AM
CSO

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

GILEAD SCIENCES INC
Tanner Linnea
7575 West 103rd Ave. #102
Westminster CO 80021-5426
US

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

22-081

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

YES 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:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

2. TELEPHONE NUMBER

303-410-3243

3. PRODUCT NAME

LETAIRIS™ (ambrisentan)

6. USER FEE I.D. NUMBER

PD3006914

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

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT

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? YES 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

CBER, HFM-99

1401 Rockville Pike

Rockville, MD 20852-1448

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

{See appended electronic signature page}

Linnea Tanner

TITLE

Director, Regulatory Affairs

DATE

12/13/2006

9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$.00

Form FDA 3397 (12/03)

ACTION PACKAGE CHECKLIST

Application Information		
BLA # NDA # 22-081	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type NDA
Proprietary Name: Letairis Established Name: ambrisentan Dosage Form: Tablets		Applicant: Gilead Sciences, Inc.
RPM: Dan Brum		Division: DCRP Phone # 301-796-0578
<p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed <input type="checkbox"/> Corrected</p> <p>Date:</p>
❖ User Fee Goal Date		6/18/07
❖ Action Goal Date (if different)		6/15/07
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (<i>specify type and date for each action taken</i>)		<input checked="" type="checkbox"/> None
❖ Advertising (<i>approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (<i>indicate dates of reviews</i>)		<input type="checkbox"/> Requested in AP letter <input checked="" type="checkbox"/> Received and reviewed 4/26/07

❖ Application Characteristics	
Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): 1 (NME)	
NDAs, BLAs and Supplements: <input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input checked="" type="checkbox"/> Orphan drug designation	
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input checked="" type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies
NDAs and NDA Supplements: <input type="checkbox"/> OTC drug	
Other:	
Other comments:	
❖ 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 <ul style="list-style-type: none"> Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<p>❖ Exclusivity</p> <ul style="list-style-type: none"> • NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>) 	<p><input checked="" type="checkbox"/> Included</p>
<ul style="list-style-type: none"> • Is approval of this application blocked by any type of exclusivity? <ul style="list-style-type: none"> • NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>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.</i> • NDAs: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) • NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) • NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (<i>Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.</i>) 	<p><input checked="" type="checkbox"/> No <input type="checkbox"/> Yes</p> <p><input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:</p> <p><input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA # and date exclusivity expires:</p> <p><input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA # and date exclusivity expires:</p> <p><input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA # and date exclusivity expires:</p>
<p>❖ Patent Information (NDAs and NDA supplements only)</p>	
<ul style="list-style-type: none"> • Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<p><input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.</p>
<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. • [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). 	<p>21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified</p> <p>21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)</p> <p><input type="checkbox"/> No paragraph III certification Date patent will expire</p>
<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 section below (Summary Reviews).</i>) • [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's</p>	<p><input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>

notice of certification?

(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)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

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 section below (Summary Reviews).

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) 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 section below (Summary Reviews).

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

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) 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 (b)(2) 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

<p>within the 45-day period).</p> <p>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 section below (Summary Reviews).</p> <p>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.</p>	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)	5/26/07 (DD); 6/XX/07 (OD)
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)	NA
Labeling	
❖ Package Insert	
<ul style="list-style-type: none"> Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	6/14/07
<ul style="list-style-type: none"> Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	6/13/07
<ul style="list-style-type: none"> Original applicant-proposed labeling Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	12/18/06 NDA 21-290 Tracleer (bosentan)
❖ Patient Package Insert	
<ul style="list-style-type: none"> Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	NA
<ul style="list-style-type: none"> Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	NA
<ul style="list-style-type: none"> Original applicant-proposed labeling Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	NA NA
❖ Medication Guide	
<ul style="list-style-type: none"> Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	6/12/07
<ul style="list-style-type: none"> Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	6/6/07
<ul style="list-style-type: none"> Original applicant-proposed labeling Other relevant labeling (e.g., most recent 3 in class, class labeling) 	12/18/06 NDA 21-290 Tracleer (bosentan)
❖ Labels (full color carton and immediate-container labels)	
<ul style="list-style-type: none"> Most-recent division-proposed labels (only if generated after latest applicant submission) 	NA
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	5/25/07
❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)	<input checked="" type="checkbox"/> DMETS 6/1/07 <input checked="" type="checkbox"/> DSRCS 6/1, 6/4/07 <input checked="" type="checkbox"/> DDMAC 6/1, 6/4/07 <input checked="" type="checkbox"/> SEALD 6/1, 6/4/07 <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs

Administrative Documents	
Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	6/12/07 ADRA Review
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> • Center Director's Exception for Review memo • If AP: OC clearance for approval 	NA NA
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies	<input type="checkbox"/> None
<ul style="list-style-type: none"> • Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) 	Action Letter
<ul style="list-style-type: none"> • Incoming submission documenting commitment 	Pending as of 6/14/07
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	<input checked="" type="checkbox"/>
❖ Internal memoranda, telecons, email, etc.	<input checked="" type="checkbox"/>
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) 	6/11/07
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date</i>) 	<input checked="" type="checkbox"/> No mtg 5/19/06
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date</i>) 	<input checked="" type="checkbox"/> No mtg 8/27/03
<ul style="list-style-type: none"> • Other (e.g., EOP2a, CMC pilot programs) 	NA
❖ Advisory Committee Meeting	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date of Meeting 	NA
<ul style="list-style-type: none"> • 48-hour alert or minutes, if available 	NA
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	NA
CMC/Product Quality Information	
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	5/16/07, 6/6/07,
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	
<ul style="list-style-type: none"> • <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) 	3/30/07
<ul style="list-style-type: none"> • <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) 	
<ul style="list-style-type: none"> • <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) 	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) 	Date completed: 6/12/07 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (<i>indicate date(s)</i>) • Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) 	NA <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	5/1/07
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6/13/07
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input type="checkbox"/> No 5/22/07
❖ ECAC/CAC report/memo of meeting	See P/T review 5/1/07
❖ Nonclinical inspection review Summary (DSI)	<input checked="" type="checkbox"/> None requested
Clinical Information	
❖ Clinical review(s) (<i>indicate date for each review</i>)	5/16/07
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	12/13/06
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)	4/30/07
❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>)	5/17/07
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested
• Clinical Studies	4/12/07; 5/31/07
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/16/07
❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/7/07

Appendix A to Action Package Checklist

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

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication **AND** a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.