

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207620Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 10/31/2016
See OMB Statement on Page 3.

**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

207620

NAME OF APPLICANT/NDA HOLDER

Novartis Pharmaceuticals Corporation

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)

To Be Determined

ACTIVE INGREDIENT(S)

(sacubitril/valsartan)

STRENGTH(S)

50mg, 100mg, 200mg

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

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

1. GENERAL

a. United States Patent Number

7,468,390

b. Issue Date of Patent

December 23, 2008

c. Expiration Date of Patent

November 27, 2023

d. Name of Patent Owner

Novartis AG

Address (of Patent Owner)

Lichtstrasse 35 CH-4056 Basel Switzerland

City/State

ZIP Code

FAX Number (if available)

011 41 61 324 8001

Telephone Number

011 41 61 324 1111

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 f.e.)

One Health Plaza

City/State

East Hanover, New Jersey

ZIP Code

07936

FAX Number (if available)

General Counsel

Telephone Number

862-778-8300

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 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

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

5. No Relevant Patents

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

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



11/13/2014

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

David Kurlandsky

Address

One Health Plaza

City/State

East Hanover, New Jersey

ZIP Code

07936

Telephone Number

862-778-5806

FAX Number (if available)

973-781-8064

E-Mail Address (if available)

david.kurlandsky@novartis.com

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRASStaff@fda.hhs.gov

"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 number."

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7620 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Identify the precise words of the approval labeling that describe with specificity the patented method of use.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 10/31/2016
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207620

NAME OF APPLICANT/NDA HOLDER

Novartis Pharmaceuticals Corporation

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)

To Be Determined

ACTIVE INGREDIENT(S)

(sacubitril/valsartan)

STRENGTH(S)

50mg, 100mg, 200mg

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

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

1. GENERAL

a. United States Patent Number

8,101,659

b. Issue Date of Patent

January 24, 2012

c. Expiration Date of Patent

January 14, 2023

d. Name of Patent Owner

Novartis AG

Address (of Patent Owner)

Lichtstrasse 35 CH-4056 Basel Switzerland

City/State

ZIP Code

FAX Number (if available)

011 41 61 324 8001

Telephone Number

011 41 61 324 1111

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 f.e.)

One Health Plaza

City/State

East Hanover, New Jersey

ZIP Code

07936

FAX Number (if available)

Telephone Number

862-778-8300

E-Mail Address (if available)

General Counsel

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 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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(s) (as listed in the patent)	Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input type="checkbox"/> Yes <input type="checkbox"/> No
--	---

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

5. No Relevant Patents

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



11/13/2014

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

David Kurlandsky

Address

One Health Plaza

City/State

East Hanover, New Jersey

ZIP Code

07936

Telephone Number

862-778-5806

FAX Number (if available)

973-781-8064

E-Mail Address (if available)

david.kurlandsky@novartis.com

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
 Food and Drug Administration
 Office of Chief Information Officer
 Paperwork Reduction Act (PRA) Staff
 PRAStaff@fda.hhs.gov

"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 number."

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
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- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7620 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Identify the precise words of the approval labeling that describe with specificity the patented method of use.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 10/31/2016
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1. GENERAL

a. United States Patent Number

8,404,744

b. Issue Date of Patent

March 26, 2013

c. Expiration Date of Patent

January 14, 2023

d. Name of Patent Owner

Novartis AG

Address (of Patent Owner)

Lichtstrasse 35 CH-4056 Basel Switzerland

City/State

ZIP Code

FAX Number (if available)

011 41 61 324 8001

Telephone Number

011 41 61 324 1111

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.)

One Health Plaza

City/State

East Hanover, New Jersey

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07936

FAX Number (if available)

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862-778-8300

E-Mail Address (if available)

General Counsel

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

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4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

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

5. No Relevant Patents

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

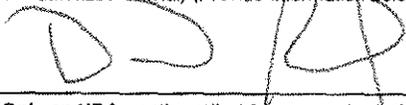
6. Declaration Certification

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



11/13/2014

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

David Kurlandsky

Address

One Health Plaza

City/State

East Hanover, New Jersey

ZIP Code

07936

Telephone Number

862-778-5806

FAX Number (if available)

973-781-8064

E-Mail Address (if available)

david.kurlandsky@novartis.com

This section applies only to requirements of the Paperwork Reduction Act of 1995

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRASStaff@fda.hhs.gov

"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 number."

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7620 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Identify the precise words of the approval labeling that describe with specificity the patented method of use.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

**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

207620

NAME OF APPLICANT/NDA HOLDER

Novartis Pharmaceuticals Corporation

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)

To Be Determined

ACTIVE INGREDIENT(S)

(sacubitril/valsartan)

STRENGTH(S)

50mg, 100mg, 200mg

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

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

1. GENERAL

a. United States Patent Number

8,796,331

b. Issue Date of Patent

August 5, 2014

c. Expiration Date of Patent

January 14, 2023

d. Name of Patent Owner

Novartis AG

Address (of Patent Owner)

Lichtstrasse 35 CH-4056 Basel Switzerland

City/State

ZIP Code

FAX Number (if available)

011 41 61 324 8001

Telephone Number

011 41 61 324 1111

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.)

One Health Plaza

City/State

East Hanover, New Jersey

ZIP Code

07936

FAX Number (if available)

Telephone Number

862-778-8300

E-Mail Address (if available)

General Counsel

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 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, 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(s) (as listed in the patent) 1-3, 5-8 Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.)
The treatment of heart failure (NYHA class II-IV) (b) (4)

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



11/13/2014

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

David Kurlandsky

Address

One Health Plaza

City/State

East Hanover, New Jersey

ZIP Code

07936

Telephone Number

862-778-5806

FAX Number (if available)

973-781-8064

E-Mail Address (if available)

david.kurlandsky@novartis.com

This section applies only to requirements of the Paperwork Reduction Act of 1995.

DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.

The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer
Paperwork Reduction Act (PRA) Staff
PRAStaff@fda.hhs.gov

"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 number."

INFORMATION AND INSTRUCTIONS FOR FORM 3542a

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

General Information

- * To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- * Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- * Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- * Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- * Only information from form 3542 will be used for Orange Book publication purposes.
- * Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7620 Standish Place, Rockville, MD 20855.
- * The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- * Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Identify the precise words of the approval labeling that describe with specificity the patented method of use.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

Department of Health and Human Services Food and Drug Administration		Form Approved: OMB No. 0910-0513 Expiration Date: 10/31/2016 See OMB Statement on Page 3.	
PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT <i>For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use</i>		NDA NUMBER 207620	
		NAME OF APPLICANT/NDA HOLDER Novartis Pharmaceuticals Corporation	
<i>The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.</i>			
TRADE NAME (OR PROPOSED TRADE NAME) To Be Determined			
ACTIVE INGREDIENT(S) (sacubitril/valsartan)		STRENGTH(S) 50mg, 100mg, 200mg	
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 <i>only</i> information relied upon by FDA for listing a patent in the Orange Book.			
For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.			
FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.			
For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.			
1. GENERAL			
a. United States Patent Number 8,877,938		b. Issue Date of Patent November 4, 2014	c. Expiration Date of Patent May 27, 2027
d. Name of Patent Owner Novartis AG		Address (of Patent Owner) Lichtstrasse 35 CH-4056 Basel Switzerland	
		City/State	
		ZIP Code	FAX Number (if available) 011 41 61 324 8001
		Telephone Number 011 41 61 324 1111	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.) One Health Plaza	
		City/State East Hanover, New Jersey	
		ZIP Code 07936	FAX Number (if available)
General Counsel		Telephone Number 862-778-8300	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?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No	
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> 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 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

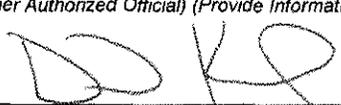
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

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

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

5. No Relevant Patents

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

6. Declaration Certification	
<p>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.</p> <p>Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.</p>	
<p>6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)</p> 	<p>Date Signed</p> <p>11/13/2014</p>
<p>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).</p>	
<p>Check applicable box and provide information below.</p>	
<input type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input checked="" type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
<p>Name</p> <p>David Kurlandsky</p>	
<p>Address</p> <p>One Health Plaza</p>	<p>City/State</p> <p>East Hanover, New Jersey</p>
<p>ZIP Code</p> <p>07936</p>	<p>Telephone Number</p> <p>862-778-5806</p>
<p>FAX Number (if available)</p> <p>973-781-8064</p>	<p>E-Mail Address (if available)</p> <p>david.kurlandsky@novartis.com</p>
<p>This section applies only to requirements of the Paperwork Reduction Act of 1995.</p> <p>*DO NOT SEND YOUR COMPLETED FORM TO THE PRA STAFF EMAIL ADDRESS BELOW.*</p> <p>The burden time for this collection of information is estimated to average 20 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden, to:</p> <p style="text-align: center;"> Department of Health and Human Services Food and Drug Administration Office of Chief Information Officer Paperwork Reduction Act (PRA) Staff PRAStaff@fda.hhs.gov </p> <p style="text-align: center;"><i>"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 number."</i></p>	

INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7620 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already granted. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
 - 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.
- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement (pending method of use).

- 4.2) For each pending method of use claimed by the patent, identify by number the claim(s) in the patent that claim the pending use of the drug. An applicant may list together multiple patent claim numbers and information for each pending method of use, if applicable. However, each pending method of use must be separately listed within this section of the form.
- 4.2a) Identify the precise words of the approval labeling that describe with specificity the patented method of use.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY

NDA # 207620

SUPPL # n/a

HFD # 110

Trade Name Entresto

Generic Name LCZ696 (sacubitril/valsartan)

Applicant Name Novartis Pharmaceuticals Corp.

Approval Date, If Known: Target date, July 1, 2015, PDUFA goal August 17, 2015

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.

n/a

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:

n/a

d) Did the applicant request exclusivity?

YES

NO

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

5 years

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

YES NO

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

n/a

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#

Note: Based on the new combination drug guidance, we were advised to mark no to this answer. One if the drugs is valsartan, the other is a NCE.

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.

=====
Name of person completing form: Alexis Childers
Title: Sr. Project Manager
Date: June 16, 2015

Name of Office/Division Director signing form: Norman Stockbridge, MD, PhD
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

ALEXIS T CHILDERS
06/16/2015

NORMAN L STOCKBRIDGE
06/16/2015

Debarment Certification

Novartis Pharmaceuticals Corporation certifies that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this application.



Masha Berkhin, PharmD
Global Program Regulatory Director
Drug Regulatory Affairs



Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 207620	NDA Supplement # NA	If NDA, Efficacy Supplement Type: NA <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Entresto Established/Proper Name: LCZ696 (sacubitril/valsartan) Dosage Form: Tablets		Applicant: Novartis Pharmaceuticals Corp. Agent for Applicant (if applicable): N/A
RPM: Alexis Childers, RAC		Division: Cardiovascular & Renal Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p style="margin: 0;"><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p style="margin: 5px 0 0 20px;"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: _____ </p> <p style="margin: 5px 0 0 20px;"><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> Proposed action: July 7, 2015 User Fee Goal Date is <u>August 17, 2015</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

❖ Application Characteristics ³	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only): <i>(confirm chemical classification at time of approval)</i></p> <p> <input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC <input type="checkbox"/> Breakthrough Therapy designation </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> 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 </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ 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"> Indicate what types (if any) of information were issued 	<input type="checkbox"/> None <input checked="" type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other: Information Advisory
❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? If so, specify the type 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
<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. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action & date: Approval 7Jul15
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	
<ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) 	2/9/15, 6/19/15 1/28/15, 6/11/15
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: 2/12/15 DMEPA: 6/1/15, 6/16/15 DMPP/PLT : 6/4/15 OPDP: 6/8/15 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other:DMPH 5/26/15
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	2/12/15
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>June 24, 2015</u> If PeRC review not necessary, explain: _____ 	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	Included
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	Included
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	1/23/14 Pre-NDA 1/22/15 Top-Line
• EOP2 meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• Mid-cycle Communication (<i>indicate date of mtg</i>)	3/19/15
• Late-cycle Meeting (<i>indicate date of mtg</i>)	6/3/15
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)	12/6/13 CMC pre-NDA
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	7/7/15
Division Director Summary Review (<i>indicate date for each review</i>)	6/22/15
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	6/12/15
PMR/PMC Development Templates (<i>indicate total number</i>)	3
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	1/20/15, 5/15/15, 7/2/15
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	In clinical review dated 5/15/15

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	5/22/15 <input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	6/8/15
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	2/3/15, 5/20/15
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	1/27/15, 5/14/15, 6/26/15
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 7/2/15
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1/30/15, 5/15/15
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	5/18/15
❖ ECAC/CAC report/memo of meeting	4/9/15
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	5/15/15, 6/30/15
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	2/5/15 Micro
❖ Environmental Assessment (check one) (original and supplemental applications)	
<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>)	5/11/15
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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

/s/

ALISON L BLAUS

07/07/2015

Signing on behalf of Alexis Childers



NDA 207620

INFORMATION REQUEST

Novartis Pharmaceuticals Corporation .
Attention: Masha Berkhin, PharmD.
Global Program Regulatory Director.
One Health Plaza, Building 100
East Hanover, NJ 07936-1080

Dear Dr. Berkhin:

Please refer to your New Drug Application (NDA) dated September 30, 2014, received September 30, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Entresto(sacubitril/valsartan)Tablets.

We are reviewing the Chemistry, Manufacturing, and Controls (CMC) 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.

We accept the proposed dissolution acceptance criterion of $Q = \frac{(b)}{(4)}\%$ at $\frac{(b)}{(4)}$ minutes $\frac{(b)}{(4)}$. As discussed during the June 11, 2015, teleconference, we recommend further optimization of the dissolution method $\frac{(b)}{(4)}$ as a post-marketing commitment (PMC). The goals of the in vitro dissolution study under the PMC are: 1) to optimize the dissolution method parameters $\frac{(b)}{(4)}$ and 2) to set an adequate dissolution acceptance criterion for the drug product using the full dissolution profile data collected from an adequate number of commercial batches (i.e., n=12 batches/each strength).

This Post-Marketing Commitment should be fulfilled within 12 months from the action date for:

- 1) Development of a new dissolution method for all the strengths with demonstrated discriminating ability, $\frac{(b)}{(4)}$
- 2) Setting of the final dissolution acceptance criterion for Entresto™ (sacubitril/ valsartan) Tablets, 200, 100, and 50 mg using the new method and the overall multipoint dissolution profile data from a minimum of 12 commercial batches per strength, manufactured under the same

conditions as those used for the manufactured of the batches used in pivotal clinical trials. The FDA will be open to providing feedback during the method's development process as needed.

We propose the following schedule for the study:

Dissolution Method Development Report Submission: January 1, 2016
Final Report Submission: July 1, 2016

The final report can be submitted as a CBE-30 supplement to the NDA. Please note that if deemed appropriate, the supplement may be upgraded to a prior approval supplement, depending on the outcome of the study. If agreed, please provide your concurrence with the proposed PMC and schedule, in writing, no later than Wednesday, June 24, 2015.

If you have any questions, please contact Maryam Changi, Regulatory Business Process Manager, at (240) 402-2725.

Sincerely,

Wendy I. Wilson-Lee, Ph.D.
Branch Chief (Acting), Branch 1
Division of New Drug Products 1
Office of New Drug Products
OPQ/CDER/FDA

Wendy I.
Wilson -S

Digitally signed by Wendy I.
Wilson -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=13
00396790, cn=Wendy I. Wilson
-S
Date: 2015.06.23 13:05:55
-0400



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207620

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Novartis Pharmaceuticals Corporation
One Health Plaza
Building 100
East Hanover, NJ 07936-1080

ATTENTION: Masha Berkhin, Pharm.D.
Global Program Regulatory Director

Dear Dr. Berkhin:

Please refer to your New Drug Application (NDA) dated and received December 17, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sacubitril/Valsartan Tablets, 24 mg/26 mg, 49 mg/51 mg, 97 mg/103 mg.

We also refer to your correspondence, dated and received April 24, 2015, requesting review of your proposed proprietary name, Entresto.

We have completed our review of the proposed proprietary name, Entresto and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your April 24, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact CDR Darrell Lyons, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4092. For any other information regarding this application, contact Alexis Childers, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0442.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
06/19/2015



NDA 207620

MEETING MINUTES

Novartis Pharmaceuticals Corp.
Attention: Albina Taigounov
Associate Director – Global Regulatory CMC
One Health Plaza, Building 339 – Room 1152
East Hanover, NJ 07936

Dear Ms. Taigounov:

Please refer to your New Drug Application (NDA) dated December 17, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LCZ696 (sacubitril/valsartan) Tablets, 50 mg, 100 mg, 200 mg.

We also refer to the meeting between representatives of your firm and the FDA on April 30, 2015. The purpose of the meeting was to discuss the alignment with the FDA on the proposed control strategy for the LCZ696 due to the uniqueness of the compound and the synthesis.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact Olga Simakova, Regulatory Business Process Manager, at (240) 402-3814.

Sincerely,

{See appended electronic signature page}

Wendy Wilson-Lee, PhD
Branch Chief, Branch I (Acting)
Division of New Drug Products I
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type A
Meeting Category: Chemistry - Other
Meeting Date and Time: April 30, 2015, 11:30 am to 12:30 pm
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903
Application Number: NDA 207620
Product Name: LCZ696 (sacubitril/valsartan) Tablets
Indication: Treatment of heart failure
Sponsor/Applicant Name: Novartis Pharmaceuticals Corp.

FDA ATTENDEES

Office of Pharmaceutical Quality

Thomas Oliver, PhD Division Director (acting)
Wendy Wilson-Lee, PhD Branch Chief (acting)
Mohan Sapru, PhD CMC Lead (acting)
Richard Lostritto, PhD Associate Director for Science (acting), Office of Policy for
Pharmaceutical Quality
Anamitro Banerjee, PhD Drug Substance Reviewer
Olga Simakova, PhD Regulatory Business Process Manager

SPONSOR ATTENDEES

Diane Zezza – Global Head Regulatory Affairs CMC
Dawn Bell – Sr. Global Program Head, Cardio-Metabolic LCZ
Fedra Maria Limoncini – Franchise Head Regulatory CMC
Albina Taigounov – Associate Director, Global Regulatory CMC
Michael Motto – Project Leader Technical Development
Masha Berkhin – Global Program Regulatory Director
Patricia Kay-Mugford – Global Regulatory Therapeutic Area Lead Critical Care

1.0 BACKGROUND

On April 16, 2015, Novartis Pharmaceuticals Corp. submitted a request for a Type A, face-to-face meeting to discuss and ensure the alignment with the FDA on the proposed control strategy for the LCZ696 due to the uniqueness of the compound and the synthesis. The meeting package (slides) was submitted on April 21, 2015.

FDA sent Preliminary Comments to Novartis Pharmaceuticals Corp. on April 29, 2015.

2. DISCUSSION

Question: Does the Agency agree with the Novartis position on the following aspects of the LCZ696 manufacturing and controls?

- Uniqueness of LCZ696 and Novartis approach to ensure that all quality attributes relevant to the patient are controlled
- Control strategy (b) (4) of the (b) (4) active components sacubitril and valsartan
- Characterization and control of sacubitril (b) (4)
- (b) (4)

FDA Response: Based on our review of the information in the NDA submission and the Type A meeting briefing presentation, we recommend that sacubitril (b) (4) and valsartan be designated the regulatory drug substances. However, as noted in our pre-NDA meeting response (June 25, 2014 pre-NDA Meeting, Response to Question 6b), we find the proposed (b) (4) control strategy as outlined in the NDA submission acceptable to support commercial manufacturing.

Also, as noted in our pre-NDA meeting response, we will rely on the (b) (4) to demonstrate stability of the two drug substances. We consider the proposed (b) (4) sufficient to ensure the stability of sacubitril (b) (4). If a (b) (4) is desired or if you wish to assign a re-test period to sacubitril (b) (4), a stability package supporting the proposed (b) (4)/re-test period will need to be submitted for review.

Because sacubitril is a new molecular entity, we would like assurance that the proposed analytical procedures used to test and release sacubitril (b) (4) are capable and appropriate for their intended purposes. Provide method validation results for the analytical procedures listed on the sacubitril (b) (4) specification. Method validation results are not required for compendial analytical procedures.

Discussion: Novartis requested clarification on (b) (4). Specifically, the applicant inquired if the proposed control strategy (b) (4) was acceptable. The Agency indicated that designation of the regulatory drug substances and the control strategy applied to the regulatory drug substances were two separate issues. The Agency confirmed that the proposed control strategies for sacubitril (b) (4), valsartan, (b) (4) were acceptable. (b) (4)

[REDACTED] (b) (4)

Novartis inquired about [REDACTED] (b) (4). The Agency indicated that no change in the established name would be needed because the salt nomenclature policy requires the established name to be based on the free acid sacubitril.

The Agency recommended that Novartis generate stability data for sacubitril [REDACTED] (b) (4). The Agency reiterated that the stability of [REDACTED] (b) (4) would be acceptable if supported by the data. Novartis inquired if the Agency reviewed the twelve (12) months of stability data at accelerated conditions provided for sacubitril [REDACTED] (b) (4) in the January 2015 amendment. The Agency thanked Novartis for pointing out the location of the data and indicated that no additional stability data would be needed unless a [REDACTED] (b) (4) months was desired. Novartis also reiterated the commitment to provide an updated sacubitril [REDACTED] (b) (4) specification with a tightened assay limit, as requested by the Agency.

The Agency requested Novartis provide method validation results for the analytical procedures listed on the sacubitril [REDACTED] (b) (4) specification. The Agency noted that method validation results are not required for compendial analytical procedures. Novartis noted that the requested method validation results were included in the April 15, 2015 amendment. The Agency thanked Novartis for pointing out the location of the requested information and committed to follow-up with Novartis if additional information was needed.

Novartis discussed the recent [REDACTED] (b) (4) and asked if the OPQ review team could provide any additional insight into the expected action date or timeline for resubmitting the [REDACTED] (b) (4). It was recommended that Novartis resubmit the [REDACTED] (b) (4) 60 days before the action date and contact the clinical division regarding the expected action date for the NDA.

Novartis inquired if there were any additional outstanding issues that the Agency wanted to discuss. The Agency indicated that there were no outstanding issues to discuss at this time.

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/s/

WENDY I WILSON-LEE
05/27/2015



NDA 207620

INFORMATION REQUEST

Novartis Pharmaceuticals Corp.
Attention: Masha Berkhin, PharmD
Global Program Regulatory Director
One Health Plaza, Building 100
East Hanover, NJ 07936

Dear Dr. Berkhin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LCZ696 (sacubitril and valsartan) Tablets, 50 mg, 100 mg, 200 mg. We refer to your December 17, 2014, submission and subsequent amendments.

We are reviewing the Product Quality 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. Section 3.2.P.8.1 Stability Summary of the submission includes the description of a protocol deviation due to "inconsistency in dissolution data." We cannot determine an appropriate drug product expiration date without assurance of the validity of the supporting registration stability data. Provide confirmatory stability results, for all drug product stability tests, for the most recent stability sample pulls (18 months for the HDPE bottle configuration, 24 months for the (b) (4) blister configuration) at long-term conditions for all drug product registration stability batches for each tablet strength. The confirmatory testing should be conducted at the commercial drug product stability testing site listed in the NDA submission – (b) (4)
2. Based on the provided data, we recommend that you revise the dissolution acceptance criterion to $Q = \frac{(b)}{(4)}\%$ at (b) (4) minutes instead of the proposed $Q = \frac{(b)}{(4)}\%$ at (b) (4) minutes for sacubitril and valsartan.

Please respond by May 26, 2015.

If you have any questions, call Olga Simakova, Regulatory Project Manager, at (240) 402-3814.

Sincerely,
**Wendy I.
Wilson -S**

Digitally signed by Wendy I. Wilson -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300396790,
cn=Wendy I. Wilson -S
Date: 2015.05.15 13:48:43 -04'00'

Wendy Wilson-Lee, PhD
Branch Chief, Branch I (Acting)
Division of New Drug Products I
Office of New Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

From: Simakova, Olga (CDER)
To: masha.berkhin@novartis.com
Subject: RE: Revised Information Request for NDA 207620 5/15/15
Date: Friday, May 15, 2015 5:40:00 PM
Importance: High

Dear Dr. Berkhin,

I apologize for the confusion, but please see below the revised IR for NDA 207620. Please respond to this revised version and not to the IR sent earlier today (5/15/2015, at 2:13 pm). Comment number 1 was revised.

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LCZ696 (sacubitril and valsartan) Tablets, (b) (4). We refer to your December 17, 2014, submission and subsequent amendments.

We are reviewing the Product Quality 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. Section 3.2.P.8.1 Stability Summary of the submission includes a description of a protocol deviation due to "inconsistency in dissolution data." We cannot determine an appropriate drug product expiration date without assurance of the validity of the supporting registration stability data. Provide additional results for all drug product stability tests for the current stability samples stored in HDPE bottles and (b) (4) blister under long-term conditions for all drug product registration stability batches utilizing the commercial drug product stability testing site listed in the NDA submission – (b) (4). Include as part of the results, the new time point tested.
2. Based on the provided data, we recommend that you revise the dissolution acceptance criterion to $Q = \frac{(b)}{(4)}\%$ at $\frac{(b)}{(4)}$ minutes instead of the proposed $Q = \frac{(b)}{(4)}\%$ at $\frac{(b)}{(4)}$ minutes for sacubitril and valsartan.

Please respond by May 26, 2015.

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official amendment. If you have any questions or comments feel free to contact me.

Thank you.

Sincerely,

Olga

Olga Simakova, PhD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
CDER/FDA
10903 New Hampshire Ave.
WO75, Rm. 4664
Silver Spring, MD 20993
Olga.simakova@fda.hhs.gov
(240) 402-3814

From: Simakova, Olga (CDER)
Sent: Friday, May 15, 2015 2:13 PM
To: 'masha.berkhin@novartis.com'
Subject: Information Request for NDA 207620 5/15/15

Dear Dr. Berkhin,

Please find attached a courtesy copy of the Information Request for NDA 207620. We request a written response by May 26, 2015.

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official amendment. If you have any questions or comments feel free to contact me.

Thank you.

Sincerely,

Olga

Olga Simakova, PhD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
CDER/FDA
10903 New Hampshire Ave.
WO21, Rm. 2667
Silver Spring, MD 20993
Olga.simakova@fda.hhs.gov
(240) 402-3814

Flowers, Louis

From: Flowers, Louis
Sent: Thursday, January 29, 2015 5:58 PM
To: 'Berkhin, Masha'
Subject: RE: NDA 207620: COMPLETE SUBMISSION FOR EVALUATION OF PROPOSED PROPRIETARY NAME

Hi Masha,

Since the “**REQUEST FOR PROPRIETARY NAME REVIEW**” in bold, capital letters was not identified on the 1st page of the submission, the clock did not start in December 2014.

When the Agency received your complete submission for the request for proprietary name review through the FDA Gateway on January 15, 2015, the clock started. Thanks.

Louis R. Flowers III, PharmD, MS, CPH
Captain - USPHS
Team Leader, Project Management Staff
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
BLDG 22, Room 4476
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-3158
Email: louis.flowers@fda.hhs.gov

From: Berkhin, Masha [mailto:masha.berkhin@novartis.com]
Sent: Wednesday, January 21, 2015 5:39 PM
To: Flowers, Louis
Subject: RE: NDA 207620: COMPLETE SUBMISSION FOR EVALUATION OF PROPOSED PROPRIETARY NAME

Hi Louis – I just wanted to understand why the clock does not start in December since the documents were included in the NDA.

Many thanks!

Best,
Masha

From: Flowers, Louis [mailto:Louis.Flowers@fda.hhs.gov]
Sent: Wednesday, January 21, 2015 9:07 AM
To: Berkhin, Masha
Cc: Jenkins, Darrell; Makela, Cristina; Lyons, Darrell
Subject: Re: NDA 207620: COMPLETE SUBMISSION FOR EVALUATION OF PROPOSED PROPRIETARY NAME

Hi Masha,

I am in meetings today. Please email me your question and I will respond. Thanks.

Louis R. Flowers III, PharmD, MS, CPH
Captain - USPHS
Team Leader, Project Management Staff
Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research
Food and Drug Administration
BLDG 22, Room 4476
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-3158
Email: louis.flowers@fda.hhs.gov

From: Berkhin, Masha [<mailto:masha.berkhin@novartis.com>]
Sent: Wednesday, January 21, 2015 08:57 AM Eastern Standard Time
To: Flowers, Louis
Subject: RE: NDA 207620: COMPLETE SUBMISSION FOR EVALUATION OF PROPOSED PROPRIETARY NAME

Thanks Louis. I have a question related to the timelines for my understanding. Would it be possible for us to talk via phone later today? Please let me know.

Best,
Masha

From: Flowers, Louis [<mailto:Louis.Flowers@fda.hhs.gov>]
Sent: Wednesday, January 21, 2015 8:54 AM
To: Berkhin, Masha
Cc: Jenkins, Darrell; Makela, Cristina; Lyons, Darrell
Subject: RE: NDA 207620: COMPLETE SUBMISSION FOR EVALUATION OF PROPOSED PROPRIETARY NAME

Good morning Masha,

Yes, the cover letter and the request for proprietary name review was submitted successfully. On January 15, 2015, the Agency received your proprietary name review request.

The review clock started on January 15, 2015 and the goal date is April 15, 2015. Thanks.

Louis R. Flowers III, PharmD, MS, CPH
Captain - USPHS
Team Leader, Project Management Staff
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
BLDG 22, Room 4476

10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-3158
Email: louis.flowers@fda.hhs.gov

From: Berkhin, Masha [<mailto:masha.berkhin@novartis.com>]
Sent: Monday, January 19, 2015 2:47 PM
To: Flowers, Louis
Cc: Jenkins, Darrell; Makela, Cristina
Subject: RE: NDA 207620: COMPLETE SUBMISSION FOR EVALUATION OF PROPOSED PROPRIETARY NAME

Hi Louis – the information you requested was submitted through the FDA Gateway on January 15th. Can you confirm that you have everything you need? I understand that there is a 90 day clock for a proprietary name review under an NDA. Will the review clock start from the time of original submission on December 17th?

Many thanks!

Best,
Masha

Masha Berkhin, Pharm.D.
Global Program Regulatory Director – Cardio-Metabolic
Novartis Pharmaceutical Corporation
One Health Plaza, 100 – 129
East Hanover, NJ 07936

Phone + 1 862 778 2407
Fax + 1 973 781 3590
Cell + (b) (6)
masha.berkhin@novartis.com

 NOVARTIS

From: Flowers, Louis [<mailto:Louis.Flowers@fda.hhs.gov>]
Sent: Tuesday, January 13, 2015 10:45 AM
To: Berkhin, Masha
Cc: Jenkins, Darrell; Makela, Cristina
Subject: RE: NDA 207620: COMPLETE SUBMISSION FOR EVALUATION OF PROPOSED PROPRIETARY NAME

Hi Masha,

Please submit both a cover letter and the request for proprietary name review document.

Thanks.

Louis R. Flowers III, PharmD, MS, CPH
Captain - USPHS
Team Leader, Project Management Staff
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
BLDG 22, Room 4476
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-3158
Email: louis.flowers@fda.hhs.gov

From: Berkhin, Masha [mailto:masha.berkhin@novartis.com]
Sent: Tuesday, January 13, 2015 10:35 AM
To: Flowers, Louis
Cc: Jenkins, Darrell; Makela, Cristina
Subject: RE: NDA 207620: COMPLETE SUBMISSION FOR EVALUATION OF PROPOSED PROPRIETARY NAME

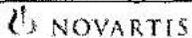
Hi Louis – just for clarity would you like me to

- a) submit only a cover letter referencing the request for proprietary name review document contained in the NDA, or;
- b) submit both a cover letter and the request for proprietary name review document?

Best,
Masha

Masha Berkhin, Pharm.D.
Global Program Regulatory Director – Cardio-Metabolic
Novartis Pharmaceutical Corporation
One Health Plaza, 100 – 129
East Hanover, NJ 07936

Phone + 1 862 778 2407
Fax + 1 973 781 3590
Cell + (b) (6)
masha.berkhin@novartis.com



From: Flowers, Louis [mailto:Louis.Flowers@fda.hhs.gov]
Sent: Monday, January 12, 2015 11:27 AM
To: Berkhin, Masha
Cc: Jenkins, Darrell; Makela, Cristina
Subject: NDA 207620: COMPLETE SUBMISSION FOR EVALUATION OF PROPOSED PROPRIETARY NAME

Dear Dr. Berkhin:

We have been notified by the Division of Cardiovascular and Renal Products in the Office of New Drugs that you have resubmitted a request for review of the proprietary name, Entresto, with NDA 207620. However, **“REQUEST FOR PROPRIETARY NAME REVIEW”** in bold, capital letters was not identified on the 1st page of the submission as requested in the Guidance for a complete submission. Please click on the link below to read the guidance that describes the information that FDA uses to evaluate proposed proprietary names.

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075068.pdf>

Please submit a cover letter to include the statement **“REQUEST FOR PROPRIETARY NAME REVIEW”** in bold, capital letters on the first page of each submission as outlined in the attached Guidance. Please reference the original NDA submissions (eCTD #, SDN, and date).

If you have any questions or comments, please do not hesitate to contact me, Darrell Jenkins and Cristina Makela.

Thanks,

Louis R. Flowers III, PharmD, MS, CPH
Captain - USPHS

Team Leader, Project Management Staff
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
BLDG 22, Room 4476
10903 New Hampshire Avenue
Silver Spring, MD 20993
Phone: 301-796-3158
Email: louis.flowers@fda.hhs.gov

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/s/

LOUIS R FLOWERS
05/14/2015



NDA 207620

MEETING REQUEST GRANTED

Novartis Pharmaceuticals Corp.
Attention: Albina Taigounov
Associate Director – Global Regulatory CMC
One Health Plaza, Building 339 – Room 1152
East Hanover, NJ 07936

Dear Ms. Taigounov:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LCZ696 (sacubitril/valsartan) Tablets, 50 mg, 100 mg, 200 mg.

We also refer to your April 16, 2015, correspondence requesting a Type A meeting to ensure the alignment with the FDA on the proposed control strategy for the LCZ696 due to the uniqueness of the compound and the synthesis. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting.

The meeting is scheduled as follows:

Date: April 30, 2015
Time: 11:30 am to 12:30 pm
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Invited CDER Participants:

Office of Pharmaceutical Quality

Thomas Oliver, PhD
Wendy Wilson-Lee, PhD
Mohan Sapru, PhD
Anamitro Banerjee, PhD
Sherita McLamore-Hines, PhD
Olga Simakova, PhD

Division Director (acting)
Branch Chief (acting)
Application Technical Lead
Application Technical Lead
Reviewer
Regulatory Business Process Manager

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

Please e-mail me any updates to your attendees at olga.simakova@fda.hhs.gov, at least one week prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Olga Simakova 240-535-9702 or 240-402-3814.

Please refer to the following link for visiting the White Oak Campus:
<http://www.fda.gov/aboutfda/workingatfda/buildingsandfacilities/whiteoakcampusinformation/cm241748.htm>

If you have any questions, please contact Olga Simakova, Regulatory Business Process Manager, at (240) 402-3814.

Sincerely,

{See appended electronic signature page}

Olga Simakova, PhD
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Foreign Visitor Data Request Form

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

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/s/

OLGA SIMAKOVA
04/22/2015

Lyons, Darrell

From: Lyons, Darrell
Sent: Friday, April 10, 2015 1:56 PM
To: 'Berkhin, Masha'
Cc: Jenkins, Darrell; Flowers, Louis; Makela, Cristina
Subject: RE: Proprietary Name for NDA 207620 Entresto

Hi Masha,

To request a re-review of the above proprietary name or to submit a new proprietary name for consideration; please submit a new, complete, request within 14 days of this communication. Include the statement "**REQUEST FOR PROPRIETARY NAME REVIEW**" in bold capital letters, at the top of your cover letter and on the first page of the main submission document (please refer to the complete submission guidance link below). The review of this name will be initiated when the new submission is received.

A new review clock using the same PDUFA IV review performance goal dates applies to the written request for the submission of alternate proposed proprietary names or reconsideration of the primary proposed proprietary name with supporting data.

If you require additional information on developing proprietary names for drugs or proposing alternative proprietary names for consideration, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding any other aspects of the proprietary name review process, please feel free to contact me directly.

Best Regards,

Darrell Lyons

Darrell Lyons, BSN, RN
Commander, USPHS
FDA, Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office: (301) 796-4092
darrell.lyons@fda.hhs.gov

From: Berkhin, Masha [<mailto:masha.berkhin@novartis.com>]
Sent: Thursday, April 09, 2015 3:51 PM
To: Lyons, Darrell

Cc: Jenkins, Darrell; Flowers, Louis; Makela, Cristina
Subject: RE: Proprietary Name for NDA 20762 Entresto

Dear Darrell – this is to follow-up on my voicemail. Based on the call this afternoon with the Agency I wanted to ask you what the next steps should be for the Proprietary Name application. As the Agency agreed to review another proposal for LCZ696 dose expression could we ask for an extension for re-submission of the proprietary name application?

Thanks very much in advance.

Best,
Masha

Masha Berkhin, Pharm.D.
Global Program Regulatory Director – Cardio-Metabolic
Novartis Pharmaceutical Corporation
One Health Plaza, 100 – 129
East Hanover, NJ 07936

Phone + 1 862 778 2407
Fax + 1 973 781 3590
Cell + (b) (6)
masha.berkhin@novartis.com



From: Lyons, Darrell [<mailto:Darrell.Lyons@fda.hhs.gov>]
Sent: Friday, March 27, 2015 10:43 AM
To: Berkhin, Masha
Cc: Jenkins, Darrell; Flowers, Louis; Makela, Cristina
Subject: Proprietary Name for NDA 20762 Entresto

Dear Dr. Berkhin:

Please refer to our February 9, 2015, Proprietary Name Request Conditionally Acceptable Letter for your proposed proprietary name, Entresto.

As indicated in the Conditional Approval, if any of the proposed product characteristics as stated in your January 15, 2015, submission are altered prior to approval of the marketing application (**e.g., the strength expression**), the proprietary name should be resubmitted for review.

To request a re-review of the above proprietary name or to submit a new proprietary name for consideration; please submit a new, complete, request within 14 days of this communication. Include the statement "**REQUEST FOR PROPRIETARY NAME REVIEW**" in bold capital letters, at the top of your cover letter and on the first page of the main submission document (please refer to the complete submission guidance link below). The review of this name will be initiated when the new submission is received.

A new review clock using the same PDUFA IV review performance goal dates applies to the written request for the submission of alternate proposed proprietary names or reconsideration of the primary proposed proprietary name with supporting data.

If you require additional information on developing proprietary names for drugs or proposing alternative proprietary names for consideration, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs,
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding any other aspects of the proprietary name review process, please feel free to contact me directly.

Best Regards,

Darrell Lyons, BSN, RN
Commander, USPHS
FDA, Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office: (301) 796-4092
darrell.lyons@fda.hhs.gov

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/s/

DARRELL LYONS
04/13/2015

Executive CAC

Date of Meeting: April 7, 2015

Committee: Karen Davis Bruno, Ph.D., OND IO, Chair
Abby Jacobs, Ph.D., OND IO, Member
Paul Brown, Ph.D., OND IO, Member
Tim McGovern, Ph.D., OND IO, Member
Jean Wu, M.D., Ph.D., Pharm Tox Supervisor (acting)
William T. Link, Ph.D., Presenting Reviewer

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #207-620

Drug Name: AHU377

Sponsor: Novartis

Mouse Carcinogenicity Study

Study No. 804258 was performed in CD-1 mice (70/sex/group) employing oral doses of 150, 400 and 1200 mg/kg/day, for 104 weeks. Exposure multiples, based on C_{max} (mouse/human MRHD) achieved in the study, were 14x and 46x for AHU377 in males and females, respectively, and 16x and 23x for LBQ657 (the active metabolite) in males and females, respectively. AUC was not calculated. No statistically significant differences were seen in mortality or the incidence of any neoplastic lesion in male and female mice in this study.

Rat Carcinogenicity Study

Study No. 804259 was performed in Wistar rats (50/sex/group) employing oral doses of 50, 150 and 400 mg/kg/day, for 104 weeks. Exposure multiples, based on C_{max} (rat/human MRHD) achieved in the study, were 0.63x and 0.88x for AHU377 in males and females, respectively, and 1.55x and 3.55x for LBQ657 (the active metabolite) in males and females, respectively. AUC was not calculated..

No statistically significant differences were seen in mortality or the incidence of any neoplastic lesion in male and female rats in this study.

Executive CAC Recommendations and Conclusions

Mouse study:

- The Committee concurred that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms in the study.

Rat study:

- The Committee concurred that the study was acceptable, noting prior Exec CAC concurrence with the protocol.

- The Committee concurred that there were no drug-related neoplasms in the study.

Karen Davis Bruno, Ph.D.

Chair, Executive CAC

cc:\

/Division File, DCRP

Albert De Felice /Team leader, DCRP

William T. Link /Reviewer, DCRP

Alexis Childers/CSO/PM, DCRP

/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
04/09/2015

KAREN L DAVIS BRUNO
04/09/2015



NDA 207620

MID-CYCLE COMMUNICATION

Novartis Pharmaceuticals Corp.
Attention: Masha Berkhin, PharmD
Senior Global Program Regulatory Manager, Drug Regulatory Affairs
One Health Plaza
Building 100
East Hanover, NJ 07936

Dear Dr. Berkhin:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for LCZ696 (sacubitril/valsartan) Tablets, 50 mg, 100 mg, 200 mg.

We also refer to the teleconference between representatives of your firm and the FDA on 19 March 2015. The purpose of this teleconference was to provide you with an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Alexis Childers, Sr. Regulatory Project Manager at (301) 796-0442.

Sincerely,

{See appended electronic signature page}

Aliza Thompson, M.D.
Cross Discipline Team Leader
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MID-CYCLE COMMUNICATION

Meeting Date and Time: 19 March 2015, 9:30-10:30 am

Application Number: 207620

Product Name: LCZ696 (sacubitril/valsartan) Tablets

Indication: treatment of heart failure (NYHA II-IV)

(b) (4)

Applicant Name: Novartis Pharmaceuticals Corp.

Meeting Chair: Aliza Thompson, M.D.

Meeting Recorder: Alexis Childers, RAC

FDA ATTENDEES

**Division of Cardiovascular and Renal Products*

Aliza Thompson, M.D.	Clinical Team Leader
Mary Ross Southworth, PharmD	Deputy Director for Safety
Tzu-Yun McDowell, Ph.D.	Clinical Reviewer
Kim Smith, MD, MS	Clinical Reviewer
Alexis Childers, RAC	Sr. Regulatory Health Project Manager
Edward Fromm, R.Ph., RAC	Chief, Regulatory Health Project Manager

**Office of Pharmaceutical Quality*

Wendy Wilson, Ph.D.	Chemistry Lead
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**Office of Surveillance and Epidemiology*

Susan Lu, RPH,	Safety Evaluator Team Leader
Margie Goulding, Ph.D.	Epidemiology Team Leader
Somya Dunn, PharmD	Team Leader, DRISK
Chi-Ming Tu, PharmD	DMEPA Team Leader
Janine Stewart, PharmD	DMEPA Reviewer

EASTERN RESEARCH GROUP ATTENDEES

Patrick Zhou	Independent Assessor
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APPLICANT ATTENDEES

Patrice Matchaba, M.D.	Franchise Head Critical Care
Rob Kowalski, PharmD.	Global Head of Regulatory
Marty Lefkowitz, M.D.	Therapeutic Area Head
Robert Hilkert, M.D.	Medical Unit Head
Victor Shi, M.D.	Global Program Medical Director
Natalie Ezzet, Ph.D.	Global Integrated Information Sciences (IIS) Franchise Head

Guenther Mueller-Velten, Ph.D.	Senior Global Group Head – Biostatistics
Denise Leclair, M.D.	Therapeutic Area Safety Lead
Hendrik Streefkerk, M.D.	Brand Safety Leader
Thomas Langenickel, M.D.	Director Translational Medicine
Laura Dill Morton, Ph.D. DACVP, DABT,	Executive Director- Pre Clinical Safety
Heidi Schoenfeld, Ph.D.	Senior Investigator – Pre Clinical Safety
Paula Rinaldi	US Head of Regulatory Affairs
Caroline Boulton	Global Regulatory Franchise Head
Patricia Kay-Mugford	Global Regulatory Therapeutic Area Lead
Masha Berkhin, Pharm.D.	Global Program Regulatory Director
Diane Zezza, Ph.D.	Global Head Regulatory CMC
Fedra Maria Limoncini	Franchise Head Regulatory CMC
Albina Taigounov	Associate Director Regulatory CMC
Michael Motto	Project Leader Technical Development

1.0 INTRODUCTION

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 or may not be able to consider your response before we take an action on your application during this review cycle.

2.0 SIGNIFICANT ISSUES

There are currently no significant review issues to discuss.

3.0 INFORMATION REQUESTS

All information requests are on track. The Division will continue to submit requests as needed.

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

Clinical safety concerns

Dr. McDowell stated that a major safety concern is the risk of angioedema in blacks. Dr. McDowell noted that in the overall trial population, the incidence of angioedema in the LCZ696 arm was low and that the majority of cases were not serious. However, the incidence of angioedema was higher in blacks than caucasians and was also higher in blacks in the LCZ696 arm than in the enalapril arm. She further noted that the incidence of angioedema was highest among blacks treated with LCZ696 in the United States. Although the small number of black subjects enrolled in the trial limits interpretation of these data, the findings are nonetheless concerning as a large portion of heart failure patients in the United States are black and data indicate that blacks are more susceptible to angioedema induced by ACE and neprilysin

inhibitors. Hence, at this time, the clinical reviewers believes that a post marketing study may be needed to better characterize the risk of serious angioedema events in black patients treated with LCZ696 in the United States. Towards this end, Dr. McDowell suggested that Novartis begin to explore claims or observational databases that might be suitable to evaluate this risk in the postmarketing setting.

In response to questions from Novartis:

- Dr. Southworth explained that key criteria for selecting a database include reliable ascertainment of race and an ability to identify cases of serious angioedema. She also noted that there was literature related to this topic from which methodologies could be referenced.
- Dr. Thompson clarified that a synopsis outlining Novartis's proposed plan was sufficient and that a complete protocol did not need to be submitted at this time.

Dr. Thompson also commented that it would be helpful to understand the extent to which ongoing trials might provide additional data that could address the risk of angioedema in blacks treated with LCZ696.

5.0 ADDITIONAL COMMENTS

Chemistry

Dr. Wilson stated that there is ongoing internal discussion regarding labeling the strength of LCZ696 as a single entity versus as a fixed dose combination and that an internal meeting has been scheduled for the week of March 23, 2015 to discuss the issue. The Agency will inform Novartis of any recommended changes to the labeled strength or any additional requests for information as soon as possible.

Novartis stated that there have been previous interactions with the Agency on this issue and that information pertaining to this issue was submitted to the NDA. Dr. Wilson confirmed that the team has reviewed the information and will take the applicant's arguments into consideration, but explained that the Agency needs to come to its own conclusion on the matter. She further explained that the Agency's guidance document on the regulatory classification of pharmaceutical co-crystals discusses co-crystals with one active and one inactive ingredient, whereas LCZ696 contains two active ingredients. This is a different scenario than that described in the guidance and the Agency has to take this difference into consideration.

Dr. Thompson noted that the Agency's final determination on the labeled strength may have bearing on the proprietary name determination. In response to a question from Novartis, OSE confirmed that there is a 90 day review period for Proprietary Name requests under an NDA.

Other issues discussed during the meeting

- Novartis asked if the Division was planning to take an action ahead of the PDUFA goal date. Dr. Thompson stated that the Division is planning to take an early action but could not commit to a particular date.

- Novartis indicated that they plan to [REDACTED] ^{(b) (4)}
[REDACTED] Dr. Wilson stated that she would keep Compliance abreast of the situation.
- Novartis asked whether comments on the carton container would be provided during labeling negotiations or whether it might be possible to receive comments sooner. Novartis is willing to print carton container labels at their own risk if comments can be provided early. Dr. Wilson indicated that the Agency will work with Novartis to finish early but emphasized that labels can change until an action is taken and reminded Novartis that labels cannot be approved prior to the action date.
- Novartis asked for feedback on efficacy claims proposed in labeling. Dr. Thompson stated that it was premature to discuss labeling claims and indicated that further input was needed from the Division Director and Signatory Authority.

6.0 ADVISORY COMMITTEE MEETING

There are no plans at this time for an Advisory Committee Meeting.

7.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The Late-Cycle Meeting is scheduled for 08 June 2015. Labeling negotiations are expected to begin 25 May 2015.

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/s/

ALIZA M THOMPSON
04/07/2015



NDA 207620

INFORMATION REQUEST

Novartis Pharmaceuticals Corp.
Attention: Masha Berkhin, PharmD
Global Program Regulatory Director
One Health Plaza, Building 100
East Hanover, NJ 07936

Dear Dr. Berkhin:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for LCZ696 (sacubitril/valsartan) Tablets, 50 mg, 100 mg, 200 mg. We refer to your December 17, 2014, submission.

We are reviewing the Product Quality 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.

Drug Substance

1. [REDACTED] (b) (4)

2. Confirm that the validation data provided in the (b) (4) section are for the latest versions of the analytical methods described in the (b) (4) monograph.

3. Based on the validation data provided in this submission, the (b) (4)

[REDACTED] Update the method such that it can (b) (4)

Drug Product

1. The proposed acceptance criteria for impurity (b) (4) and impurity (b) (4) in the drug product specification are NMT (b) (4)% and NMT (b) (4)%, respectively. These limits are excessively broad and not reflective of the data. Revise the acceptance criteria for these impurities to be more reflective of the data and manufacturing capability.

2. You indicate that data is available for samples stored and tested after 6 months under accelerated conditions, 48 months under long term, and 48 months intermediate conditions. Provide this data to support exclusion of the (b) (4) test in the drug product release specification or update the drug product specification to include a test for (b) (4).

3. Clearly delineate which tests and packaging configurations will be performed as part of the drug product post approval stability protocol.

4. Clearly define your Quality Target Product Profile (QTPP).

Process

1. (b) (4)

2. Regarding manufacturing process development, for each unit operation submit the following information to the Pharmaceutical Development section (3.2. P.2.3):

a. Data to support selection of critical process parameters. Indicate what the scale of the performed studies was.

b. Data to support proposed ranges for critical process parameters of the commercial process, including approach to scale up the parameters from pilot to commercial scale. Include summary result of the studies.

3. In compliance with 21 CFR 314.50 (d)(1)(ii)(c) a complete description of the commercial scale manufacturing process is required. You can either revise the manufacturing process description in section 3.2.P.3.3 to include set points/ranges for the process parameters, batch size and equipment type and size for all unit operations of the drug product manufacturing process or submit proposed commercial scale Master Batch Records to Section 3.2.R. Include the amounts of excipients used in (b) (4).

4. Regarding the film coating operation:

a. (b) (4)

Please explain.

5. (b) (4)

6. It is indicated in the submission that the (b) (4)

Provide the following information to support evaluation of adequacy of the control strategy to mitigate risks of a (b) (4):

a. Describe the results of (b) (4)

Comment on why drug substance used in these batches (b) (4)

- (b) (4)
- b. To demonstrate (b) (4) provide available data from development and commercial scale batches of (b) (4)
- c. Provide (b) (4) (b) (4) from development and commercial scale batches.
- d. Provide any available (b) (4) content uniformity data from development and commercial scale batches.
7. Regarding Comparability Protocol for the new manufacturing site of drug product:
- a. Manufacturing process development indicates that at the (b) (4) site the process was (b) (4). In the protocol you propose the batch size of (b) (4) kg at the new site. Justify the proposed batch size and provide data to demonstrate that there is (b) (4) at the new site.

If you have any questions, call Olga Simakova, Regulatory Project Manager, at (240) 402-3814.

Sincerely,

{See appended electronic signature page}

Wendy Wilson-Lee, PhD
Branch Chief, Branch I (Acting)
Division of New Drug Products I
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

**Wendy I.
Wilson -S**

Digitally signed by Wendy I.
Wilson -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=1300
396790, cn=Wendy I. Wilson -S
Date: 2015.02.19 11:21:49 -05'00'



NDA 207620

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Novartis Pharmaceuticals Corp.
Attention: Masha Berkhin, PharmD
Senior Global Program Regulatory Manager, Drug Regulatory Affairs
One Health Plaza
Building 100
East Hanover, NJ 07936

Dear Dr. Berkhin:

Please refer to your New Drug Application (NDA) dated 17 December 2014, received 17 December 2014, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA), for LCZ696 (sacubitril/valsartan) Tablets, 50 mg, 100 mg, 200 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to: <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is 15 August 2015.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by 25 May 2015.

In addition, the planned date for our internal mid-cycle review meeting is 11 March 2015. We are not currently planning to hold an advisory committee meeting to discuss this application.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information:

Biopharmaceutics

1. Your dissolution method development report contains dissolution profiles but does not contain dissolution data (individual, mean, and standard deviation). Provide complete dissolution data (individual, mean, and standard deviation) for all the profiles reported in the NDA.
2. Provide the PK profiles and PK parameters for the pivotal bioequivalence study (CLCZ696B2114) for the 50 mg to-be-marketed formulation (final market image) and clinical service form in SAS transport file format.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). We encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

Formatting Comments:

In Highlights

1. Each summarized statement or topic in Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: Not all statements in HL contain a reference; see Dosage Forms and Strengths as an example.

2. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment: Established pharmacologic class (EPC) for both components must be included and conform to the following format, “(Product) is a combination of a (EPC) and a (EPC) indicated for (indication).” See 21 CFR 201.57(a)(6) for additional information.

Content Comments:

3. The Product Title line must contain the route of administration. See 21 CFR 201.57(a)(1).
4. Details of drug interaction pharmacokinetic studies should be included in Section 12.3. Details of drug interaction pharmacokinetic studies should not be repeated in Section 7. See 21 CFR 201.57(c)(13)(C) and 201.57(c)(8). Please provide a forest plot of the data from PK studies for both drug interactions and the special populations presented in Section 12.3.
5. Please note that on December 4, 2014 the Food and Drug Administration published a Final Rule in the Federal Register [Docket No. FDA-2006-N-0515 (formerly Docket No. 2006N-0467)] regarding the Requirements for Pregnancy and Lactation Labeling. All applications pending on the effective date of the final rule [June 30, 2015] will be required to comply within four years after the effective date. You are encouraged to comply with this rule in advance of the effective date in your current NDA submission. We encourage you to review the Draft Guidance for Industry, “Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format” located at the following URL:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by **25 February 2015**. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for 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.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Cardiovascular and Renal Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, please call Alexis Childers, Sr. Regulatory Project Manager, at (301) 796-0442.

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 L STOCKBRIDGE
02/12/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207620

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Novartis Pharmaceuticals Corporation
One Health Plaza
Building 100
East Hanover, NJ 07936-1080

ATTENTION: Masha Berkhin, Pharm.D.
Global Program Regulatory Director

Dear Dr. Berkhin:

Please refer to your New Drug Application (NDA) dated and received December 17, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sacubitril/Valsartan Tablets, 50 mg, 100 mg, 200 mg.

We also refer to your correspondence, dated and received January 15, 2015, requesting review of your proposed proprietary name, Entresto.

We have completed our review of the proposed proprietary name, Entresto and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your January 15, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact CDR Darrell Lyons, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4092. For any other information regarding this application, contact Alexis Childers, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0442.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
02/09/2015



NDA 207620

NDA ACKNOWLEDGMENT

Novartis Pharmaceuticals Corporation
Attention: Masha Berkhin, Pharm.D.
Global Program Regulatory Director
Drug Regulatory Affairs
One Health Plaza, Bldg. 100
East Hanover, NJ 07936-1080

Dear Dr. Berkhin:

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

Name of Product: LCZ696 (sacubitril/valsartan) Tablets, 50 mg, 100 mg, and 200 mg

Date of Application: December 17, 2014

Date of Receipt: December 17, 2014

Our Reference Number: NDA 207620

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 15, 2015, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited 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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, please contact:

Alexis Childers, RAC
Sr. Regulatory Health Project Manager
(301) 796-0442

Sincerely,

{See appended electronic signature page}

Edward Fromm, R.Ph., RAC
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 J FROMM
01/05/2015

From: [Knight, Yvonne](#)
To: [Berkhin, Masha \(masha.berkhin@novartis.com\)](#)
Cc: [Knight, Yvonne](#)
Subject: Information Request for NDA 207620 (Prompt Response)
Date: Wednesday, December 17, 2014 3:43:01 PM
Importance: High

Good afternoon Ms. Berkhin,

We have an information request concerning Novartis' New Drug Application (NDA) for NDA 207620. We request a prompt response to this IR request no later than **Friday COB January 16, 2015**.

1. (b) (4) is used in synthesis of starting material (b) (4). (b) (4)
Include in your acceptance criteria for (b) (4) limits
for (b) (4) to control (b) (4).
2. Intermediates for the synthesis of (b) (4) (b) (4).
(b) (4) studies for the intermediates are not provided. Provide data for these (b) (4)
studies and proposed (b) (4) for all intermediates.
3. (b) (4) (b) (4) is a critical intermediate for the manufacture of
(b) (4). Provide structural characterization, including NMR data, for the
intermediate (b) (4).
4. Provide comparative XRPD and IR spectra for (b) (4)

Please confirm receipt of this Information Request. Also, please provide me with a courtesy copy via email when you submit your official amendment? Note: Official amendments need to be submitted by due date in order to be included in the review cycle. If you have any questions or comments feel free to contact me.

Best Regards,

Yvonne Knight, MS
Regulatory Health Project Manager
Division of New Drug Quality Assessment
FDA/CDER/OPS/ONDQA
10903 New Hampshire Avenue
Bldg. 21, Room 2667
Silver Spring, MD 20993-0002
Phone: 301.796.2133
Email: yvonne.knight@fda.hhs.gov

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/s/

YVONNE L KNIGHT
12/17/2014



IND 104628

TOP LINE MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Masha Berkhin, PharmD
Senior GPRM, DRA
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Berkhin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LCZ 696.

We also refer to the meeting between representatives of your firm and the FDA on September 22, 2014. The purpose of the meeting was to discuss top-line results of your pivotal phase III study, PARADIGM-HF.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Alexis Childers, Regulatory Project Manager at (301) 796-0442.

Sincerely,

{See appended electronic signature page}

Ellis Unger, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes & Sponsor Presentation

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Top-Line Results

Meeting Date and Time: September 22, 2014, 12:30 pm
Meeting Location: White Oak Building 22, Conference Room: 1311

Application Number: IND 104628
Product Name: LCZ696 (sacubitril/valsartan)
Indication: Treatment of heart failure
Sponsor/Applicant Name: Novartis Pharmaceuticals Corporation

Meeting Chair: Ellis Unger M.D.
Meeting Recorder: Alexis Childers

FDA ATTENDEES

**Office of Drug Evaluation I*

Ellis Unger, M.D.	Director
Robert Temple, M.D.	Deputy Director

**Division of Cardiovascular and Renal Products*

Norman Stockbridge, M.D., Ph.D.	Director
Stephen M. Grant, M.D.	Deputy Director
Mary Ross Southworth, PharmD	Deputy Director for Safety
Martin Rose, M.D.	Clinical Team Leader
Aliza Thompson, M.D.	Clinical Team Leader
Melanie Blank, M.D.	Clinical Reviewer
Tzu-Yun McDowell, Ph.D.	Clinical Reviewer
Nhi Beasley, M.D.	Clinical reviewer
William Link, Ph.D.	Pharmacologist
Alexis Childers, RAC	Sr. Regulatory Health Project Manager
Edward Fromm, R.Ph., RAC	Chief, Regulatory Health Project Manager

**Office of New Drug Quality Assessment*

Sandra Suarez, Ph.D.	Biopharmaceutics reviewer
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**Office of Clinical Pharmacology*

Sreedharan Sabarinath, Ph.D.	Clinical Pharmacology Reviewer
Rajanikanth Madabushi, Ph.D.	Clinical Pharmacology Team Leader

**Office of Biostatistics, Division of Biometrics I*

Hsien Ming Hung, Ph.D.	Director
Jialu Zhang, Ph.D.	Statistician

**Office of Surveillance and Epidemiology*

Jie Li, Ph.D., MBBS	Epidemiologist
Kim Lehrfeld, PharmD	Team Leader, DRISK
Danny Gonzalez, PharmD, M.S.	Risk Management Analyst, DRISK

SPONSOR ATTENDEES

Patrice Matchaba, M.D.	Franchise Head Critical Care
------------------------	------------------------------

Marty Lefkowitz, M.D.	Therapeutic Area Head
Victor Shi, M.D.	Global Program Medical Director
Fabian Chen, M.D.	Clinical Indication Leader
Bob Hilkert, M.D.	Medical Unit Head
Dawn Bell, PharmD.	Global Program Head
Natalie Ezzet, Ph.D.	Global Integrated Information Sciences (IIS) Franchise Head
Jim Gong, Ph.D.	Associate Director Statistical Scientist (IIS)
Hendrik Streefkerk, M.D.	Brand Safety Leader
Paula Rinaldi	Technical Research and Development
Rob Kowalski, PharmD.	Global Head of Regulatory
Caroline Boulton,	Global Regulatory Franchise Head
Trish Kay-Mugford,	Global Regulatory Therapeutic Area Lead
Masha Berkhin, Pharm.D.	Senior Global Program Regulatory Manager
Chin Koerner	Executive Director, Novartis FDA Liaison
(b) (4), M.D.	Consultant
(b) (4), M.D.	Consultant

1.0 BACKGROUND

LCZ696, which consists of sacubitril and valsartan moieties, is being developed by Novartis for the treatment of heart failure. Sacubitril is an experimental neprilysin inhibitor and valsartan is an approved angiotensin II receptor blocker (ARB). Thus, LCZ696 is described as a neprilysin-angiotensin receptor inhibitor (ARNI). Novartis was conducting a randomized, double-blind pivotal phase 3 outcome study, PARADIGM-HF, comparing the efficacy and safety of LCZ696 to enalapril in patients with heart failure and reduced ejection fraction (HFrEF), when in March 2014, the Data Monitoring Committee recommended early closure of the trial because of compelling efficacy.

Novartis intends to submit a rolling NDA with final submission in December 2014, along with a request for priority review. Novartis requested this meeting to discuss the topline results of their pivotal phase 3 trial. A separate Pre-NDA meeting was held on June 25, 2014 and a CMC Pre-NDA meeting was held on August 14, 2014.

2. DISCUSSION

Novartis presented the attached slides. Highlights from the discussion are discussed below.

Introduction: Novartis stated that the heart failure program consisted of 3 trials. The pivotal phase 3 trial compared the effects of LCZ696 and enalapril on the composite primary endpoint of time to the first occurrence of heart failure hospitalization or cardiovascular (CV) death in patients with HFrEF. The trial was powered at 80% for CV death. The secondary endpoints, powered at 20%, consisted of all-cause mortality, the Kansas City Cardiomyopathy Questionnaire (KCCQ), new onset atrial fibrillation, and renal progression. Patients had to be on a stable dose of a beta-blocker (BB) for at least 4 weeks prior to the screening visit unless contraindicated or not tolerated. Mineralocorticoid receptor antagonists (MRAs) were not required. Diuretics were not required. (Novartis indicated that some heart failure patients are managed without diuretics.) At baseline, 70% of the patients were classified as NYHA Class 2 with 55% of patients on MRAs and approximately 90% on BBs.

The trial included a two-part sequential run-in period where enalapril was administered to subjects at 10 mg BID (unless patients were previously not on an ACE or on low dose, in which case they had the option of starting on enalapril 5 mg BID and titrating up to 10 mg BID as tolerated). If subjects tolerated enalapril after 2-4 weeks ($K^+ \leq 5.4$ mmol/L, $eGFR \geq 30$ mL/min, no decrease of $eGFR > 35\%$ from Visit 1, no symptomatic hypotension, $SBP \geq 95$ mmHg, and no postural symptoms), enalapril was discontinued. One day later patients were started on LCZ696 at 100 mg BID and titrated to 200 mg BID after one to two weeks. Patients stayed on LCZ696 for 2-4 weeks. If LCZ696 was tolerated (using the same criteria as for the enalapril period) the patient was randomized. The median duration of follow-up during the run-in period was 16 days for enalapril and 29 days for LCZ 696. Approximately 10% of patients discontinued during each of the two parts of the run-in phase. About 6% discontinued for non-fatal adverse events such as cough, hyperkalemia, renal dysfunction, hypotension, etc. Other causes of discontinuation during the run-in—withdrawal of consent, protocol deviations, loss to follow-up and death—occurred in 0.5% of patients in each period.

Efficacy discussion: Novartis stated that a significant p-value was achieved with a 20% reduction in CV death and HF hospitalization. Statistical stopping guidelines for a compelling benefit had been prespecified. At the third interim analysis the one-sided nominal p-value of < 0.001 in favor of LCZ696 for both death from CV causes and the primary endpoint (CV death and HF hospitalization) were met. Subgroup analyses showed consistency.

The sponsor was asked why the mean baseline heart rate was not less than 72 bpm if subjects were receiving adequate beta blockade. Novartis stated that the typical heart rate for heart failure patients is in the low 70s.

A 2.7-mmHg difference was observed throughout the study on systolic blood pressure (SBP). Novartis stated that when they adjusted the primary endpoint analysis for time-varying systolic BP during the course of the study (using a Cox-regression model with treatment and region as fixed factors and SBP as time-dependent covariate), the treatment effect of LCZ696 was maintained.

Results for secondary endpoints were discussed. Twenty percent of the total alpha was given to the KCCQ, a 23-item questionnaire. Close to 5-point reduction (worsening) in score was observed in the enalapril arm with a 3-point reduction in the LCZ696 arm. Novartis thought the difference between groups, 1.3 to 1.8 points, was consistent with other trials and was clinically important.

Results of the key exploratory endpoints were discussed. Some improvement and less worsening in NYHA functional class were observed in the LCZ696 group. There was a 16% reduction in all-cause mortality and a 25% reduction in recurrent hospitalization.

Novartis asked if the label should describe LCZ696 as superior to the comparator. The Division stated that if LCZ696 were to be approved the results of the study would be described in Section 14 of labeling and would probably support a superiority claim. However, the indication statement would not include language regarding superiority.

Safety discussion: Adverse events were similar between LCZ696 and enalapril. Fewer serious adverse events (SAEs) and discontinuations for adverse events (AEs) were reported in the LCZ696 group than in the enalapril group. More cardiac SAEs were reported in the enalapril group. However, hypotension and dizziness were reported more frequently with LCZ696. Elevations of serum creatinine to specified levels (2.5 and 3.0 mg/dL) and discontinuation for renal impairment were more common in the enalapril group.

A higher incidence of angioedema was reported with LCZ696, but no cases of airway compromise were reported. Novartis stated that approximately 40% of angioedema cases were reported at month 1 and

most occurred within the first year. Novartis also stated that discontinuation for angioedema was infrequent and was less frequent than in the hypertension studies; the Division requested that data from these trials be submitted.

Novartis stated that there was no signal for cognitive impairment. Both narrow and broad SMQs for dementia were similar between LCZ696 and enalapril.

Questions posed during the meeting:

- 1) Novartis considers that the overall benefit/risk of LCZ696 is favorable for heart failure patients for the proposed indication. Does the Division agree?

Discussion: The Division agreed.

Novartis asked if an AC is necessary and if there is no AC, is it possible to finish the review prior to 8 months. The Division stated that we believe an AC is unlikely at this point, but a final decision will be made when the application is filed. The Division is cautiously optimistic that an early action could be taken on the application.

- 2) What is the Agency's view on the [REDACTED] (b) (4)?

Discussion: The Division stated that data should be included in the application to support the claim. The sponsor should defend the clinical meaningfulness of the effect shown, perhaps by identifying a subset with a larger effect.

- 3a) Based on our review of the data Novartis is not proposing a REMS. Does the Agency agree?

Discussion: The Division agreed that it is unlikely that a REMS will be needed.

- 3b) Novartis believes that the below clear labeling strategy is sufficient to address the risk of angioedema related to concomitant inhibition of neprilysin and ACE. Does the Agency agree?

Proposed contraindication:

[REDACTED] (b) (4)

Warnings & Precautions: To include risk of angioedema

Discussion: The Division declined to give advice without specifics of cases for angioedema. The Division agreed with the idea of [REDACTED] (b) (4)

- 4) Does FDA agree with the concept for the starting dose recommendation?

Discussion: The Division agreed.

- 5) Does the FDA agree with the proposed plan for [REDACTED] (b) (4) [REDACTED] ?

Discussion: The Division stated that [REDACTED] (b) (4)

(b) (4). The Division plans to consult the Division of Neurology Products.

It was agreed that the Division would review and comment on a protocol amendment that includes the approach to (b) (4).

- 6) Can the Agency confirm that the content of the NDA is acceptable for review to support approval of the proposed indication?

Discussion: The Division stated that both the content and technical aspects that have been discussed appear to be acceptable for the submission of an application.

3.0 PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

4.0 PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

5.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

6.0 ISSUES REQUIRING FURTHER DISCUSSION

None

7.0 ACTION ITEMS

None

8.0 ATTACHMENTS AND HANDOUTS

Power point presentations: LCZ696: PARADIGM-HF Top Line Results

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/s/

ELLIS F UNGER
10/22/2014



IND 104628

MEETING MINUTES

Novartis Pharmaceuticals Corporation
Attention: Masha Berkhin, PharmD
Senior GPRM, DRA
One Health Plaza
East Hanover, NJ 07936-1080

Dear Dr. Berkhin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LCZ696.

We also refer to the meeting between representatives of your firm and the FDA on June 25, 2014. The purpose of the meeting was to obtain concurrence on the proposed presentation and format for an electronic NDA submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Alexis Childers, SR. Regulatory Project Manager at (301) 796-0442.

Sincerely,

{See appended electronic signature page}

Ellis Unger, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: June 25, 2014 3:00-4:30 pm
Meeting Location: White Oak, Bldg 22, Rm 1311

Application Number: 104,628
Product Name: LCZ696 (sacubitril/valsartan)
Indication: **Treatment of heart failure**
Sponsor/Applicant Name: Novartis

Meeting Chair: Ellis Unger, M.D.
Meeting Recorder: Alexis Childers, RAC

FDA ATTENDEES

**Office of Drug Evaluation I*

Ellis Unger	Director
<i>*Division of Cardiovascular and Renal Products</i>	
Norman Stockbridge, M.D., Ph.D.	Director
Stephen M. Grant, M.D	Deputy Director
Mary Ross Southworth, PharmD	Deputy Director for Safety
Martin Rose, M.D.	Clinical Team Leader
Melanie Blank, M.D.	Clinical Reviewer
Tzu-Yun McDowell, Ph.D.	Clinical Reviewer
William Link, Ph.D.	Pharmacologist
Alexis Childers, RAC	Sr. Regulatory Health Project Manager
Edward Fromm, R.Ph., RAC	Chief, Regulatory Health Project Manager

**Office of New Drug Quality Assessment*

Olen Stephens, Ph.D.	Acting Branch Chief
Kasturi Srinivasachar, Ph.D.	Chemist, Team Lead
Sherita McLamore-Hines, Ph.D.	Chemist
Sandra Suarez, Ph.D.	Biopharmaceutics reviewer

**Office of Clinical Pharmacology*

Sreedharan Sabarinath, Ph.D.	Clinical Pharmacology Reviewer
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**Office of Biostatistics, Division of Biometrics I*

Jialu Zhang, Ph.D.	Statistician
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**Office of Scientific Investigations*

Sharon Gershon Pharm.D.	OSI Reviewer, Pharmacologist
-------------------------	------------------------------

**Office of Surveillance and Epidemiology*

Jie Li, Ph.D., MBBS	Epidemiologist
Somya Dunn, MD	Risk Management Analyst, DRISK

EASTERN RESEARCH GROUP ATTENDEES

Patrick Zhou Independent Assessor

SPONSOR ATTENDEES

In person

Patrice Matchaba, M.D.	Franchise Head Critical Care
Marty Lefkowitz, M.D.	Therapeutic Area Head
Victor Shi, M.D.	Global Program Medical Director
Fabian Chen, M.D.	Clinical Indication Leader
Bob Hilkert, M.D.	Medical Unit Head
Dawn Bell, PharmD.	Global Program Head
Natalie Ezzet, Ph.D.	Global Integrated Information Sciences (IIS) Franchise Head
Jim Gong, Ph.D.	Associate Director Statistical Scientist (IIS)
Hendrik Streefkerk, M.D.	Brand Safety Leader
Thomas Langenickel, M.D.	Director Translational Medicine
Heidi Schoenfeld, Ph.D.	Senior Investigator – Pre Clinical Safety
Michael Motto, Ph.D.	Technical Research and Development
Sheryl Leroy,	Regulatory CMC Franchise Head
Caroline Boulton,	Global Regulatory Franchise Head
Trish Kay-Mugford,	Global Regulatory Therapeutic Area Lead
Masha Berkhin, Pharm.D.	Senior Global Program Regulatory Manager
Mathieu Weitbruch, Pharm.D.	Global Program Regulatory Director
Chin Koerner	FDA Liaison

On phone

Rob Kowalski, PharmD.	Global Head of Regulatory
Simon Walsh,	Global IIS Franchise Head
Fedra Maria Limoncini,	Regulatory CMC
Dominique Baranowski-Lahaye,	Regulatory CMC

1.0 BACKGROUND

LCZ696 (sacubitril/valsartan) is being developed by Novartis for the treatment of heart failure. One component of LCZ696, sacubitril, is an angiotensin receptor neprilysin inhibitor (ARNI) and the other component is valsartan, an approved angiotensin II receptor blocker (ARB). Novartis was conducting a randomized, double-blind pivotal phase 3 outcome study, PARADIGM-HF, comparing the efficacy and safety of LCZ696 to enalapril in patients with heart failure and reduced ejection fraction (HFrEF). In March 2014, the Data Monitoring Committee for PARADIGM-HF recommended early closure of the trial because of compelling efficacy.

Novartis plans to submit an NDA in December 2014 with a request for priority review. They requested the pre-NDA meeting to discuss form and content. A top-line discussion will occur around August.

2.0 DISCUSSION

NOTE: Novartis provided responses/clarifications to the FDA preliminary comments 1a, b,c, 2a, b, 3, 4, 5, 6b, 8 and additional items 7, 8, 22 via email on 6/24/14. Their responses are included in the discussions below.

Module 2 Questions

1. **Content of the Summary of Clinical Efficacy**

- a) Does the FDA agree with the proposal to assess efficacy, and associated content and subgroup analyses planned for the submission, specifically within the Summary of Clinical Efficacy (SCE; CTD Module 2.7.3)?

FDA response: You will be submitting the results of 3 clinical studies, one pivotal trial and two phase 2 studies, to support the efficacy and safety of LCZ696 in patients with HFrEF. You do not plan to pool efficacy data across the heart failure (HF) studies because PARADIGM-HF provides the primary mortality and morbidity data in support of the proposed indication in the largest number of HF subjects studied in a single trial and due to the different patient populations, comparators and endpoints evaluated across the three studies. You also do not plan to summarize the efficacy data from the completed hypertension studies in the Summary of Clinical Efficacy. You also plan to perform subgroup analyses for the primary endpoint and its components (cardiovascular death or heart failure hospitalization).

We agree with your overall plan. In addition, we would like for you to do the following additional subgroup analyses for PARADIGM:

- weight tertiles because body weight might affect exposure,
- 3 groups of renal function (eg., 30- < 60 mL/min, 60- < 90 mL/min and ≥ 90 mL/min) because the main route of excretion of AHU377 is renal,
- subjects enrolled in the USA,
- beta blocker use,
- diuretic use, and
- digoxin use.

You state that there will be a subgroup analysis of subjects with NYHA class I and II but the trial only was to include class II and above. How many subjects with NYHA class I were enrolled in PARADIGM-HF?

Novartis Response:

We will perform the additional subgroup analyses as suggested. For the beta blocker, diuretic, and digoxin use we plan to provide a sub-group analysis showing efficacy for patients taking these drugs at baseline vs. patients not taking these drugs at baseline.

Please note 93% of patients were on a beta blocker at study entry, is the analysis for this group still needed?

A total of 429 (5.1%) patients were randomized with NYHA Class 1. Of these 429 patients, only 33 patients entered the run-in period with NYHA Class 1 (protocol violation) while 396 patients entered the run-in period with NYHA Class \geq 2 and improved their clinical status to NYHA Class 1 at the time of randomization.

Meeting discussion: The Division stated they still want an analysis by use of beta blockers at time of randomization. FDA suggested that the sponsor consider estimating equivalent doses for all concomitant beta blockers and analyzing and presenting the efficacy data by daily beta blocker dose in quartiles or quintiles.

- b) Does the FDA agree to the proposed approach to satisfy the requirements for an Integrated Analysis of Efficacy?

FDA response: It is not clear from your plan if you plan to submit an ISE. You should submit an integrated summary that describes why the totality of your efficacy data supports approval. To the degree possible, your summary of efficacy should include the components of an integrated summary of effectiveness (ISE) as per the draft “Guidance for Industry Integrated Summary of Effectiveness” (tabular results of individual studies, descriptions of demographics across studies, efficacy results across studies and any analysis issues that you anticipate will be a focus of our review, for instance, ejection fraction and the decision to limit the population to subjects with EF \leq 35% partway through PARADIGM-HF, subpopulation results, clinical information relevant to dosing, persistence of efficacy and/or development of tolerance and exploratory investigations).

Novartis Response:
The SCE will include the components of an ISE as suggested above.

Meeting discussion: No further discussion.

- c) The primary efficacy data from PARADIGM-HF will be submitted to obtain the following indication; “TRADE NAME is indicated for the treatment of heart failure (NYHA II-IV). TRADE NAME is superior to enalapril in reducing the rate of cardiovascular death and heart failure hospitalizations. TRADE NAME was also shown to reduce all-cause mortality compared to enalapril.”
The proposal is currently based on the content of the DMC letter, pending availability of the data. Does FDA agree in principal with the proposed indication, including a statement regarding superiority relative to enalapril?

FDA response: We cannot provide specific advice without some knowledge of the outcomes of PARADIGM-HF. If the data support your claims, a suitable indication might read: TRADE NAME is indicated to reduce the rate of cardiovascular death and heart failure hospitalization in patients with reduced ejection fraction heart failure (b) (4) (NYHA classes II-IV). Any description of the superiority of LCZ696 to enalapril is likely to appear in the Clinical Trials section as opposed to the indication statement.

Novartis Response:
We would like to discuss further at the meeting.

Meeting discussion: Novartis expressed understanding that a final decision regarding the indication cannot be made until the reviews are complete, and provided the following for clarification:

- They plan to describe the patient population and ejection fraction (EF) in the clinical section. They stated that the inclusion criteria in the original protocol required an ejection fraction of <40% but >35% which was later amended to <35%. Approximately 1000 patients were enrolled prior to the amendment. Novartis asked whether the label could include information regarding patients with an EF between 35% and 40%, because such patients may still show a benefit. FDA agreed that if a sizable portion of subjects were enrolled with an ejection fraction between 35% and 40% and the results for the primary endpoint in that subgroup were generally consistent with the overall population, the labeled population would include patients with ejection fractions <40%.
- Regarding superiority, Novartis stated that PARADIGM-HF was specifically designed to show superiority, and they believe the data will bear this out. The Division stated that the results will need to be reviewed, and noted that if superiority is discussed in any section of the label, the drug can be marketed as such. Dr. Stockbridge stated that the indication statement is meant to explain who the drug is intended for and what the drug is intended to treat. It is unlikely that superiority of LCZ696 over another drug will be included in the indication statement.



2. **Content of the Summary of Clinical Safety**

- a) Does the FDA agree with the proposal to assess safety and associated content planned for the submission, specifically within the Summary of Clinical Safety (SCS; CTD Module 2.7.4)?

FDA response: You plan to provide safety data and analyses from your heart failure and hypertension studies in the SCS. You do not plan to pool the data from the heart failure studies. You will pool the data from the hypertension studies. This overall plan is acceptable. Please ensure that all components of the ISS are included in the SCS including a thorough discussion of the preclinical safety issues. We have the following additional requests:

For AEs of special interest, please also submit time to event analyses. If these cannot be done because of limited data, please state so. For the renal impairment analysis, please also submit analyses for change in serum creatinine from baseline. For the hyperkalemia analysis, please also submit analyses by baseline use of potassium sparing diuretics.

We would like for you to address the potential for theoretical safety concerns such as neurological diseases (from amyloid accumulation) and cancer promotion. Please submit analysis for neurological AEs of interest. You may want to collect more data on neurological impact (b) (4)

Novartis Response:

The following will be provided from PARADIGM-HF (as requested):

- **Time to event analyses for the AEs of special interest (we understand this to be time to first event).**
- **Renal impairment and hyperkalemia analyses as suggested.**

We also agree to discuss the potential for theoretical safety concerns such as neurological disease and cancer promotion in the NDA. We will submit an analysis for neurological AEs from PARADIGM-HF based on the broad SMQ Dementia. Furthermore, we will submit an analysis for cancer promotion based on the broad SMQ Malignancies.

We would like to discuss your comment regarding further data collection on neurological impact at the meeting.

Meeting discussion: No additional discussion.

- b) Does the FDA agree to the proposed approach to satisfy the requirements for an Integrated Analysis of Safety?

FDA response: You plan to include an ISS in the SCS with an integrated analysis of safety data in the SCS appendix. We agree with this approach. The ISS should include a discussion of safety issues identified in the preclinical studies.

Novartis Response:
Agree.

Meeting discussion: No additional discussion.

- c) Does the FDA agree that Novartis has sufficiently characterized the effect of LCZ696 on amyloid- β ?

FDA response: Plan to discuss this at our meeting.

Meeting discussion: Based on literature reviews that indicated there is increased amyloid- β with neprilysin in knock-out mice, Novartis conducted a study in monkeys where an increase was also seen. Novartis also conducted a 2-week trial in healthy volunteers where CSF A β 1-40, 1-42, and 1-38 were measured. There were slightly greater increases in CSF A β 1-38 in the LCZ696 group compared to placebo but no significant difference in CSF A β 1-40, 1-42 between groups. Novartis asserted that this study provides evidence that LCZ696 does not result in clinically meaningful increases in CSF amyloid- β in human.. They will look at the AE's from PARADIGM-HF for neurological events and [REDACTED] (b) (4). It was agreed that this will be discussed further when the top-line results are available to determine if the Division still has concerns.

Module 5 Questions

3. Overall Summary of Clinical Content Proposal

Does the FDA agree with the proposed clinical content of Module 5, including the plan for submission of case report forms, patient narratives, etc. as provided in Table 2-3?

FDA response: Yes. Please also submit CRFs for all subjects that discontinued drug in PARADIGM-HF.

Novartis Response:
Agree.

Meeting discussion: No additional discussion.

4. Statistical Analysis, Datasets and Programs

Does the FDA agree with the proposed statistical content of the LCZ696 NDA, including the plan for submission of datasets and programs?

FDA response: Yes. In addition, we are also interested in some of the exploratory analyses that you performed, such as on recurrent events. Please submit the SAS code and details in your calculation.

Novartis Response:
We will provide as requested.

Meeting discussion: No additional discussion.

Description of Dosage Form/ Module 3 Questions

5. Description of Dosage Form

Does the FDA agree with the proposed description of LCZ696 and expression of the dosage strengths in the dossier and future label?

FDA response: With regard to the LCZ696 expression in the NDA submission (dossier), your nomenclature is adequate to communicate the differences in the product strength. With regard to future labelling, the general format of “TRADENAME with modifier (established name), dosage form” is acceptable, but the ultimate acceptability of the tradename and modifier will need to be approved by DMEPA.

Novartis Response:
We would like to discuss further at the meeting.

Meeting discussion: Novartis explained that valsartan in LCZ696 is 60% more bioavailable and they are concerned that medication errors will occur if individual pill strengths are listed. They think the format of “TRADENAME 200 mg (sacubitril/valsartan) tablets” would reduce errors. The Division stated this is still under discussion with DMEPA and will be discussed during review of the application.

6. **Content of Module 3**

a) Does the FDA agree with the structure and content proposed for Module 3 of the NDA?

FDA response: From a technical standpoint (not content related), the proposed format of Module 3 for the planned NDA is acceptable with the following changes described below in 2b.

Meeting discussion: No additional discussion.

b)  (b) (4)

FDA response: Based on all available data to date, we do not agree with your approach to  (b) (4)

(b) (4)

(b) (4)

We are open to a CMC-only meeting to discuss any issues that have not been clarified.

Novartis Response:

As suggested by the FDA we will seek a separate CMC meeting on further CMC topics; however a few points of clarification would be helpful for us on Wednesday and we would like to discuss briefly.

Meeting discussion: Novartis and the Division confirmed that though the product does not

(b) (4)

Both parties reaffirmed that a (b) (4)

(b) (4)

Novartis recently became aware of an (b) (4) and requested potential aid from the Agency. The Division asked that the sponsor submit a letter with their CMC-only meeting request so we can get the appropriate personnel involved.

- c) Will the FDA accept updated stability data during the first 30 days after the submission of the complete original application and consider the additional data for the evaluation of the shelf-life?

FDA response: Yes

Meeting discussion: No further discussion.

Module 4 Questions

7. Content of Module 4

Can the FDA confirm that the non-clinical safety development program is adequate to support the registration of LCZ696 for the treatment of heart failure and agree with the structure and content proposed for Module 4?

FDA response: Yes. The program was adequate, and we agree with the proposed Module 4 format.

Meeting discussion: No additional discussion.

Regulatory/Other Questions

8. Adequacy of the Dossier for Review and Cross-Reference to Diovan NDA

- a) Does the FDA agree that a cross-reference can be made to the previously submitted Diovan NDA in section 1.4.4 of the eCTD?

FDA response: Yes, you can cross reference information submitted to another application either in a cross reference document under module m1.4.4 (cross reference to other applications), or use cross application links.

1. To use the first option (placing a cross reference document in m1.4.4), a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information (eCTD and/or non- eCTD) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) the eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (7) the document leaf title and (8) the submission identification (e.g., submission serial number, volume number, electronic folder, file name, etc.) of the referenced document along with a hypertext link to the location of the information, when possible.
2. To use the second option (cross application links), both applications would need to be in eCTD format and reside on the same server. The applications need to include the appropriate prefix in the href links (e.g. nda, ind.). Also, when cross application links are used, it's

strongly recommended that a cross reference document be placed in m1.4.4, in case any of the links don't work and in the leaf titles of the documents, it is recommended that the leaf title indicate the word "cross reference" and application number (e.g. Cross Ref to nda123456). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application and the application number that is being referenced.

Prior to using cross application linking in an application, it is recommended that sponsor submit an "eCTD cross application links" sample, to ensure successful use of cross application links.

To submit an eCTD cross application links sample, sponsor would need to request two sample application numbers from the ESub team - esub@fda.hhs.gov. For more information on eCTD sample, please refer to the Sample Process web page which is located at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

Novartis Response:
We would like to discuss further at the meeting.

Meeting discussion: Novartis stated that the DIOVAN NDA is all paper. They clarified that they will be providing a general cross-reference to DIOVAN in case nonclinical needs information particular to DIOVAN. They will be providing a complete application needed for review of LCZ696.

b) Does the FDA agree that the proposed content of the NDA is appropriate and complete?

FDA response: From a technical standpoint (not content related), the proposed format for the planned NDA is acceptable. However, please see additional comments below:

- The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be linked to the referenced studies in m5.
- It is acceptable and preferred to provide a single heading node (i.e. m3.2.P and m3.2.p.4 sections) with attribute of "ALL" and differentiating documents with clear and concise leaf titles that indicates the file's true content. In other words, provide a single 3.2.p section and use the leaf titles to differentiate between strengths, manufacturers and excipients, where applicable.
- Only submit eCTD sections with documents. Sections that are not applicable should not be provided (e.g. 3.2.A – Not applicable).

Until preliminary results are available, it is unclear if the content is acceptable.

Meeting discussion: No additional discussion.

9. **PDUFA Review Clock**

Will LCZ696 be reviewed under PDUFA 5 “The Program” or PDUFA 4?

FDA response: The currently available information is that sacubitril is a NME, so we believe that the application will be reviewed under the Program.

Meeting discussion: No additional discussion.

10. **Exclusivity Determination**

Will LCZ696 be considered a fixed-combination drug product for purposes of determining whether LCZ696 or its components will be eligible to receive 5-year new chemical entity exclusivity?

FDA response: Exclusivity determinations are made at the time of approval. Regarding eligibility for 5-year NCE exclusivity for certain fixed combination drug products, please note that the guidance to which you refer, *New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products*, is in draft form. The provisions of the guidance will be implemented only after the guidance is published in final. As described at 21 CFR 314.50(j), an applicant should include in its NDA a description of the exclusivity to which the applicant believes it is entitled. FDA will consider the applicant’s assertions regarding exclusivity in the review of the application. Please also note that the NME determination for an application is distinct from and independent of the NCE determination and any related exclusivity determinations.

Meeting discussion: No additional discussion.

11. **Advisory Committee**

Pending availability of data and assuming a very clear positive benefit/risk, does the FDA consider that an Advisory Committee will be necessary for LCZ696?

FDA response: We cannot answer this question at this time because of lack of information about the outcomes in PARADIGM-HF.

Meeting discussion: No additional discussion.

4.0 **ADDITIONAL COMMENTS**

NOTE: Sponsor responses and discussion during the meeting are noted only under pertinent items. All other items did not have any follow up.

Biopharmaceutics Comments

We have the following comments regarding the biopharmaceutics information (not limited to) that should be provided in your NDA.

1. **Dissolution Method:** Include the dissolution method report supporting the selection of the proposed testing conditions. The report should include the following information:
 - a) The pH solubility profile;
 - b) Detailed description of the in dissolution method being proposed for the evaluation of your product (both components) and the developmental parameters (*i.e.*, *selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.*) used to select the proposed dissolution method as the optimal test for your product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. If possible, the dissolution profile should be complete and cover at least 85% of drug release of the label amount or whenever a plateau (*i.e.*, no increase over 3 consecutive time-points) is reached. We recommend use of at least six samples per testing variable;
 - c) Provide the complete dissolution profile data (*individual, mean, SD, profiles*) for your product. The dissolution data should be reported as the amount of drug released with time;
 - d) Provide data to support the discriminating capability of the proposed dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (*i.e.*, aberrant formulations and manufacturing conditions) for the most relevant manufacturing variables (*e.g.*, drug substance particle size, drug substance solid state, and hardness). In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent.

2. **Dissolution Acceptance Criteria:** For the selection of the dissolution acceptance criteria of each component of your proposed product, the following points should be considered:
 - The dissolution profile data from the pivotal clinical batches should be used for the setting of the dissolution acceptance criteria of your product (*i.e.*, specification-sampling time point and specification value).
 - Specifications should be established based on average in vitro dissolution data for each lot under study, equivalent to USP Stage 2 testing (n=12).
 - The last time point should be the time point where at least 85% of drug has release. If the maximum amount release is less than 80%, the last time point should be the time when the plateau of the release profile has been reached.
 - The dissolution acceptance criterion should be set in a way to ensure consistent performance from lot to lot and this criterion should not allow the release of any lots with dissolution profiles outside those that were tested clinically.
 - Note that the discriminating ability is not only determined by the dissolution method settings but also by the selected specification-sampling time point and specification value.

We remind you that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA. However, the acceptability of

the proposed dissolution criterion for your product will be made during the NDA review process based on the totality of the provided dissolution data.

3. Note that if you are not planning on doing dose proportionality studies to support the approval of the strengths not tested in pivotal clinical trials, a waiver request of the BA studies should be included in the NDA submission. The biowaiver will be granted if the following requirements are met:
 - The proposed lower and higher strengths of your product have the same dosage form;
 - The lower strengths are proportionally similar in its active and inactive ingredients to the higher strengths;
 - The lower and highest strength products have the same manufacturing process; and
 - Dissolution profile comparisons between the higher and lower strengths in three different media meet the similarity requirements (e.g., $F2 > 50$ for all the strengths).
4. It is not clear based on the data included in the meeting package whether any formulation and/or manufacturing changes were made from the Phase 3 clinical trial drug product. We remind you that bridging studies are needed to support changes formulation/manufacturing/etc.) that may happen throughout the product's development. Major changes should be supported with in vivo BE studies and minor changes with dissolution data (e.g., dissolution profile comparisons with similarity testing).

Clinical Comments

5. Please submit all versions of the protocol for the PARADIGM-HF and the date of any amendments. Please ensure that a Summary of Changes for each version is included.
6. Submit all versions of Statistical Analysis Plan (SAP) for PARADIGM-HF. Please ensure that a Summary of Changes for each version is included.
7. Please submit all SAS codes and datasets used to create your analyses found in the main sections of your Summary of Clinical Efficacy, Summary of Clinical Safety, and PARADIGM-HF clinical study report. If a SAS code contains a macro, please also include the macro code.

Novartis response: We understand that FDA agrees with Novartis proposal regarding provision of datasets and programs described in section 2.2 and Table 2.6 of the pre-NDA Briefing Book (question 4). According to this proposal, all raw and derived efficacy, safety, and PK datasets (PK for Paradigm only) with programming specifications as well as SAS programs for the primary and secondary efficacy analyses only will be provided for the individual HF studies (Paramount, Paradigm, and Titration). In addition, as requested, SAS programs for recurrent event analysis of the primary composite endpoint will also be included.

Meeting discussion: The Division confirmed that all SAS programs/datasets should be provided as stated in the question 7, in addition to the datasets and programs described in section 2.2 and Table 2.6 of the pre-NDA briefing book. Considering that the sponsor does not plan to pool heart failure studies in the Summary of Clinical Efficacy and Summary of Clinical Safety, the majority of requested programs/datasets should be included in the section 2.2 of the pre-NDA Briefing Book.

8. Please submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the NDA. The table should contain the following:
 - a. title of the table or figure in NDA
 - b. a hyperlink to the location of the table or figure with page number
 - c. a hyperlink to the SAS code used to create the table or figure, and
 - d. the names of the datasets used to create the table or figure. For derived (analysis) datasets used to conduct your analyses, you should indicate the CRF pages and tabulation datasets from which the information was derived.

Novartis response: We will provide this table. However, as described in section 2.2 and Table 2.6 of Novartis pre-NDA Briefing Book (and above), all raw and derived efficacy, safety, and PK datasets (PK for Paradigm only) with programming specifications as well as SAS programs for the primary and secondary efficacy analyses only will be provided for the HF studies. Datasets will be provided as SAS datasets in SAS transport format (SAS XPORT V.5). The metadata descriptions of the datasets (e.g., the content and structure) will be within the Data Derivation and Handling Methods Documents, data definition tables and associated annotated CRFs/eCRFs for each study. These will also be provided in PDF format, with the appropriate navigational links.

9. In the NDA (for example with the review aid), please submit an annotated version of these pre-NDA meeting minutes that include a hyperlink, when applicable, to the analysis and/or documents requested.
10. An adjudication dataset should be submitted that contains one line per event. The columns in the dataset should include the study number, unique subject id, treatment arm, flag that indicates subject is included in the ITT analysis, flag that indicates the subject is included in the safety analysis, event type being adjudicated (i.e., death, hospitalization for heart failure, etc.), date of event, what triggered the event for adjudication (i.e., investigator, laboratory result, etc.), the investigator's assessment of the event, each adjudicators' adjudication (in chronological order across the dataset) date of each adjudication, and final adjudication result.
11. Please submit all adjudication packages exactly and completely as seen by the adjudicators, including all source documents and query results. If adjudication packages were prepared but not sent to the CEC, please submit these also. Please bookmark the electronic adjudication packages for ease of review.

12. Your final clinical study report should include a comprehensive description of the algorithm used to identify potential endpoint events. If your algorithm changed over time, you should also provide detailed information on its evolution, including when and why changes were made. If changes were made to the algorithm, you should describe whether the algorithm was used for potential events that occurred prior to the changes to identify additional events for adjudication.
13. Please provide a dataset(s) for time to event (both safety and efficacy) censoring subjects without an event at the date of last known information about the event of interest (not vital status check at the end of the study). Include whether censoring was determined by a patient visit or by telephone call. This data set should allow one to analyze by ITT as well as on-treatment. The events should include all adjudicated events and any important composite endpoints.
14. Please submit a dataset that contains all subjects that were unblinded. The dataset should include the unique subject ID, the treatment received, who requested unblinding, the date of unblinding, and the reason for unblinding.
15. Please submit a dataset that contains all subjects with submitted CRFs, adjudication packages, and/or narratives. The dataset should include the following variables: unique subject id, flag for submitted adjudication package, flag for submitted CRF, and flag for submitted narrative.
16. Please include a list of datasets that you assert are of high quality for review. Explain how you assessed the quality of your datasets, and what you did to ensure your datasets are suitable for NDA review.
17. Please submit all informed consent document(s). Please describe any country- or region-specific variations.
18. Please note that CRFs include all clinical documents collected about the patient regardless of whether they are labeled “CRFs”, e.g., Medwatch forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.
19. Please provide sample clinical trial kits, from both arms, identical to those used during PARADIGM-HF. Ship them to Ms. Alexis Childers’ desk address in the same packaging that was used for shipping to investigative sites.
20. Please submit your site monitoring plan and all amendments for PARADIGM-HF.
21. Please submit a description of the responsibilities of each ARO or CRO used in PARADIGM-HF.
22. Please submit your data management plan for PARADIGM-HF, including all manual and programmatic checks. Submit SAS codes that were used to create or clean up your analyses datasets. All versions of your site monitoring plans and any amendments along with applicable dates should be submitted. If changes to your site monitoring plans were not

documented contemporaneously by formal signed amendments, please explain the process for amending.

Novartis response: The Data Management Plan will outline the edit checks/reports that are used to clean data for the Paradigm-HF trial: Edit checks are validated checks in the OC RDC system and reports are validated reports run in Novartis JREVIEW system. Dataset programs to create the clinical study reports, tables, figures and listings are not used as data cleaning tool, however, any data issue identified when developing and running these programs are communicated to the data management team and appropriate action taken.

Meeting discussion: Novartis clarified that the SAS code that was used to create or clean up their analyses datasets are not available. The Division stated they would like a better understanding of the QC process and asked Novartis to provide examples of data validation reports in the application.

23. Please include all charters for committees involved in conducting PARADIGM-HF (e.g., DSMB, Steering Committee, etc.)
24. At the time of the NDA submission, please include meeting minutes of all groups with any responsibility for the management of the trial, e.g. Executive Committee, Clinical Endpoint Committee, Steering Committee, and DMC. Please include agendas and copies of any presentations. For a meeting that was cancelled or where no minutes were taken, please include a place holder for that meeting noting such and signed by a member of the clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.
25. Submit all newsletters and communications to investigational sites and national coordinators from the group(s) responsible for the conduct of your trials. Please bookmark the newsletters and communications by date.
26. Please submit, to the IND as soon as possible, an encrypted SAS dataset of the randomization list including the randomization number, treatment arm, and stratification factors (if any) for your Phase 3 trial. Please include an unencrypted copy of a DEFINE.PDF file describing the randomization list variables. A copy of the encryption key should be included with your NDA submission of the trial results.
27. Please submit MedDRA coding dictionaries for AEs of interest as SAS transport files.
28. Please provide a statement of Good Clinical Practice confirming that all clinical studies were conducted under the supervision of an Institutional Review Board and with adequate informed consent procedures. If you were granted an IRB Waiver during this trial because a specific site operated under a Central Ethics Committee (CEC) and/or Local Ethics Committees (EC) which we agreed maintain the same oversight responsibilities as IRBs, please reference the waiver and include the date.

29. In your NDA submission, please include a rationale for assessing the applicability of the foreign data collected from your registration trial to U.S. population/practice of medicine.
30. Attached as an appendix to these preliminary responses is an information request provided by the Office of Scientific Investigations. This document includes data requests that are to be addressed in your initial submission.

Meeting discussion: Novartis stated they will provide items I and II of the OSI request, but prefer not to submit item III (site level dataset) because it is not mandatory and would require a lot of work. The Division confirmed it is not mandatory but emphasized the tool is extremely helpful to the Division especially if the review is priority. Without the tool, selection of site inspections may be delayed.

31. Liver Data: Separate from the primary efficacy and safety datasets, additional datasets will need to be provided according to the specifications provided in an email to Masha Berkhin on June 19, 2014. Please provide these in the original submission.
 - a. Please be aware that we wish to use eDISH to assess the likelihood that your new compound causes liver toxicity and identifying potential "Hy's Law" cases of elevated ALT or AST >3xULN and TBL >2xULN (or more in Gilbert syndrome) is just the first step. The next two steps are: 1) looking at all the liver test data for patients of interest over the time of observation, to appreciate the time-related elevations and which of the tests rises first, and then 2) evaluating the narrative data gathered to adjudicate the probable cause of the abnormal findings. This may require additional questions, tests, examinations to search for the cause, and only after ruling out other causes can a presumptive diagnosis of probable drug-related liver injury (DILI) be made. Liver biopsy is not definitive, and there is no single test or finding that proves DILI. For the adjudication to be successful, your investigators must search actively for the cause of all cases of elevated ALT or AST >3xULN and TBL >2xULN. Finding a probable, very likely, or definite cause of the liver injury other than the drug is very important. The eDISH program includes the capability to create time-course graphs for each subject, and to read the narrative summaries. We will want to review the data independently. Estimation of the likelihood that the liver injury was caused by the drug being studied is frequently difficult and requires information to rule out or rule in other possible causes.

Therefore, we recommend that the narratives be written by *physicians or other medical personnel* skilled in medical differential diagnosis. Pertinent negative findings should be included in any narrative. The data that needs to be gathered by the investigator are those that can establish or rule out other causes, such as acute viral hepatitis A or B (less often C or E), biliary disease such as stones or tumors, cardiac failure or shock, acute alcoholic or autoimmune hepatitis.

Clinical Pharmacology

32. Please submit a completed Clinical Pharmacology Review Aid document.

33. Please include Child-Pugh classification for hepatic impairment in the study report for Study LCZ696B2203.
34. You should justify the selection of candidate drugs for the *in vivo* drug-drug interaction (DDI) studies performed and explain the DDI liability of LCZ696 based on the *in vivo* as well as *in vitro* studies.
35. Please provide a table with list of clinical studies and the identification of formulation of LCZ696 used. The table should identify studies that used final marketing image formulation (FMI), and provide information on bridging if the formulations used were different from FMI.
36. It appears that that the food effects study for LCZ696 was conducted using a 400 mg strength tablet formulation. This 400 mg tablet formulation was not used in the Phase 3 study and you are not planning to seek approval for it. Therefore, you should explain whether the results from the food effect study can be extrapolated to the FMI strengths.
37. Please use the enclosed “Clinical Pharmacology Summary Aid” for preparing the NDA package.

Additional request during the meeting:

- Provide dates of database lock
- Please propose a way to analyze the primary efficacy endpoint by change in systolic BP that occurred during the treatment protocol to help us understand if there is an effect of LCZ696 beyond what can be explained by blood pressure reduction alone.

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. See above comments.
- A preliminary discussion regarding REMS is postponed until the data driven discussion occurs in Q3.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidance's.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, "Guidance for

Industry Assessment of Abuse Potential of Drugs”, available at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

None

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

/s/

ELLIS F UNGER
07/14/2014

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 207620

LATE-CYCLE MEETING MINUTES

Novartis Pharmaceuticals Corp.
Attention: Masha Berkhin, PharmD
Global Program Regulatory Director
One Health Plaza
Building 100
East Hanover, NJ 07936

Dear Dr. Berkhin:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for LCZ696 (sacubitril/valsartan) Tablets.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on June 3, 2015.

A copy of the official minutes of the LCM is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Alexis Childers, Sr. Regulatory Project Manager, at (301) 796-0442.

Sincerely,

{See appended electronic signature page}

Aliza Thompson, M.D.
Cross Discipline Team Leader
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: June 3, 2015, 6:00-7:00 pm
Meeting Location: Teleconference

Application Number: 207620
Product Name: LCZ696 (sacubitril/valsartan) Tablets
Indication: Treatment of Heart Failure
Applicant Name: Novartis

Meeting Chair: Aliza Thompson, MD
Meeting Recorder: Alexis Childers, RAC

FDA ATTENDEES

**Office of Drug Evaluation I*

Ellis F. Unger, M.D. Director

**Division of Cardiovascular and Renal Products*

Norman Stockbridge, M.D., Ph.D. Director
Aliza Thompson, M.D. Cross Discipline Team Leader
Mary Ross Southworth, Pharm.D. Deputy Director for Safety
Tzu-Yun McDowell, Ph.D. Clinical Reviewer
Kim Smith, M.D., M.S. Clinical Reviewer
Alexis Childers, RAC Sr. Regulatory Health Project Manager
Edward Fromm, R.Ph., RAC Chief, Regulatory Health Project Manager

**Office of Pharmaceutical Quality*

Wendy Wilson, Ph.D. Chemistry Lead

**Office of Surveillance and Epidemiology*

Thao Tran, Pharm.D., BCPS Safety Evaluator

EASTERN RESEARCH GROUP ATTENDEES

Marc Goldstein Independent Assessor

APPLICANT ATTENDEES

Patrice Matchaba, M.D. Franchise Head - CVM
Marty Lefkowitz, M.D. Therapeutic Area Head
Robert Hilkert, M.D. Medical Unit Head
Victor Shi, M.D. Global Program Medical Director
Guenther Mueller-Velten, Ph.D. Senior Global Group Head – Biostatistics
Denise Leclair, M.D. Therapeutic Area Safety Lead

Hendrik Streefkerk, M.D.
Thomas Langenickel, M.D.
Dawn Bell, Pharm.D.
Rob Kowalski, PharmD.
Paula Rinaldi
Caroline Boulton
Patricia Kay-Mugford
Masha Berkhin, Pharm.D.
Diane Zezza, Ph.D.
Fedra Maria Limoncini
Albina Taigounov
Michael Motto

Brand Safety Leader
Director Translational Medicine
Senior Global Program head - CVM
Global Head of Regulatory
US Head of Regulatory Affairs
Global Regulatory Franchise Head
Global Regulatory Therapeutic Area Lead
Global Program Regulatory Director
Global Head Regulatory CMC
Franchise Head Regulatory CMC
Associate Director Regulatory CMC
Project Leader Technical Development

BACKGROUND

NDA 207620 was submitted on December 17, 2014 for LCZ696 (sacubitril/valsartan) Tablets for the treatment of heart failure (NYHA class II-IV) (b) (4). The PDUFA goal date is August 17, 2015. On May 26, 2015, FDA issued a background package in preparation for the Late-Cycle Meeting with Novartis. In the background package, FDA indicated that no substantive review issues had been identified to date. Only the items listed below, which were included in the background package, were discussed during the meeting.

INFORMATION REQUESTS

The following Product Quality information requests were sent on May 15, 2015:

1. Section 3.2.P.8.1 Stability Summary of the submission includes a description of a protocol deviation due to “inconsistency in dissolution data.” We cannot determine an appropriate drug product expiration date without assurance of the validity of the supporting registration stability data. Provide additional results for all drug product stability tests for the current stability samples stored in HDPE bottles and (b) (4) blister under long-term conditions for all drug product registration stability batches utilizing the commercial drug product stability testing site listed in the NDA submission – (b) (4).
Include as part of the results, the new time point tested.
2. Based on the provided data, we recommend that you revise the dissolution acceptance criterion to $Q = \frac{(b)}{(4)}\%$ at $\frac{(b)}{(4)}$ minutes instead of the proposed $Q = \frac{(b)}{(4)}\%$ at $\frac{(b)}{(4)}$ minutes for sacubitril and valsartan.

Discussion during the meeting: Dr. Wilson indicated that Novartis’ response has been received and is being reviewed. Currently, OPQ is not in agreement with $Q = \frac{(b)}{(4)}\%$ at $\frac{(b)}{(4)}$ min. OPQ is recommending $Q = \frac{(b)}{(4)}\%$ at $\frac{(b)}{(4)}$ min. Novartis indicated that they would discuss the request internally. Dr. Wilson volunteered a separate teleconference if needed.

Novartis asked for further comment on the need for stability testing. Dr. Wilson indicated that Novartis should continue to prepare samples. If further testing is not needed, Novartis will be informed.

POSTMARKETING REQUIREMENTS/POSTMARKETING COMMITMENTS

We are currently reviewing your May 6, 2015 submission containing a proposed post-marketing study to assess the incidence of serious angioedema in black patients with heart failure exposed to LCZ696 in the United States. We do not have additional comments at this time; however, you should begin to think about timelines for:

- Final Protocol Submission
- Study/Trial Completion
- Final Report Submission

Discussion during the meeting: Novartis asked whether the Division believed any other PMRs or PMCs would be necessary. The Division indicated that none were being considered at this time.

MAJOR LABELING ISSUES

Comments from the Statistical Reviewer:

Statements similar to those found in the Vytorin (ezetimibe and simvastatin) label should be added to the proposed label.

- The Vytorin label has a Limitations of Use statement in Section 1 (Indications and Usage) that includes the following language: "No incremental benefit of Vytorin on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established..."
- In the Clinical Studies (Section 14) description of the SHARP trial, it states "The study design precluded drawing conclusions regarding the independent contribution of either ezetimibe or simvastatin to the observed effect."
- In the Clinical Studies (Section 14) description of the "Primary Hyperlipidemia" indication, it describes the trials of the components. The label for LCZ696 should similarly describe the Val-HeFT trial.

Discussion during the meeting: From Dr. Lawrence's point of view, the major issue is how to interpret the trial. He stated that, in general, with a combination product, there needs to be evidence that both components contribute to the effect. This was not shown in PARADIGM-HF. Dr. Lawrence believes that valsartan did not add anything to the treatment effect. At best, valsartan is equivalent to enalapril and not superior since valsartan was never compared to enalapril. He suggested that the Val-HeFT trial be mentioned in the label and that statements similar to those found in the Vytorin label be included.

In response to Dr. Lawrence's feedback, Novartis made the following comments:

- LCZ696 has a mortality benefit. In contrast, Vytorin does not have a mortality claim. Novartis does not believe that the Vytorin label is an appropriate precedent for the LCZ696 label.

- Enalapril, the active comparator in PARADIGM-HF, is the standard of care and has a mortality claim. LCZ696 was superior to enalapril in PARADIGM-HF and the label should convey this.
- There are important differences between Val-HeFT and PARADIGM-HF. Val-HeFT tested add-on therapy to an ACE inhibitor and showed a reduction in hospitalizations and no mortality benefit. PARADIGM-HF compared LCZ696 with an ACE inhibitor and showed both a hospitalization and mortality benefit. Novartis does not believe including information from Val-HeFT would be helpful to prescribers.

Labeling claims:

The Division provided comments on the applicant's proposed labeling on May 20, 2015. The applicant responded via email on May 29, 2015 with a revised label and companion rationale document (these documents were also submitted to the NDA on June 4, 2015). The applicant requested discussion during the Late-Cycle meeting of the following claims they are seeking to include in Section 14 of the label:

1.



2.



(b) (4)

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(b) (4)

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Dr. Thompson stated that the Agency will review the additional data Novartis has provided in greater detail and will continue to discuss these issues internally.

OTHER

Proprietary Name Review: The name Entresto, with a fixed-dose combination strength expression, is currently under review.

Container Label and Carton Labeling Review: The revised container labels and carton labeling submitted on May 15, 2015 are currently under review.

Discussion during the meeting: The Agency reiterated that the Proprietary Name Review and Container Label and Carton Labeling Reviews are ongoing and that the reviewers are

aware of the targeted action date. Novartis asked if any other GCP or GMP inspections are expected. The Agency stated that no other inspections are planned and that current inspections are being closed out.

Novartis asked for additional information on the targeted action date for the application. Dr. Thompson indicated that the Agency was targeting July 1 or 2, 2015.

Novartis asked when they could expect additional feedback on the label. The Agency indicated that it would try to return the label within a week of the meeting but noted that there were rate-limiting factors (i.e., that Dr. Stockbridge and Unger would be out of the country attending meetings).

Novartis asked if they should expect other information requests since primary reviews are complete. The Agency indicated that Novartis would receive a response to their PMR proposal. The Agency also noted that the application had not been fully reviewed by others (e.g., the signatory authority) and hence, there may be additional information requests.

Note: This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

ALIZA M THOMPSON
06/24/2015