

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-990**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## Patent Certification

### Paragraph III Certification

US Patent 4,572,909 for salts of amlodipine was to expire on July 31, 2006, and now is set to expire on January 31, 2007 as a result of the pediatric extension.

US Patent 4,879,303 for amlodipine besylate was to expire on March 25, 2007, and is now set to expire on September 25, 2007 as a result of the pediatric extension.

Novartis will not market Exforge® until expiration of the patents listed above.

*Donna Vivelo*

\_\_\_\_\_  
Donna Vivelo  
Director  
Drug Regulatory Affairs

*1/26/06*

\_\_\_\_\_  
Date

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

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

NDA NUMBER

21-990

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)

EXFORGE®

ACTIVE INGREDIENT(S)

Amlodipine Besylate and Valsartan

STRENGTH(S)

5/160 mg; 10/160 mg; 5/320 mg and 10/320 mg  
(Amlodipine Besylate to Valsartan respectively)

DOSAGE FORM

Tablets

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

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

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

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

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

**1. GENERAL**

a. United States Patent Number

5,399,578

b. Issue Date of Patent

3/21/1995

c. Expiration Date of Patent

3/21/2012

d. Name of Patent Owner

Novartis Corporation

Address (of Patent Owner)

608 5th Avenue

City/State

New York, NY

ZIP Code

10020

FAX Number (if available)

212-246-0185

Telephone Number

212-307-1122

E-Mail Address (if available)

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

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

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

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

Yes

No

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

Yes

No

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

**2. Drug Substance (Active Ingredient)**

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

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

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

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

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

2.6 Does the patent claim only an intermediate?  Yes  No

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

**3. Drug Product (Composition/Formulation)**

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

3.2 Does the patent claim only an intermediate?  Yes  No

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

**4. Method of Use**

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

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

4.2 Patent Claim Number (as listed in the patent) 6 and 7 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

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

**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

*Gregory Ferraro*

12/15/05

**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  
Gregory Ferraro

Address  
One Health Plaza

City/State  
East Hanover, NJ

ZIP Code  
07936

Telephone Number  
862 778-7831

FAX Number (if available)  
973-781-8064

E-Mail Address (if available)  
gregory.ferraro@novartis.com

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

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

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

# 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 supplemental 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. 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 July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 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://forms.psc.gov/forms/fdahtm/fdahtm.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.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

#### 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

21-990

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)

EXFORGE®

ACTIVE INGREDIENT(S)

Amlodipine Besylate and Valsartan

STRENGTH(S)

5/160 mg; 10/160 mg; 5/320 mg and 10/320 mg  
(Amlodipine Besylate to Valsartan respectively)

DOSAGE FORM

Tablets

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

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

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

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

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

**1. GENERAL**

a. United States Patent Number

6,294,197

b. Issue Date of Patent

9/25/2001

c. Expiration Date of Patent

6/18/2017

d. Name of Patent Owner

Novartis AG

Address (of Patent Owner)

Lichtstrasse 35

City/State

Basel

ZIP Code

Switzerland

FAX Number (if available)

41 61 324 8001

Telephone Number

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.)

City/State

ZIP Code

Telephone Number

FAX Number (if available)

E-Mail Address (if available)

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

Yes

No

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

Yes

No

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

**2. Drug Substance (Active Ingredient)**

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

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

**4. Method of Use**

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

- 4.1** Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No
- 4.2** Patent Claim Number (as listed in the patent) 26, 37, 52 and 53 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No
- 4.2a** If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)  
A method of treating hypertension

**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

*Gregory Ferraro*

12/16/05

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  
Gregory Ferraro

Address  
One Health Plaza

City/State  
East Hanover, NJ

ZIP Code  
07936

Telephone Number  
862 778-7831

FAX Number (if available)  
973-781-8064

E-Mail Address (if available)  
gregory.ferraro@novartis.com

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

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

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

**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 supplemental 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. 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 July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 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://forms.psc.gov/forms/fdahtm/fdahtm.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.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

**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

21-990

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)

EXFORGE®

ACTIVE INGREDIENT(S)

Amlodipine Besylate and Valsartan

STRENGTH(S)

5/160 mg; 10/160 mg; 5/320 mg and 10/320 mg  
(Amlodipine Besylate to Valsartan respectively)

DOSAGE FORM

Tablets

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

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

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

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

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

**1. GENERAL**

a. United States Patent Number

6,395,728

b. Issue Date of Patent

5/28/2002

c. Expiration Date of Patent

7/8/2019

d. Name of Patent Owner

Novartis AG

Address (of Patent Owner)

Lichtstrasse 35

City/State

Basel

ZIP Code

Switzerland

FAX Number (if available)

41 61 324 8001

Telephone Number

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.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

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

Yes

No

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

Yes

No

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

**2. Drug Substance (Active Ingredient)**

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

**3. Drug Product (Composition/Formulation)**

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

**4. Method of Use**

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

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

**5. No Relevant Patents**

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

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

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

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

Date Signed

*Gregory Ferraro*

*12/15/05*

**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

Gregory Ferraro

Address

One Health Plaza

City/State

East Hanover, NJ

ZIP Code

07936

Telephone Number

862 778-7831

FAX Number (if available)

973-781-8064

E-Mail Address (if available)

gregory.ferraro@novartis.com

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

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

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

# 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 supplemental 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. 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 July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 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://forms.psc.gov/forms/fdahtm/fdahtm.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.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.

- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

#### 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 # 21-990

SUPPL #

HFD # 110

Trade Name Exforge Tablets

Generic Name amlodipine and valsartan

Applicant Name Novartis Pharmaceuticals Corporation

Approval Date, If Known 6/20/07

### 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)(2)

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

YES  NO

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

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES  NO

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

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

YES  NO

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

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

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

YES  NO

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

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES  NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES  NO

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

NDA# 19-787 Norvasc (amlodipine besylate) Tablets

NDA# 20-665 Diovan (valsartan) Capsules

NDA# 21-283 Diovan (valsartan) Tablets

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

IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

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

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

YES  NO

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

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

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

YES  NO

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

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

YES  NO

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

YES  NO

If yes, explain:

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

YES  NO

If yes, explain:

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

Studies A2201, A2307, A2305, A2306

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

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

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

Investigation #1

YES  NO

Investigation #2

YES  NO

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

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

Investigation #1

YES  NO

Investigation #2

YES  NO

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

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

Studies A2201, A2307, A2305, A2306

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

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

Investigation #1

IND # 65,174      YES       ! NO   
! Explain:

Investigation #2

IND # 65,174      YES       ! NO   
! Explain:

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

Investigation #1

YES       ! NO   
Explain:      ! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

---

Name of person completing form: Quynh Nguyen, Pharm.D.  
Title: Regulatory Health Project Manager, Division of Cardiovascular and Renal Products  
Date: 6/20/07

Name of Office/Division Director signing form: Norman Stockbridge, M.D., Ph.D.  
Title: Director, Division of Cardiovascular and Renal Products

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

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

/s/

-----  
Norman Stockbridge  
6/21/2007 09:36:41 AM

## PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-990 Supplement Type (e.g. SE5): n/a Supplement Number: n/a

Stamp Date: 2/22/06 PDUFA Goal Date: 12/22/06

HFD 110 Trade and generic names/dosage form: Exforge (amlodipine besylate/valsartan) Tablets

Applicant: Novartis Pharmaceuticals Corporation Therapeutic Class: antihypertensive

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

Yes. Please proceed to the next section.

No. PREA does not apply. Skip to signature block.

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

Indication(s) previously approved (please complete this section for supplements only): n/a

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

Number of indications for this application(s): 1

Indication #1: Treatment of hypertension.

Is this an orphan indication?

Yes. PREA does not apply. Skip to signature block.

No. Please proceed to the next question.

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

Yes: Please proceed to Section A.

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

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Other: Pediatric data is available for amlodipine besylate and there is an ongoing pediatric program for valsartan.

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

**Section B: Partially Waived Studies**

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

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
 Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

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

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

**Section C: Deferred Studies**

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

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
 Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

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

Date studies are due (mm/dd/yy): \_\_\_\_\_

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

**Section D: Completed Studies**

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

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
 Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

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

NDA 21-990

Page 3

This page was completed by: Quynh Nguyen, Pharm.D.

*{See appended electronic signature page}*

---

Regulatory Project Manager

cc: NDA 21-990  
HFD-960/ Rosemary Addy or Grace Carmouze

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG  
DEVELOPMENT, HFD-960, 301-594-7337.  
(revised 6-23-2005)**

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: \_\_\_\_\_

Is this an orphan indication?

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

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

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

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

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

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

**Section B: Partially Waived Studies**

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

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

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

*If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is*

complete and should be entered into DFS.

**Section C: Deferred Studies**

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

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

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

Date studies are due (mm/dd/yy): \_\_\_\_\_

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

**Section D: Completed Studies**

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

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

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

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA 21-990  
HFD-960/ Rosemary Addy or Grace Carmouze

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

(revised 6-23-2005)

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

/s/

-----  
Quynh Nguyen  
12/15/2006 08:36:09 PM

**NDA 21-990**

VAA489A

Exforge® (amlodipine besylate and valsartan)

**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.

*Donna Vivelo*

---

Donna Vivelo  
Director  
Drug Regulatory Affairs

*1/23/06*

---

Date

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

TO BE COMPLETED BY APPLICANT

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

Please mark the applicable checkbox.

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

Clinical Investigators	See attached spreadsheets.	

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

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Robert Glazer, MD	TITLE Executive Director
FIRM/ORGANIZATION Novartis Pharmaceuticals Corp.	
SIGNATURE 	DATE FEB. 10, 2006

#### Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

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

## DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning \_\_\_\_\_, who participated as a clinical investigator in the submitted study \_\_\_\_\_, is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

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

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

NAME Robert Glazer, MD	TITLE Executive Director
FIRM/ORGANIZATION Novartis Pharmaceuticals Corp	
SIGNATURE 	DATE FEB. 10, 2006

### Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14-72  
Rockville, MD 20857

**USER FEE PAYMENT & PDUFA/FDAMA VALIDATION SHEET**

Must be completed for ALL original NDAs, efficacy supplements and initial rolling review submissions

NDA # 21-990 SUPP TYPE & # N-000 Division 110 UFID # 3006424

Applicant Name: Novartis Drug Name: "Exforge" amlodipine besylate and valsartan tab

For assistance in filling out this form see the Document Processing Manual for complete instructions and examples.

1. Was a Cover Sheet submitted?  
 Yes       No
2. Firm in Arrears?  
 Yes       No
3. Bundling Policy Applied Appropriately? Refer to Draft "Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees"  
<http://www.fda.gov/cder/guidance> NA  
 Yes       No (explain in comments)
4. Administrative Split? (list all NDA#s and Divisions)  

NDA #/Doc Type	Div.	Fee? (Y/N)
5. Type 6?  
 Yes       No  
 Type 6 to which other application?  
 NDA # \_\_\_\_\_ Supp Type & # \_\_\_\_\_
6. Clinical Data Required for Approval? (Check one)  
 Yes\*  
 Yes, by reference to another application  
 NDA # 19987 Supp Type & # NA  
 No

\* Yes if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., adding an adverse reaction, contraindication or warning to the labeling).

7. 505(b)(2) application? (NDA original applications only) Refer to Draft "Guidance for Industry Applications Covered by Section 505(b)(2)"  
<http://www.fda.gov/cder/guidance>  
 Yes       No       To be determined
8. Subpart H (Accelerated Approval/Restricted Distribution)?  
 Yes       No       To be determined
9. Exclusion from fees? (Circle the appropriate exclusion. For questions, contact User Fee staff)  
List of exclusions:  
 No fee - administrative split  
 No fee - 505b2  
 Supplement fee - administrative split  
 9 - No fee Subpart H supplement- confirmatory study  
 11 - No fee Orphan Exception  
 13 - No fee State/Federal exemption from fees
10. Waiver Granted?  
 Yes (letter enclosed)       No  
 Select Waiver Type below: Letter Date: \_\_\_\_\_  
 Small Business       Barrier-to-Innovation  
 Public Health       Other (explain)
11. If required, was the appropriate fee paid? NA  
 Yes       No
12. Application Review Priority  
 Priority       Standard       To be determined
13. Fast Track/Rolling Review Presubmission?  
 Yes       No

Comments  
  
Cheryl Ann Borden  
 PM Signature/Date

This form is the initial data extraction of information for both User Fee payment and PDUFA/FDAMA data elements. The information entered may be subject to change due to communication with the User Fee staff. This form will not reflect those changes. Please return this form to your document room for processing.

C: original archival file HFD-007      Processor Name & Date \_\_\_\_\_      QC Name & Date \_\_\_\_\_



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-990

**NDA ACKNOWLEDGMENT**

Novartis Pharmaceuticals Corporation  
Attention: Ms. Donna Vivelo  
One Health Plaza  
East Hanover, New Jersey 07936-1080

Dear Ms. Vivelo:

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

Name of Drug Product: Exforge® (amlodipine besylate/valsartan ) — 5/160,  
10/160, 5/320, and 10/320 mg Tablets

Review Priority Classification: Standard (S)

Date of Application: February 22, 2006

Date of Receipt: February 22, 2006

Our Reference Number: NDA 21-990

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 April 23, 2006, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be December 22, 2006.

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

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We acknowledge receipt of your request for a waiver of pediatric studies for this application. We are waiving the requirement for pediatric studies for this application.

NDA 21-990

Page 2

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

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Cardiovascular and Renal Products, Room 4165  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, please call:

Cheryl Ann Borden, MSN, RN, CCRN, CCNS  
Regulatory Health Project Manager  
(301) 796-1046

Sincerely,

*{See appended electronic signature page}*

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

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

/s/

-----  
Edward Fromm  
3/10/2006 09:04:26 AM

<b>MEMORANDUM</b>	<b>Division of Medication Errors and Technical Support</b> <b>Office of Surveillance and Epidemiology</b> <b>(HFD-420; White Oak Bldg. 22, Mail Stop 4447)</b> <b>Center for Drug Evaluation and Research</b>
-------------------	--

**TO:** Norman Stockbridge, M.D.  
 Director, Division of Cardiovascular and Renal Products, HFD-110

**THROUGH:** Linda Y. Kim-Jung, Pharm.D., Team Leader  
 Denise Toyer, Pharm.D., Deputy Director  
 Carol Holquist, R.Ph., Director  
 Division of Medication Errors and Technical Support, HFD-420

**FROM:** Todd Bridges, R.Ph., Safety Evaluator  
 Division of Medication Errors and Technical Support, HFD-420

**DATE:** July 19, 2006

**SUBJECT:** DMETS Label and Labeling Review  
 Drug: Exforge  
 (Amlodipine Besylate/Valsartan Tablets) \_\_\_\_\_  
 5 mg/160 mg, 5 mg/320 mg, 10 mg/160 mg, and 10 mg/320 mg  
 NDA #: 21-990  
 Sponsor: Novartis Pharmaceutical Corporation

**PROJECT #:** 05-0313-1

This memorandum is in response to a July 3, 2006 request from the Division of Cardiovascular and Renal Products (HFD-110) for a review of the container labels, carton and insert labeling of Exforge.

In the review of the labels and labeling, DMETS has focused on safety issues relating to possible medication errors. DMETS has identified the following areas of improvement, which might minimize potential user error.

A. GENERAL COMMENTS

1. We note that the product strength is dependent on the active moiety rather than the besylate salt. Additionally, we recognize that the sponsor qualifies this by including the statement "equiv. to..." on the principal display panel. However this presentation crowds the label. We recommend revising to read:

- a. Exforge  
 (Amlodipine and Valsartan) Tablets  
 xx mg/xxx mg

or

b. Exforge

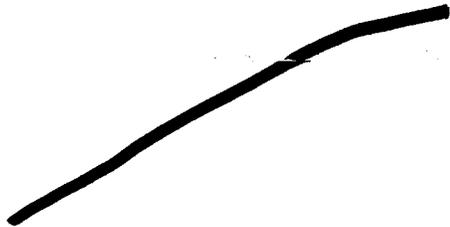
---

xx mg\*/xxx mg

\*Each tablet contains Amlodipine Besylate equivalent to xx mg Amlodipine

DMETS prefers the first example (a) as an option because this nomenclature is consistent with USP recommendations on “labeling of salts of drugs”.

2. The established name should be revised so that there  between Amlodipine and Valsartan. See example above.
3. Ensure that the established name is at least one-half the size of the proprietary name in accordance with 21 CFR 201.10(g)(2).
4. Relocate the product strength to immediately follow the established name. Additionally, increase the prominence (i.e., the font size) of the product strength commensurate with the proprietary and established names, ensuring that the product strength is more prominent than the net quantity.
5. DMETS notes that the colors for the proposed  and 5 mg/160 mg product strengths are similar. The same is true for the proposed 5 mg/320 mg and 10 mg/ 320 mg strengths (see container labels below). This may lead to product selection errors resulting in the wrong strength being dispensed and/or administered. We recommend that all of the available product strengths for Exforge utilizes a contrasting color or other means (e.g., boxing) so that each strength is readily distinguished with other strengths and thus minimizing the potential for product selection errors.



6. The letter “x” is presented with an extension and arrow tip. This can be distracting and may lead to misinterpretation of the product name. As presented, the letter “X” almost looks like the letter “Y”. Present the entire proprietary name in the same font type, size, and color so that no one portion of the name is overly emphasized.
7. Presenting the proprietary name in all capital letters makes it difficult to read. Revise so that only the first letter of the proprietary name is capitalized.
8. Revise the statement “Dosage: See package insert” to read “*Usual* Dosage: See package insert”. We refer you to 21 CFR 201.55 for guidance.

9. The grey font for the established name on the white background is difficult to read. Additionally, the \_\_\_\_\_ and 10 mg/160 mg strengths written in light purple and orange, respectively, are difficult to read on white background. Utilize a better contrasting font color for the text to improve readability.
10. The blue box surrounding the net quantity gives it more prominence than the product strength. Revise so that the blue box is removed.
11. Ensure that all Unit-of-Use bottles (i.e., 30 count) have a Child-Resistant Closure in accordance with the Poison Prevention Packaging Act.

B. CONTAINER LABEL

1. Unit-Dose Blister

See GENERAL COMMENTS A1 through A4.

2. Professional Sample (7 count)

See GENERAL COMMENTS A1 through A4.

3. Professional Sample (30 count)

a. See GENERAL COMMENTS A1 through A9 and A11.

b. Decrease the prominence of the net quantity statement by de-bolding. As currently presented, the net quantity appears more prominent than the product strength.

4. Commercial (30 count and 90 count)

See GENERAL COMMENTS A1 through A11.

C. CARTON LABELING

1. Professional Sample (7 count)

a. See GENERAL COMMENTS A1 through A9.

b. Increase the prominence of the statement “Physician Sample - Not for Sale” and relocate the statement to above the proprietary name.

c. Relocate the net quantity statement (i.e., 7 tablets) so it appears away from the product strength, preferably at the bottom of the principal display panel. This should aid in decreasing the risk of confusion between the net quantity and the product strength.

2. Commercial Unit-Dose (100 count)

a. See GENERAL COMMENTS A1 through A10.

b. Increase the prominence of the “Rx only” statement.

- c. Revise the net quantity statement to detail the number blisters cards in carton [e.g., 100 tablets (10 x 10 tablet blister cards)].

D. PACKAGE INSERT LABELING

1. See GENERAL COMMENTS A1 and A3.
2. CLINICAL PHARMACOLOGY (Pharmacodynamics; Exforge)

The statement "Exforge \_\_\_\_\_ has been shown to be \_\_\_\_\_ effective...." \_\_\_\_\_ . Revise accordingly.

3. HOW SUPPLIED

Since the sponsor has communicated to the Division (via an email from Donna Vivello) that the \_\_\_\_\_ , all references to \_\_\_\_\_ should be deleted.

We would be willing to meet with the Division for further discussion, if needed. If you have any questions concerning this memorandum, please contact Diane Smith, Project Manager, at 301-796-0538.

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

/s/

-----  
Todd Bridges  
8/29/2006 11:52:54 AM  
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung  
8/29/2006 01:32:35 PM  
DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
8/30/2006 03:42:59 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
8/31/2006 09:14:58 AM  
DRUG SAFETY OFFICE REVIEWER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 21-990

Novartis Pharmaceuticals Corporation  
Attention: Ms. Donna Vivelo  
Director, Drug Regulatory Affairs  
One Health Plaza  
East Hanover, NJ 07936-1080

Dear Ms. Vivelo:

Please refer to your 22 February 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Exforge (amlodipine besylate and valsartan), 5/160, 10/160, 5/320, and 10/320 mg Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b)(2) of the Act on 24 April 2006 in accordance with 21 CFR 314.101(a).

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

If you have any questions please call:

Cheryl Ann Borden, MSN, RN, CCRN, CCNS  
Regulatory Health Project Manager  
(301) 796 1046.

Sincerely,  
*[See appended electronic signature page]*  
Norman Stockbridge, M.D., Ph.D.  
Director  
Division of Cardiovascular and Renal Drug  
Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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

/s/

-----  
Norman Stockbridge  
4/28/2006 06:06:15 PM



## MEMORANDUM

DEPARTMENT OF HEALTH & HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

DATE: December 13, 2006

FROM: Abraham Karkowsky, M.D., Ph.D. Acting Deputy Director, Division of  
Cardiovascular and Renal Products HFD-110

TO: Norman Stockbridge, M.D., Ph.D, Director, Division of Cardiovascular and  
Renal Products HFD-110

SUBJECT: Approval of Exforge (valsartan- amlodipine besylate combination product)

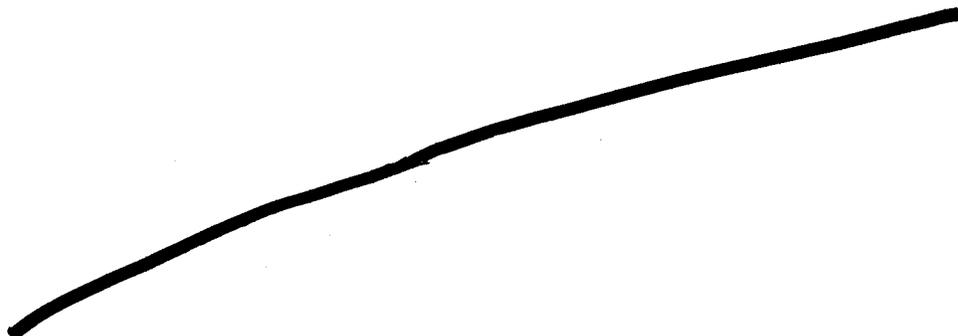
This memo supports to the approval recommendation of Exforge (valsartan-amlodipine besylate combination product) for the treatment of hypertension. Exforge is a product of convenience and should be used when the doses of both drugs are appropriate for patients with hypertension.

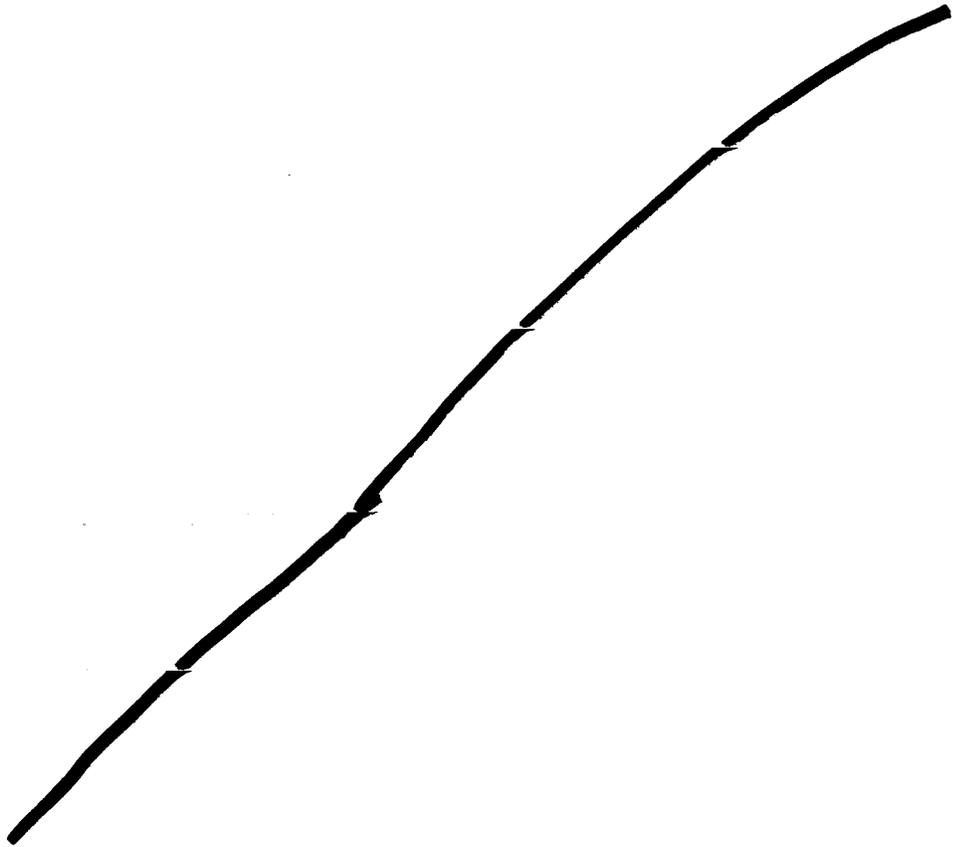
With respect to labeling, both components, valsartan and amlodipine contribute to the blood pressure effect of Exforge, however, the blood pressure lowering effect of Exforge \_\_\_\_\_ when compared to the effects of the individual components.

\_\_\_\_\_ The labeling, of the combination product should, therefore, be limited to the hypertension indication.

I have also removed all claims in the Exforge labeling \_\_\_\_\_

\_\_\_\_\_ There are several reasons outlined further in the review. In summary:





The following reviews were used in the construction of this memo:

- Chemistry review by Sarker, H., Ph.D., dated 8 December 2006.
- Pharmacology/toxicology review by Jagadeesh, G., Ph.D., dated 8 November 2006.
- Clinical pharmacology review by Mishina, Elena, V., Ph.D., dated 1 November 2006.
- Statistical Review by Liu, Q., M.D., M.S., dated 3 November 2006.
- Clinical review by Moreschi, G., M.D., M.P.H. dated 1 November 2006.
- DMETS review by Bridges, Todd, R. Ph., dated 19 July 2006 and by Arnawine, K.C., Pharm.D., dated 5 November 2006.
- DSRCs review by Mills, S.R., B.S.N., R.N., dated 28 November 2006.
- DDMAC review by Hubbard, L M., R.Ph. dated 13 November 2006.

Miscellaneous:

DMETS found the name Exforge acceptable. Their comments regarding labeling have been considered by the Division's modification of the proposed label. I have appended additional comments regarding packaging to the end of this review. This information should be transmitted to the sponsor.

There were no DSI audits requested. The components of the combination product are approved. The Division considered it unlikely that any unusual safety concerns would be detected by individual site reviews. Furthermore, the Division considered the likelihood of finding significant deviations from the protocol, which might alter its conclusions as small, since there were a large number of study sites, none of which supplied a significant proportion of the overall population. The yield from inspecting any one or two sites, therefore, appeared minimal.

**Chemistry:**

The sponsor proposes to market the following dose-strengths. The clinical studies used the individual component drugs. Included in the table is the Division's rationale for their approval for the combination products (see Clinical Pharmacology).

**Table 1: Dose-strengths of Exforge and specifics of their composition and rationale for approval.**

		Valsartan			
				160	320
Amlodipine	—		*		
	5.0		^	X^ Mo	X* BL
	10.0			X* Mo	X^ BL

X- Proposed formulations for marketing. \* Biopharm equivalence established. ^- Waiver granted BL-bilayer formulation  
 Mo-Monolithic formulation

Doses 160/5 and 160/10 are termed "monolithic" (they are mixtures of valsartan and amlodipine) as a single mixture. Dose strengths 320/5 and 320/10 are termed "bilayer" formulations. The amlodipine and valsartan are included in separate layers within the formulation.

The chemist review finds the submission approvable. All inspections reports were considered as approvable.

The chemist recommended an interim expiration date of 12 months. The FDA reviewers considered the dissolution specifications used to establish longer expiration dates as unacceptable but sufficient to serve as the rationale for a 12-month current expiration date. During this year the sponsor is charged with obtaining dissolution data following the sponsor's current method and the Agency's defined dissolution specifications.

**Clinical pharmacology review:**

The pivotal clinical studies used the individual components, valsartan and amlodipine, in defining the blood pressure effects of the combination. The proposed marketed formulations and the means by which the specific to-be-marketed formulations were validated are shown in Table 1. There were three BA studies done. One for a dose strength not planned for marketing and two planned for marketing were assessed and found bioequivalent to the to-be-marketed formulation.

The other doses were granted a waiver based on the following considerations:

- Valsartan and amlodipine each exhibit linear and dose proportional pharmacokinetics.
- The manufacturing process for the combination product and the individual approved components is identical.
- In vitro dissolution profiles of both valsartan and amlodipine as the individual components, in three different dissolution medium, were similar to the marketed image formulation (f2 test).
- The composition of the — valsartan/amlodipine fixed combination is compositionally proportional to the 160/10 mg formulation of the to-be marketed formulation. The 160/10 mg formulation was waived based on the performance of the — formulation.

There were minimal effects of food on the kinetics of the components of Exforge. The only alteration was a small decrease in the C<sub>max</sub> of valsartan with food (16%), AUC of valsartan, and C<sub>max</sub> and AUC of amlodipine were unchanged by food.

Biopharmaceutics recommended the following dissolution procedures and solutions:

For valsartan:

Apparatus	USP II (paddle)
Medium:	0.067 M phosphate buffer, pH 6.8, 37° C
Dissolution volume	900 ml
Rotation speed	50 rpm
Specification:	Q= _____

For amlodipine

Apparatus	USP II (paddle)
Medium:	0.1N HCl, pH 1.0, 37° C
Dissolution volume	900 ml
Rotation speed	50 rpm
Specification:	Q= _____

Pharmacology:

The sponsor performed a 13-week toxicology oral gavage study in rats (10 animals/gender/dose) of monotherapy amlodipine (15 mg/kg/day) and valsartan (240 mg/kg/day) and combination doses of valsartan/ amlodipine (in mg/kg/day ) of 48/3; 120/7.5 and 240/15. The results suggest that the effect on the target organs: gastrointestinal tract, kidney, heart, liver, ovary and bone marrow, can be attributed to the consequence of one of the monotherapy components. There was, however, an increase in the frequency of glandular erosions in the stomach in the two higher dose combination treatments compared to the monotherapy treatment.

A similar conclusion was derived from the 13-week gavage study in marmosets, at doses of monotherapy amlodipine (10 mg/kg/day decreased to 5 mg mg/kg/day) and valsartan (160 mg/kg/day decreased to 80 mg/kg/day) and combination doses of valsartan/ amlodipine (in mg/kg/day) of 40/2.5; 80/5 and 160/10. The vulnerable target

organs were the gastrointestinal tract (predominantly colon and cecum), as well as heart, kidney and adrenal glands. The effects with the combination product were also seen in with one of the other of the monotherapy components.

The two toxicology studies do not raise any unusual concerns related to the combination product.

An oral embryo-fetal development study did not indicate that there was evidence of teratogenicity. Maternal toxicity as determined by a decrease in body weight gain and food consumption was evident at doses > 160/10 mg/kg/day of valsartan/amlodipine combination. Similar toxicity was observed with amlodipine at 20 mg/kg/day. The current labeling contains a black box warning based on the warning included in the valsartan labeling. Despite the lack of a teratogenic effect in this segment 2 study, no alteration of the current warning is appropriate.

#### Clinical/Statistical:

In support of the efficacy of Exforge, the sponsor submitted five short-term studies and two open-label extension studies.

Of these five studies, one of the short-term studies was an open-label comparison of amlodipine/valsartan against lisinopril/hydrochlorothiazide in patients with more severe grades of hypertension. The study was a titration to response study. Subjects were started on lisinopril/hydrochlorothiazide (10/12.5) or valsartan/amlodipine (160/5). Maximum doses were lisinopril/hydrochlorothiazide (20/12.5) and valsartan/amlodipine (160/10). The study randomized 130 patients; 64 randomized to valsartan/amlodipine and 66 to lisinopril/hydrochlorothiazide. This study adds little in defining the effect of the combination of valsartan/amlodipine on blood pressure.

There were two factorial studies, which appropriately define the efficacy and safety of the combination product throughout their approved dose ranges relative to the individual components and to placebo. Study A2201 explored the whole dose range of valsartan, but defines only a truncated portion of the dose range for amlodipine. Study A2207 supplements the information available from study A2201 by studying the effects of the two highest approved doses of valsartan with the highest dose of amlodipine.

There were in addition, two studies of add-on therapy to fixed dose monotherapy. In study A2305 amlodipine 0 (placebo), 5 or 10 mg were added to subjects on stable 160 mg dose of valsartan. In study A2306 valsartan 0 (placebo) or 160 mg was added to stable 10 mg amlodipine.

The results of both the factorial and add-on studies are clearly suggestive that both valsartan and amlodipine contribute to the effect of Exforge on blood pressure. The results of the two factorial studies also indicate that the effect of use of the two components was less than additive. The two add-on studies confirm the small additional effect of add-on therapy to the monotherapy dose.

Study A2201 was a multinational, multicenter, double-blind, randomized, placebo-controlled, factorial study in patients with mild-moderate hypertension. The study allocated patients to daily doses of valsartan (0, 40, 80, 160, 320 mg) and amlodipine (0, 2.5 and 5.0 mg). With the exception of the 320/5 mg valsartan/amlodipine group all subjects were started on their randomized doses. This last dose was titrated to the randomized dose after 1 week at half dose of each component.

Approximately 2/3 of the sites were in the USA. The remainder of the sites was from Western Europe, Canada and Mexico. The study enrolled 1911 subjects. The demographics of those enrolled were: 53% male, 10% black with a mean age of 54 years.

Study A2307 was also a multinational, multicenter, double-blind, randomized, placebo-controlled, factorial study in patients with mild-moderate hypertension. The study allocated patients to doses of valsartan (0, 160 and 320 mg) and amlodipine (0 and 10 mg). All subjects, except those randomized to the valsartan 320/ amlodipine 10 mg dose were started on their randomized dose. The valsartan 320/amlodipine 10 mg dose group was started at half the dose of each component before starting their targeted dose.

The study sites were all outside the USA and included sites in 10 countries: Egypt, France, Germany, Korea, Malaysia, Norway, Peru, Portugal, Spain and Taiwan. Approximately 3/4 of the study sites enrolled patients from Western Europe. The study enrolled 1250 subjects. The demographics of those enrolled were: 50% male, < 1% black and 13% Asian, the mean age was 56 years.

The primary endpoint for both studies was change in means sitting diastolic blood pressure. These results, as well as the effect on supine sitting systolic blood pressure, are shown below in tables 2 and 3 and graphed in Figures 1 and 2.

**Table 2: Placebo-subtracted diastolic blood pressure effects study A2201 and A2307.**

		Valsartan dose					
			0	40	80	160	320
Amlodipine dose	Study A2201	0	0	3.4	3.0	4.3	6.7
	<i>Study A2307</i>		0	-----	-----	4.5	4.5
	Study A2201	2.5	2.6	4.1	6.6	6.5	7.4
	<i>Study A2307</i>		-----	-----	-----	-----	-----
Study A2201	Study A2201	5.0	4.7	7.9	7.8	7.5	9.2
	<i>Study A2307</i>		-----	-----	-----	-----	-----
Study A2307	Study A2201	10	-----			-----	-----
	<i>Study A2307</i>		7.9			9.9	10.9

**Table 3: Placebo-subtracted systolic blood pressure effects study A2201 and A2307.**

			Valsartan dose				
			0	40	80	160	320
Amlodipine dose	Study A2201	0	0	5.0	6.2	8.3	8.9
	<i>Study A2307</i>		0	-----	-----	7.2	7.0
	Study A2201	2.5	5.7	8.8	11.3	10.0	11.6
	<i>Study A2307</i>		-----	-----	-----	-----	-----
	Study A2201	5.0	8.3	12.9	14.0	12.7	16.0
<i>Study A2307</i>		-----	-----	-----	-----	-----	
Study A2201	10						
<i>Study A2307</i>			11.2			14.9	15.5

**Figure 1; Effect of combination therapy on placebo-subtracted DBP and SBP A2201**

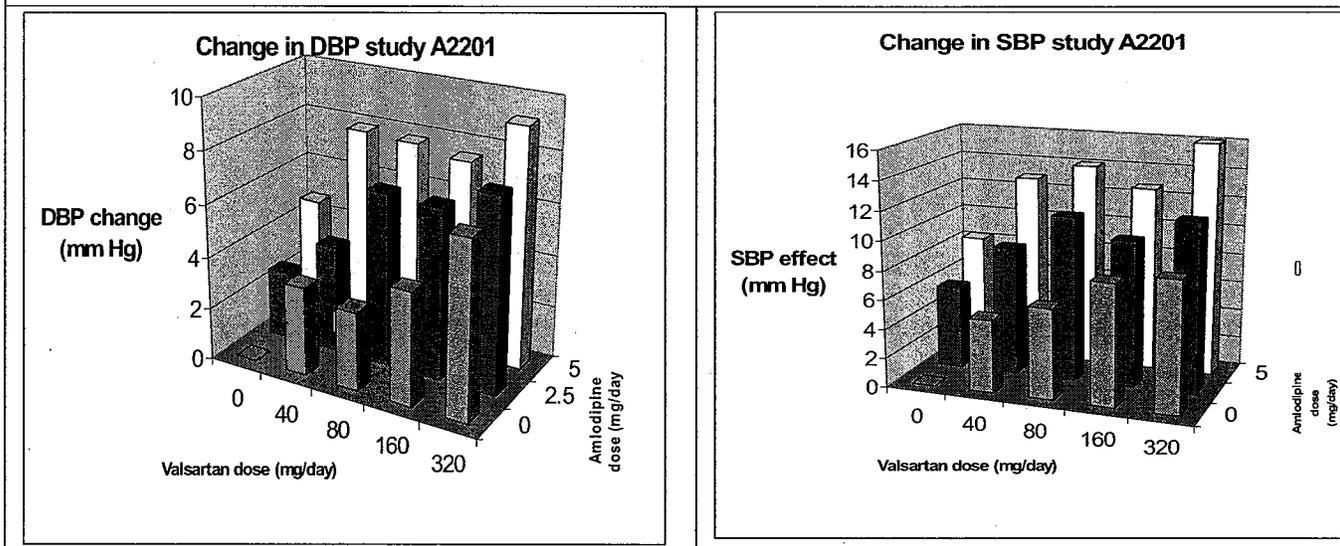
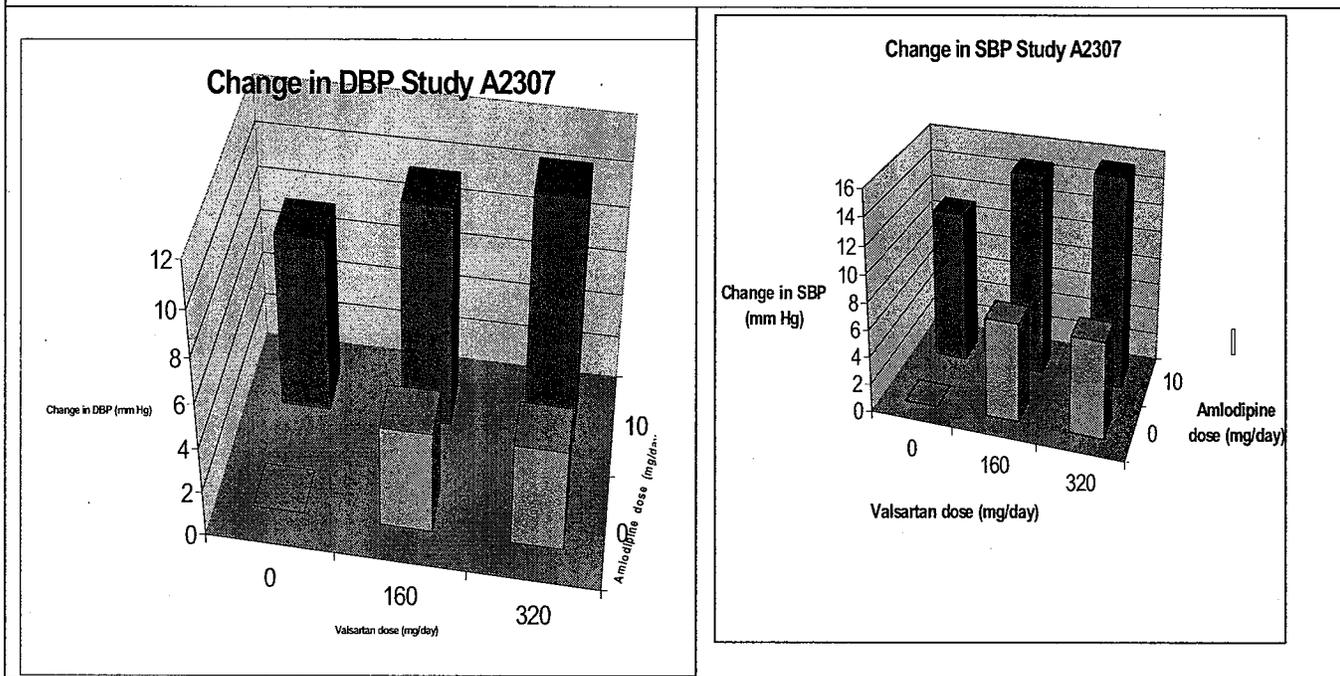


Figure 2: Effect on placebo-subtracted DBP and SBP study A2307.



The proposed and primary analysis for both study A2201 and A2307 was an analysis of covariance with valsartan, amlodipine and region<sup>1</sup> as model terms. The model also included baseline as a covariate. Both the terms for valsartan and amlodipine were highly significant ( $p < 0.001$ ) for each study. Dr. Liu, the FDA statistician, however, noted that one of the underlying assumptions of ANCOVA is the lack of interaction between the two treatments. There were, however, indications that the sum of effect of valsartan and amlodipine was less than additive compared to the effects of the sum of each of the monotherapy components.

Table 4: Effect of various combinations as well as theoretical effects assuming that the effects of valsartan and amlodipine are additive on DBP, study A2201. Positive differences are less than additive.

	Valsartan/amlodipine dose (mg/mg)							
	40/2.5	80/2.5	160/2.5	320/2.5	40/5.0	80/5.0	160/5.0	320/5.0
Sum of monotherapy	6.1	5.8	7.1	9.4	8.1	7.7	9.1	11.4
Observed change	4.1	6.7	6.6	7.5	8	7.8	7.6	9.3
Difference from sum to mono-therapies to observed	2.0	-0.9	0.6	1.9	0.1	-0.1	1.6	2.1

<sup>1</sup> The definition of region for each of the studies as follows:

Study A2201; Belgium, Canada, France, North Germany, South Germany, Mexico and the following US regions: Northeast, Mid-Atlantic, South East, Great Lakes, Great Plains, Mid-south, North-West and South-West.

Study A2307: North Germany, South Germany, Spain, Czech Republic, Portugal, Peru, Argentina, Norway Egypt, Korea, Taiwan, Malaysia and Singapore.

**Table 5: Effect of various combinations as well as theoretical effects assuming that the effects of valsartan and amlodipine are additive on SBP, study A2201. Positive differences are less than additive.**

Valsartan/amlodipine dose (mg/mg)								
	40/2.5	80/2.5	160/2.5	320/2.5	40/5.0	80/5.0	160/5.0	320/5.0
Sum of monotherapy	12.5	13.5	14.9	16.9	14.3	15.4	16.8	18.7
Observed change	9.2	10.2	10	11.8	13.4	14.5	13.2	16.2
Difference from sum to mono-therapies to observed	3.3	3.3	4.9	5.0	1.0	0.9	0.6	2.5

**Table 6: Effect of various combinations as well as theoretical effects assuming that the effects of valsartan and amlodipine are additive on DBP, study A2307. Positive differences are less than additive.**

Valsartan/amlodipine dose (mg/mg)		
	160/10	320/10
Sum of monotherapy	11.3	11.3
Observed change	9.0	9.9
Difference from sum to mono-therapies to observed	2.3	1.4

**Table 7: Effect of various combinations as well as theoretical effects assuming that the effects of valsartan and amlodipine are additive on SBP, study A2307. Positive differences are less than additive.**

Valsartan/amlodipine dose (mg/mg)		
	160/10	320/10
Sum of monotherapy	12.5	13.5
Observed change	9.2	10.2
Difference from sum to mono-therapies to observed	3.3	3.3

In order to deal with the potential interaction between components, Dr. Liu applied a multiple comparison test (Holm procedure). At least several of the dose combinations were superior to their individual components.

**Add-on studies:**

There were two add-on treatment studies. One study A2305 added amlodipine (0, 5 or 10 mg) to fixed doses of valsartan (160 mg daily). The other study A2306 added valsartan (0 or 160 mg) to fixed doses of amlodipine (10 mg).

Study 2305 was a multinational (Western and Eastern European sites) carried out in 83 clinical centers. After a 1-4 week washout period, patients were started on 160 mg of valsartan daily. If after 4 weeks their blood pressure was  $\geq 90$  and  $< 110$ , they were randomized to additional placebo or amlodipine 5 or 10 mg daily for eight weeks.

There were 947 who were randomized, approximately 315 per treatment group; 55% were male, the mean age  $\pm$  SD was  $55 \pm 10$ . Few non-Caucasians were enrolled. The effects on diastolic and systolic blood pressure are shown below.

**Table 8: Baseline and placebo subtracted (on top of valsartan) effects for study 2305.**

	Sitting DBP		Sitting SBP	
	Change from baseline	Change relative to valsartan 160	Change from baseline	Change relative to valsartan 160
Valsartan 160 mg	6.6		8.2	
Valsartan 160 mg + amlodipine 5 mg	9.6	3.1	12	3.9
Valsartan 160 mg + amlodipine 10 mg	11.4	4.8	13.9	5.7

The effect on BP from the addition of 5 and 10 mg amlodipine was small and was 3.9/3.1 and 5.7/4.8 mm Hg, respectively.

Study A2306 was a multinational study carried out primarily in Europe with an additional 11 sites located in Israel. After a 1-4 week washout period, patients were started on 10 mg of amlodipine daily. If after 4 weeks their blood pressure was  $\geq 90$  and  $< 110$ , they were randomized to additional placebo or valsartan 160 mg daily for eight weeks.

There were 944 who were randomized, approximately 477 per treatment group; 53% were male, the mean age  $\pm$  SD was  $54 \pm 12$ . Few non-Caucasians were enrolled. The effects on diastolic and systolic blood pressure of the added on valsartan are shown below.

**Table 9: Baseline and placebo (on top of amlodipine) subtracted effects for study 2306.**

	Sitting DBP		Sitting SBP	
	Change from baseline	Change relative to valsartan 160	Change from baseline	Change relative to valsartan 160
Amlodipine 10 mg	10.0		10.8	
Amlodipine 10 mg + valsartan 160 mg	11.8	1.8	12.7	1.9

The effect of the addition of valsartan to amlodipine 100 mg was small (1.9/1.8 mm Hg).

Both add-on studies were large and the sample size was probably necessary to convincingly demonstrate an effect of add-on therapy to baseline treatments.

**Long term extension studies:**

There were two long-term extension studies. Study 2201E was an extension of study 2201 and study 2307E was the extension of study 2307. The duration of treatment during the open-label extension was 52 and 54 weeks, respectively.

**Study 2301E:**

Subjects were randomized to a low dose regimen with the initial dose valsartan/amlodipine 80/2.5 mg or high dose 80/5.0 valsartan/amlodipine. If there was no hypotension or peripheral edema, the low dose was increased after 4 weeks to valsartan/amlodipine of 160/5 mg and the high dose group increased to 160/10 mg. Subjects who were still hypertensive DBP  $> 90$  mm Hg or SBP  $> 140$  mm Hg could have hydrochlorothiazide added at a dose of 12.5 mg daily,

**Study 2307E:**

Subjects completing the double blind phase of study 2307 were eligible to enter this study. Patients were started on valsartan/amlodipine of 160/2.5 and forced titrated to valsartan/amlodipine 320/5. The subjects were maintained on that dose for the 52-week duration.

**Safety:**

There is adequate safety information as outlined in Dr. Moreschi's review to define both short term and long term consequences of Exforge. There were 1,437 patients who received one or the combinations of valsartan/amlodipine during the placebo-controlled studies (A2201 and A2307). There were 2,613 patients who were enrolled in short term active or placebo comparative studies.

The number of subjects/dose for the placebo-controlled studies by dose is shown below:

**Table 10: Number of subjects in the factorial studies for monotherapies and combination therapies at the stated doses.**

		Placebo-controlled exposure				
		Valsartan				
		0	40	80	160	320
Amlodipine	0	337	127	124	335	336
	2.5	126	129	129	126	129
	5.0	128	124	128	126	127
	10.0	207			209	210

The number of subjects exposed to various treatments in the five short-term studies is shown below.

**Table 11: Short term overall exposure includes placebo-controlled, add-on and positive controlled studies.**

	Val/amlodipine	valsartan	amlodipine	Lisinopril/HCTZ	PBO	Total
	2613	1229	930	66	337	5175

The long-term safety was derived from the extensions of study 2201E and 2307E.

There were no signals that the adverse event profile substantially differed from the already described safety profile of each of its monotherapy. Below is a table that compares the adverse events during the placebo-controlled database. This table includes both higher order terms e.g., cardiac disorders as well as lower order terms e.g., diarrhea. Those events that are at least 1% greater than the monotherapy of each component are in bold. There does not appear to be any signal that the combination product either provokes or mitigates adverse events.

**Table 12: Overall exposure and adverse events in placebo-controlled studies. Bolded values are > 1 % greater than the largest of the monotherapy events.**

N=							Overall adverse events						
	0	40	80	160	320	0.0		40.0	80.0	160.0	320.0		
	0	337	127	123	335	336	0.0	38.0	50.0	48.0	37.0	36.0	
	2.5	125	129	129	126	129	2.5	53.0	47.0	47.0	41.0	47.0	
	5.0	128	124	128	126	127	5.0	51.0	46.0	52.0	<b>55.0</b>	47.0	
	10.0	207			209	210	10.0	38.0			39.0	32.4	
Cardiac disorders	0.0	0.9	2.4	2.4	1.2	1.2	Gastro-intestinal disorders	0.0	5.9	13.4	7.3	6.6	17.7
	2.5	0.8	1.6	0.0	0.8	1.6		2.5	8.8	10.1	8.5	9.5	10.1
	5.0	0.8	1.6	2.3	<b>3.2</b>	1.6		5.0	10.9	6.5	<b>14.1</b>	9.5	8.7
	10.0	2.4			0.5	2.4		10.0	6.3			4.3	4.3
Diarrhea	0.0	1.5	3.1	1.6	0.9	1.8	General disorders and administration site disorders	0.0	6.8	9.4	5.7	4.2	5.1
	2.5	0.8	1.6	0.8	1.6	<b>3.1</b>		2.5	13.6	7.0	10.1	7.9	7.8
	5.0	1.6	<b>2.4</b>	<b>3.1</b>	<b>4.0</b>	<b>3.1</b>		5.0	10.2	8.1	7.0	8.7	8.7
	10.0	0.5			1.0	0.5		10.0	15.9			12.9	11.9
Peripheral edema	0.0	3.0	5.5	2.4	1.8	0.9	Infections and infestations	0.0	11.3	15.0	19.5	11.6	8.3
	2.5	8.0	2.3	5.4	2.4	3.9		2.5	20.8	17.1	20.2	16.7	17.1
	5.0	3.1	4.8	2.3	2.4	2.4		5.0	14.1	16.9	26.6	<b>24.6</b>	<b>16.5</b>
	10.0	12.6			11.5	9.5		10.0	9.7			11.0	8.1
Nasopharyngitis	0.0	1.8	2.4	6.5	4.5	3.3	URI	0.0	2.1	2.4	3.3	1.2	0.6
	2.5	5.6	3.9	<b>7.8</b>	2.4	6.2		2.5	3.2	3.9	3.9	2.4	3.1
	5.0	3.9	4.0	<b>8.6</b>	<b>5.6</b>	3.1		5.0	3.9	<b>5.6</b>	4.7	3.2	1.6
	10.0	1.9			1.9	2.4		10.0	1.0			0.5	<b>2.4</b>
Sinusitis	0.0	1.2	0.8	30.8	1.2	0.0	Influenza	0.0	0.6	0.0	2.4	0.3	0.6
	2.5	2.4	2.3	2.0	0.8	2.3		2.5	0.0	<b>3.1</b>	0.8	<b>2.4</b>	1.6
	5.0	0.0	3.2	<b>3.1</b>	<b>2.4</b>	0.0		5.0	0.0	<b>2.4</b>	3.1	0.8	0.8
	10.0	0.0			1.4	0.5		10.0	1.0			1.0	0.5
Pharyngitis	0.0	1.5	0.8	1.6	0.3	0.0	Bronchitis	0.0	1.2	1.6	3.3	1.2	1.2
	2.5	0.8	0.8	0.0	0.0	0.8		2.5	1.6	0.8	0.0	1.6	1.6
	5.0	0.0	0.0	<b>3.1</b>	0.8	0.8		5.0	0.0	0.8	1.6	<b>3.2</b>	<b>2.4</b>
	10.0	1.0			1.0	0.5		10.0	1.9			0.5	1.0
Injury poisoning and procedural manifestations	0.0	1.8	3.9	1.6	1.2	1.2	Investigations	0.0	1.5	2.4	1.6	0.9	0.9
	2.5	3.2	1.6	0.8	3.2	1.6		2.5	0.8	0.8	<b>3.1</b>	1.6	<b>2.3</b>
	5.0	2.3	1.6	<b>3.9</b>	<b>4.8</b>	<b>4.7</b>		5.0	1.6	1.6	0.8	3.2	0.8
	10.0	1.0			1.4	1.9		10.0	0.5			0.0	0.5
Musculoskeletal and connective tissue disorder	0.0	5.3	7.1	9.8	5.1	8.3	Metabolism and nutrition	0.0	0.3	3.1	2.4	0.6	0.9
	2.5	7.2	8.5	6.2	4.2	6.2		2.5	3.2	0.8	0.8	0.8	0.8
	5.0	6.3	6.5	<b>12.5</b>	7.9			5.0	4.7	0.8	1.6	1.6	0.8
	10.0	5.3			6.2	4.3		10.0	1.4			1.0	1.4
Pain in extremity	0.0	1.5	0.8	0.0	0.0	0.3	Nervous system disorders	0.0	10.4	14.2	10.6	7.8	10.7
	2.5	2.4	0.8	0.8	1.6	0.8		2.5	12.8	10.9	7.0	12.7	8.5
	5.0	1.6	1.6	0.0	3.2	1.6		5.0	14.8	7.3	12.5	12.7	12.6
	10.0	0.5			0.5	0.0		10.0	5.8			5.3	3.3
Headache	0.0	5.9	7.1	6.5	3.6	4.5	Dizziness	0.0	0.9	3.1	0.8	1.5	3.6
	2.5	10.4	7.0	3.9	7.1	5.4		2.5	0.8	0.0	<b>2.3</b>	<b>3.2</b>	2.3
	5.0	8.6	4.0	3.9	5.6	5.5		5.0	3.9	3.2	3.1	1.6	3.9
	10.0	5.3			2.9	1.0		10.0	0.5			0.5	1.9

Psychiatric disorders	0.0	3.0	1.6	3.3	1.2	0.6	Renal and Urinary disorders	0.0	2.2	1.6	0.8	1.2	1.2
	2.5	0.8	<b>3.9</b>	3.9	<b>3.2</b>	0.8		2.5	2.4	3.1	1.6	0.8	0.0
	5.0	4.7	0.8	3.1	1.6	0.8		5.0	4.7	0.8	2.3	0.0	4.7
	10.0	1.4			1.4	1.9		10.0	0.5			0.0	0.5
Respiratory thoracic and mediastinal disorders	0.0	2.7	3.1	6.5	2.1	5.4	Skin and subcutaneous disorders	0.0	3.3	5.5	0.0	2.1	1.8
	2.5	3.2	<b>7.8</b>	<b>7.8</b>	3.2	3.9		2.5	2.4	3.1	2.3	3.2	0.8
	5.0	3.9	<b>7.3</b>	7.0	<b>7.1</b>	1.6		5.0	4.7	4.8	3.1	4.0	2.4
	10.0	1.0			1.9	1.9		10.0	0.5			2.4	1.0
Vascular disorders	0.0	2.4	0.8	0.0	0.0	0.9							
	2.5	1.6	2.3	0.0	1.6	1.6							
	5.0	1.6	<b>3.2</b>	2.3	2.4	<b>3.1</b>							
	10.0	3.4			1.9	2.4							

### Peripheral Edema:

The incidence of adverse events specifically linked to peripheral edema in the two placebo-controlled factorial studies is shown in the above Table. The sponsor, in addition, pooled other terms, potentially related to edema. These terms consisted of “edema, peripheral”, “edema”, “joint swelling”, “pitting edema”, “face edema”, “eye swelling”, “eyelid edema”, “generalized edema”, “periorbital edema”, “acute pulmonary edema”, “lymphedema”, and “swollen tongue”. This analysis captures events unlikely to be related to the usual peripheral edema as a common adverse event observed with amlodipine. The sponsor’s analysis is shown below.

**Table 13: Peripheral edema (based on a broad definition) in the factorial designed studies.**

Valsartan→ Amlodipine↓	0	40	80	160	320
0	12/337 (4%)	7/127 (6%)	4/123 (3%)	10/335 (3%)	5/336 (2%)
2.5	11/125 (9%)	5/129 (4%)	7/129 (5%)	4/126 (3%)	7/129 (5%)
5.0	4/128 (3%)	6/124 (5%)	4/128 (3%)	7/126 (6%)	4/127 (3%)
10.0	31/207 (15%)			27/209 (13%)	20/210 (10%)

In none of the studies were edema rates allocated some pre-specified statistical importance. All assessments of a decrease in edema rates are therefore, exploratory in nature and \_\_\_\_\_ There are other problems that make this observation far from convincing. The sponsor performed a post-hoc pooling of several different adverse events terms potentially reflecting edema, but not necessarily peripheral edema usually attributed to dihydropyridine calcium channel blockers. Given the post-hoc nature of this assessment, pooling all edemas appears to be one of several potential analyses.

Of all the combination product doses, only the 320 mg valsartan/10 mg amlodipine combination appears to provoke less edema than the 10 mg amlodipine monotherapy regimen. The valsartan 160/ amlodipine 10 mg does not seem to afford a convincing difference in the incidence of edema compared to the 10 mg amlodipine monotherapy. There was also no convincing effect for other doses of amlodipine with any dose of valsartan. Unless there is benefit in preventing edema by the use of low-dose valsartan in conjunction with high dose amlodipine, it would be of limited value to

recommend combination therapy to alter the natural course of amlodipine-induced edema. Only the highest dose of valsartan in conjunction with the highest dose of amlodipine would be useful. It would be imprudent to recommend a high dose valsartan be added to amlodipine regimen merely to decrease edema.

Edema rates are particularly evident at the highest amlodipine dose. There was a greater fraction of those enrolled into the amlodipine monotherapy group who received the highest amlodipine dose. A smaller fraction of patients who received combination therapy group received the highest amlodipine dose. Comparison between all amlodipine and all combination treatments for the incidence of edema, therefore, is an inappropriate analysis.

Lastly, the observation of decrease in edema in the combined 320 valsartan/10 mg amlodipine group compared to amlodipine 10 mg may be partly an artifact. Those enrolled in studies and randomized to the 320 mg/10 mg amlodipine were titrated to that dose after the first week of exposure to a 160 mg valsartan/ 5 mg amlodipine dose. Monotherapy amlodipine was started at the 10 mg dose from randomization. The duration of treatment for the combination product at the highest amlodipine dose was therefore, one week less than that of amlodipine monotherapy. It is unclear if edema as an adverse event was uniformly spaced during the entire period for the amlodipine monotherapy group or whether there was a lag phase from randomization prior to the complaint of edema. The longer the lag-phase for the production of edema, the greater the consequence of the single week less of high dose amlodipine therapy in the combined product treatment compared to the monotherapy group.

#### Long term safety

There were no deaths during the extension phase. There were 49 serious adverse events during the year exposure. The adverse events were scattered over various organ systems and in themselves did not raise any concerns regarding a specific target organ.

There were, however, several adverse events of particular interest to this reviewer.

Patient 0579-00002 was a 64-year old male who was being treated with valsartan/amlodipine 80/2.5. On day 20 of treatment he developed difficulty in breathing, tongue and body swelling and chest tightness. He was diagnosed with anaphylactic shock and treated in the ER with fluids diphenhydramine, methylprednisolone and prednisone. He was continued on his medication with the anaphylactic reaction attributed to metronidazole.

Patient 0521-0002, a 62 year old Caucasian male completed the double blind portion of study A2001 and entered the extension phase. After approximately a total of 3 months of treatment randomized and open label extension, the subject had an increase in LFTS alt=49; AST=112 and Alkaline phosphatase =69. These enzyme elevations slowly declined after discontinuation of treatment.

Patient 0117-00006, a 73 year old Caucasian male had abnormal LFTs apparently at baseline of the double blind clinical study. ALT= 116; AST =70. He completed the double-blind portion of the study and was discontinued during the open label extension. His last LFTs approached normal values ALT= 49, AST=41.

Patient 0025-00003, a 38 year old female had elevated LFTs at baseline. She was discontinued. The elevated LFTs resolved.

Patient 0521-000222, a 622 year old Caucasian male had elevated LFTs at baseline measurement and was discontinued after completing the double-blind phase. The maximal LFTs were ALT=53; AST= 112.

None of these events appear of sufficient concern to question the safety of Exforge as a treatment of hypertension.

2 Page(s) Withheld

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

     § 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

C. CARTON LABELING

1. Professional Sample (7 count)
  - a. See GENERAL COMMENTS A1 through A9.
  - b. Increase the prominence of the statement "Physician Sample - Not for Sale" and relocate the statement to above the proprietary name.
  - c. Relocate the net quantity statement (i.e., 7 tablets) so it appears away from the product strength, preferably at the bottom of the principal display panel. This should aid in decreasing the risk of confusion between the net quantity and the product strength.
2. Commercial Unit-Dose (100 count)
  - a. See GENERAL COMMENTS A1 through A10.
  - b. Increase the prominence of the "Rx only" statement.
  - c. Revise the net quantity statement to detail the number blister cards in carton [e.g., 100 tablets (10 x 10 tablet blister cards)].

D. PACKAGE INSERT LABELING

1. See GENERAL COMMENTS A1 and A3.
2. CLINICAL PHARMACOLOGY (Pharmacodynamics; Exforge)

The statement "Exforge \_\_\_\_\_ has been shown to be more effective...." \_\_\_\_\_ Revise accordingly.

3. HOW SUPPLIED

Since the sponsor has communicated to the Division (via an email from Donna Vivelo) that the 100 count package size is \_\_\_\_\_ all references to \_\_\_\_\_ should be deleted.

We would be willing to meet with the Division for further discussion, if needed. If you have any questions concerning this memorandum, please contact Diane Smith, Project Manager, at 301-796-0538.

Biopharmaceutics:

Proposed dissolution specifications, the details are to be transmitted to the sponsor.

For valsartan:

Apparatus	USP II (paddle)
Medium:	0.067 M phosphate buffer, pH 6.8, 37° C
Dissolution volume	900 ml
Rotation speed	50 rpm
Specification:	Q= _____

For amlodipine

Apparatus	USP II (paddle)
Medium:	0.1N HCl, pH 1.0, 37° C

Dissolution volume	900 ml
Rotation speed	50 rpm
Specification:	Q= _____

**Chemistry:**

Based on the available test data, twelve months shelf-life is recommended for the drug product of all strengths and container/closure systems. We conclude that the proposed dissolution method and acceptance limit for drug product are not acceptable. The method and the associated acceptance criterion may be considered as interim for one year. During this period, the applicant should generate dissolution test data, following current method and the method proposed by Agency on current drug product stability batches and first three commercial batches. The comparative dissolution test data should be submitted as a supplement by the end of 2007 with proposal for revised expiration date.

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

/s/

-----  
Abraham Karkowsky  
12/14/2006 11:25:54 AM  
MEDICAL OFFICER



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
OFFICE OF NEW DRUG QUALITY ASSESSMENT

<b>Sponsor Name:</b>	Novartis Pharmaceuticals
<b>Application Number:</b>	NDA 21-990
<b>Product Name:</b>	Exforge (amlodipine besylate/valsartan) tablets
<b>Teleconference Date and Time:</b>	December 1, 2006, 1230 EST
<b>FDA Attendees:</b>	<u>Division of Pre-Marketing Assessment I</u> Ramesh Sood, Ph.D.; Branch Chief Kasturi Srinivasachar, Ph.D.; Pharmaceutical Assessment Lead Haripada Sarker, Ph.D.; Review Chemist Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality
<b>External Attendees:</b>	Kathy Ford and Nancy Landzert, Global Regulatory CMC, et. al.

## 1.0 BACKGROUND

Novartis Pharmaceuticals, Inc. (Novartis) submitted NDA 21-990 for Exforge (amlodipine besylate/valsartan) tablets, proposed for the treatment of hypertension. Haripada Sarker, Ph.D., Review Chemist of the Division of Pre-Marketing Assessment I requested a teleconference with Novartis on 30 November 2006 to clarify the total impurity specifications and the need for an additional in process control. The issues were discussed during the teleconference on December 1, 2006.

## 2.0 DISCUSSION

### 2.1 Total Impurity Specification for Drug Product

**Teleconference Discussion:** FDA noted that the data provided did not support a proposed specification of \_\_\_\_\_ in the drug product. The observed \_\_\_\_\_ FDA recommended that the total

\_\_\_\_\_ Novartis indicated that the specification was based on batch analysis data available and committed to evaluate all data on an ongoing basis and tighten the specification accordingly. Novartis further committed to evaluate the data and provide a new total impurity specification shortly after the conclusion of the teleconference.

## 2.2 In Process Controls for Blend Uniformity

**Teleconference Discussion:** FDA requested that Novartis supply a proposal for

---

Novartis acknowledged and agreed with FDA's recommendation.

FDA requested that Novartis submit electronic desk copies with a statement to the effect that the courtesy copies were identical to those submitted to the administrative file to facilitate the review and increase efficiency. FDA recommended that the PMQ be used as point of contact for these desk copies. Novartis acknowledged and agreed with FDA's recommendations.

The teleconference ended amicably.

## 3.0 CONCURRENCE:

*{See appended electronic signature page}*

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

*{See appended electronic signature page}*

Ramesh Sood, Ph.D.  
Branch Chief  
Division of Pre-Marketing Assessment I  
Office of New Drug Quality Assessment

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

/s/

-----  
Scott Goldie  
1/9/2007 08:46:50 AM  
PROJECT MANAGER FOR QUALITY

Ramesh Sood  
1/9/2007 09:43:43 AM  
CHEMIST

**MEMORANDUM**

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

**DATE:** November 28, 2006

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

**VIA:** Quynh Nguyen, Pharm.D., Regulatory Health Project Manager  
Division of Cardiovascular and Renal Products

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

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

**SUBJECT:** DSRCS Review of Draft Patient Labeling (PPI) for Exforge, NDA 21-990.

**Background and Summary**

Exforge is an anti-hypertensive drug submitted as a new NDA on February 22, 2006. The product contains the active ingredients amlodipine besylate and valsartan in 4 different tablet dosing combinations: 5 mg/160 mg, 10 mg/160 mg, 5 mg/320 mg, 10mg /320 mg.

See the attached patient labeling (PPI) for our recommended revisions to the draft PPI submitted for Exforge (amlodipine besylate and valsartan tablets), NDA 21-990. The purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications. We have simplified the wording where possible, made it consistent with the PI and removed unnecessary information. We have also put this PPI in the patient-friendly format (specified in 21 CFR 208) that we are recommending for all FDA approved patient labeling, although this format is not required for voluntary PPIs. These recommended changes are consistent with current research to improve risk communication to a lower literacy audience.

These revisions are based on draft product labeling (PI) originally submitted February 22, 2006 and revised by the review division on November 9, 2006 and then again on November 24, 2006. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

**Comments and Recommendations**

6 Page(s) Withheld

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

     § 552(b)(5) Deliberative Process

X § 552(b)(4) Draft Labeling

**MEMORANDUM**

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

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

**Through:** Linda Y. Kim-Jung, PharmD, Team Leader  
Denise Toyer, PharmD, Deputy Director  
Carol Holquist, RPh, Director  
Division of Medication Errors and Technical Support, HFD-420

**From:** Kristina C. Arnwine, PharmD, Safety Evaluator  
Division of Medication Errors and Technical Support, HFD-420

**Date:** November 6, 2006

**Subject:** OSE Review 2006-642, Exforge (Valsartan/Amlodipine Besylate Tablets) \_\_\_\_\_ 5 mg/160 mg, 5 mg/320 mg, 10 mg/160 mg, and 10 mg/320 mg; NDA 21-990

This memorandum is in response to an October 18, 2006 request from your Division for a final review of the proprietary name, Exforge. Additionally, the package insert labeling was submitted for review and comment.

The proposed name, Exforge, was initially found acceptable in OSE Review 05-0313 (dated June 12, 2006). Since the initial review of Exforge, DMETS identified the names Oxaprozin, Estrogel, and Exubera as names that have the potential to look similar to Exforge. However, Oxaprozin, Estrogel, and Exubera will not be reviewed further due to a lack of convincing orthographic similarity in addition to differentiating product characteristics such as route of administration, product strength, dosage form, usual dose, and/or indication of use.

In the review of the package insert labeling of Exforge, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which may minimize potential user errors.

1. General Comment

Remove the word \_\_\_\_\_ from the established name presented on page one of the package insert and wherever else the word \_\_\_\_\_ appears in the established name throughout the package insert labeling. The established name should read "Amlodipine Besylate and Valsartan Tablets".

2. Information for Patients Section

Remove this section heading since there is no patient information printed below the heading.

3. How Supplied Section

Revise the statement, "Exforge (amlodipine besylate and valsartan) is available as... \_\_\_\_\_, 5/160 mg, 10/160 mg, and 5/320 mg, and 10/320 mg" so that the strength of each active ingredient is followed by a unit of measure (i.e. mg) in order to prevent confusion and the misinterpretation of the product strength. The statement should read "Exforge (amlodipine besylate and valsartan) is available as... \_\_\_\_\_

---

Additionally, revise all statements of product strength throughout the package insert accordingly.

In summary, DMETS has no objections to the use of the proprietary name, Exforge. Additionally, the Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the name, Exforge, acceptable from a promotional perspective. In addition to the above labeling recommendations, please refer to OSE Review 05-0313-1 (dated August 31, 2006) for our recommendations on the container label and carton labeling. We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Diane Smith, Project Manager at 301-796-0538.

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

/s/

-----  
Kristina Arnwine  
11/15/2006 02:52:05 PM  
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung  
11/15/2006 03:04:48 PM  
DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
11/15/2006 04:21:49 PM  
DRUG SAFETY OFFICE REVIEWER  
Also signing for Carol Holquist, DMETS Director, in her  
absence

# MEMORANDUM

**To:** Quynh Nguyen, Pharm.D. , RHPM  
Division of Cardiovascular and Renal Products (DCRP)

**From:** Lisa M. Hubbard, R.Ph.  
Senior Regulatory Review Officer  
Division of Drug Marketing and Communications (DDMAC)

**Date:** November 13, 2006

**Re:** Comments on proposed Patient Package Insert  
Exforge (amlodipine besylate/valsartan) Tablets  
NDA 21-990

---

Below are DDMAC comments on the proposed Patient Package Insert (PPI) submitted for Exforge (amlodipine besylate/valsartan), tablets. DDMAC's comments are based on the November 9, 2006 proposed package insert (PI) and PPI located in the EDR at: \\CSESUB1\N21990\N000\2006-02-22. Please let us know if you have any questions or comments.

1. DDMAC recommends listing the most serious adverse events first in order to prevent minimization of risks associated with the use of Exforge in promotional materials. Please consider listing the patient-friendly warning, "more chest pain and heart attacks....", before the precautionary information related to kidney problems. A similar order appears in the proposed PI.
2. In order to minimize the potential for overstatement of efficacy or broadening of the approved indication in promotional materials, DDMAC recommends that the following statement from the INDICATIONS AND USAGE section of the proposed PI be incorporated into the PPI using patient-friendly language: "This fixed combination drug is not indicated for the initial therapy of hypertension.)".
3. DDMAC recommends presenting precautionary information related to impaired hepatic function and congestive heart failure in a manner similar to the presentation of precautionary information related to impaired renal function, (e.g. "kidney problems. Kidney problems may get worse..."). This may prevent minimization of risks associated with the use of Exforge in promotional materials.

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

/s/

-----  
Lisa Hubbard  
11/13/2006 03:15:51 PM  
DDMAC REVIEWER

**NDA 21-990**  
**Exforge (amlodipine and valsartan) Tablets**

**Results of Fraud Investigation**

**N/A**

None of the clinical investigators were full or part-time employees of Novartis Pharmaceuticals Corporation. \_\_\_\_\_  
received from Novartis more than \$25,000 in honoraria and travel expenses for educational activities. The Sponsor states that any bias was minimized by the independent data monitoring by Novartis, by the use of multiple investigators, and by the use of double-blind placebo-controlled trials, and I agree with this.

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

/s/

-----  
Gail Moreschi  
12/18/2006 08:36:44 AM  
MEDICAL OFFICER

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS  
FOOD AND DRUG ADMINISTRATION**

WHITE OAK COMPLEX  
10903 NEW HAMPSHIRE AVE  
BLDG. 22  
SILVER SPRING, MD 20993



**US Mail 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

**This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to:  
FDA/CDER/DCaRP 5901-B Ammendale Rd. Beltsville, MD 20705-1266**

**Transmitted via email to:** donna.vivelo@novartis.com

**Attention:** Ms. Donna Vivelo

**Sponsor:** Novartis Pharmaceuticals Corporation

**Phone:** (862) 778-3572

**Subject:** Teleconference Minutes

**Date:** December 12, 2006

**Pages including this sheet:** 5

**From:** Quynh Nguyen, Pharm.D.  
**Phone:** 301-796-0510  
**Fax:** 301-796-9838  
**E-mail:** quynh.nguyen@fda.hhs.gov

Please note that you are responsible for notifying us of any significant differences in understanding regarding the teleconference outcomes.

**Teleconference with Sponsor**

**Application Number:** NDA 21-990  
**Sponsor:** Novartis Pharmaceuticals Corporation  
**Drug:** Exforge (valsartan/amlodipine besylate) Tablets  
**Type of Teleconference:** Guidance  
**Classification:** C  
**Teleconference Date:** November 13, 2006  
**Meeting Chair:** Ramesh Sood, Ph.D.  
**Recorder:** Quynh Nguyen, Pharm.D.

**List of Attendees:**

**Food and Drug Administration**

Patrick Marroum, Ph.D.	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Elena Mishina, Ph.D.	Clinical Pharmacology Reviewer, OCP
Ramesh Sood, Ph.D.	Branch Chief, Division of Pre-marketing Assessment I
Kasturi Srinivasachar, Ph.D.	Pharmaceutical Assessment Lead, Division of Pre-marketing Assessment I
Haripada Sarker, Ph.D.	Chemist, Division of Pre-marketing Assessment I
Quynh Nguyen, Pharm.D.	Regulatory Health Project Manager, Division of Cardiovascular and Renal Products

**Novartis Pharmaceuticals Corporation**

Mathias Hukkelhoven	Global Head, Drug Regulatory Affairs
Adrian Birch, Vice-President	Drug Regulatory Affairs
Gangadhar Sunkara, Ph.D.	Fellow/Lead Pharmacokineticist, Exploratory Development
Catherine Ford	Director, Global Regulatory CMC
Robert Wagner, Ph.D.	Director, Pharmaceutical and Analytical Development
Yatindra Joshi, Ph.D.	Head, Pharmaceutical and Analytical Development, US
Richard Vivilecchia	Scientist, Pharmaceutical and Analytical Development
Donna Vivalo	Drug Regulatory Affairs

**BACKGROUND**

Novartis Pharmaceuticals Corporation submitted NDA 21-990 for Exforge (valsartan/amlodipine besylate) Tablets on February 22, 2006 for the treatment of hypertension. Valsartan is an angiotensin receptor blocker approved for the treatment of hypertension. Amlodipine besylate is a calcium channel blocker approved for the treatment of hypertension. A teleconference was previously held on September 6, 2006 to discuss clinical pharmacology issues regarding the dissolution specifications and methodology for Exforge. This teleconference was scheduled at the Agency's request to follow up on clinical pharmacology issues and to discuss chemistry issues related to the drug product shelf-life for Exforge.

## DISCUSSION

### 1. Dissolution release methods and specifications for valsartan and amlodipine

Dr. Marroum opened the teleconference by stating that the Agency proposes that the sponsor use two different dissolution methods for valsartan and amlodipine in the drug product. The methods are the same as those proposed for the biowaivers as listed below.

For valsartan:

Apparatus: USP II (paddle)  
Medium: 0.067 M phosphate buffer, pH 6.8, 37°C  
Dissolution Volume: 900 ml  
Rotation Speed: 50 rpm  
Specification: Q= \_\_\_\_\_

For amlodipine:

Apparatus: USP II (paddle)  
Medium: 0.1N HCL, pH 1.0, 37°C  
Dissolution Volume: 900 ml  
Rotation Speed (rpm): 50 rpm  
Specification: Q= \_\_\_\_\_

The sponsor stated that they had not fully evaluated these methods as the release methods. Based on their preliminary data, the solubility of amlodipine is decreased by valsartan in an acidic environment. The sponsor was concerned that they would not be able to meet the specifications since for the 80- and 160-mg combination product strengths, the dissolution specifications "hovered" at Q= \_\_\_\_\_ Therefore, the sponsor suggested that a specification of Q= \_\_\_\_\_ might be more appropriate. The sponsor added that they have evaluated the effects of Tween 80 on the dissolution profile of amlodipine and valsartan and they could commit to removing the Tween 80 from the dissolution media. Some of this data had been submitted in September 2006, but the sponsor offered to submit additional data without the use of Tween 80 in the release method.

The sponsor confirmed their agreement to accept the following specifications for the actual release methods:

For valsartan:

Medium: pH 6.8, without Tween 80  
Rotation speed: 50 rpm  
Specification: Q= \_\_\_\_\_

For amlodipine:

Medium: pH 1.0, without Tween 80  
Rotation speed: 50 rpm  
Specification: Q= \_\_\_\_\_

The sponsor acknowledged their acceptance of these methods on an interim basis and agreed to provide post-approval the specifications and methods for the lots tested.

**2. Drug product shelf-life using alternative dissolution methods**

Dr. Srinivasachar asked whether the sponsor could submit the dissolution profiles on the latest stability samples prior the NDA action date. The sponsor replied that there was not enough time to submit this information since the data for the 18-month time point would not be ready until January or February 2007. The sponsor believed the drug product should qualify for an 18-month shelf-life since they provided 12-month stability data and they have accepted the release method specification of  $Q = \frac{M}{M_0}$  for amlodipine. Dr. Srinivasachar responded, however, that the sponsor did not have the data to bridge these methods, i.e., the shelf-life given would be based on data that was different than the dissolution data submitted. The sponsor offered to submit the stability data as it was being generated after approval. The sponsor stated that if they could not meet the shelf-life requirements based on the data generated, then they would not market the drug product.

The sponsor stated that they would integrate the new dissolution methods into the 18- and 24-month stability testing and also submit this data after approval. Dr. Srinivasachar stated that this would be acceptable. In the meantime, the Agency would evaluate the currently submitted data, which included 12-month stability data for the lower strengths and 9-month stability data for the higher strengths.

**CONCLUSION**

This teleconference was scheduled to reach agreement on the dissolution release methods and specifications for valsartan and amlodipine and to discuss the impact on the drug product shelf-life using alternative dissolution methods.

If you have any questions, please call:

Quynh Nguyen, Pharm.D.  
Regulatory Health Project Manager  
(301) 796-0510

Sincerely,

*{See appended electronic signature}*

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

RD:

E Mishina	12/6/06
P Marroum	12/6/06
H Sarker	12/7/06
R Sood	12/8/06

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

/s/

-----  
Ramesh Sood  
12/12/2006 03:13:48 PM

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS  
FOOD AND DRUG ADMINISTRATION**

WHITE OAK COMPLEX  
10903 NEW HAMPSHIRE AVE  
BLDG. 22  
SILVER SPRING, MD 20993



**US Mail 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

**This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law.** If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to:  
FDA/CDER/DCaRP 5901-B Ammendale Rd. Beltsville, MD 20705-1266

**Transmitted via email to:** donna.vivelo@novartis.com

**Attention:** Ms. Donna Vivelo

**Sponsor:** Novartis Pharmaceuticals Corporation

**Phone:** (862) 778-3572

**Subject:** Minutes of September 6, 2006  
Teleconference

**Date:** October 5, 2006

**Pages including this sheet:** 5

**From:** Quynh Nguyen, Pharm.D.  
**Phone:** 301-796-0510  
**Fax:** 301-796-9838  
**E-mail:** quynh.nguyen@fda.hhs.gov

Please note that you are responsible for notifying us of any significant differences in understanding regarding the teleconference outcomes.

**Nguyen, Quynh M**

**From:** donna.vivelo@novartis.com  
**Sent:** Monday, October 09, 2006 8:42 AM  
**To:** Nguyen, Quynh M  
**Subject:** Re: Minutes of Teleconference - NDA 21-990/Exforge  
**Attachments:** Tcon Minutes 9-6-06.pdf

Thank you Quynh!

Donna Vivelo  
Drug Regulatory Affairs  
Novartis Pharmaceuticals Corp.  
Phone: 862-778-3572  
Fax: 973-781-3590  
email: donna.vivelo@novartis.com

"Nguyen, Quynh M" <quynh.nguyen@fda.hhs.gov>

10/06/2006 09:36 AM

To: donna.vivelo@novartis.com  
cc:  
Subject: Minutes of Teleconference - NDA 21-990/Exforge

Dear Donna,

Please find attached the minutes from the September 6, 2006 teleconference for NDA 21-990/Exforge (valsartan/amlodipine besylate) Tablets.

Thank you,  
Quynh

*Quynh M. Nguyen, Pharm.D.*  
*Regulatory Health Project Manager*  
*FDA/CDER/QND/QDE1/DCRP*

*Tel: (301) 796-0510*  
*Fax: (301) 796-9838*  
*quynh.nguyen@fda.hhs.gov*

10/10/2006

TA -  
Tentative  
Approval

**RHPM Overview**  
**NDA 21-990**  
**Exforge (amlodipine and valsartan) Tablets,**  
**5/160, 10/160, 5/320, and 10/320 mg**

Sponsor: Novartis Pharmaceuticals Corporation  
Classification: Standard  
Submission Date: February 22, 2006  
Receipt Date: February 22, 2006  
User Fee Goal Date: December 22, 2006

**Background**

This NDA provides for Exforge (amlodipine and valsartan) fixed combination tablets for the treatment of hypertension. Amlodipine besylate is a calcium channel blocker and is approved for the treatment of hypertension (Norvasc; NDA 19-787). Valsartan is an angiotensin receptor blocker and is also approved for the treatment of hypertension (Diovan; NDA 21-283). This NDA was submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, and contains full reports of safety and effectiveness of the combination drug. However, reference is made to certain information previously submitted to the Agency for Norvasc (amlodipine besylate) Tablets.

A paragraph III patent certification is included with the application. The sponsor does not intend to market Exforge until expiration of the pediatric exclusivity for amlodipine besylate, which expires on January 31, 2007 (US Patent 4,572,9909) and September 25, 2007 (US Patent 4,879,303).

The development of Exforge was conducted under IND 65,174. Exforge was evaluated in five controlled clinical trials involving over 5,000 patients with hypertension. According to the sponsor, the results of the clinical program demonstrate that Exforge provides additional blood pressure reduction beyond each individual component, and is a safe and effective treatment for hypertension.

**Secondary Medical Review**

In his December 13, 2006 review, Dr. Karkowsky wrote the following:

This memo supports the approval recommendation of Exforge (valsartan/amlodipine besylate combination product) for the treatment of hypertension. Exforge is a product of convenience and should be used when the doses of both drugs are appropriate for patients with hypertension.

**Primary Medical Review**

In her November 1, 2006 review, Dr. Moreschi wrote the following:

In this NDA submission, the Sponsor has taken two established drugs, amlodipine and valsartan, which have been utilized for 10 or more years for the treatment of hypertension, and has combined them at various doses. Both medications have individual good efficacy and safety records. The Sponsor has demonstrated that combined, these drugs safely improve the control of hypertension over the individual medications. Also, the edema seen with amlodipine is less with the combination and there is no apparent occurrence of orthostatic events.

This Medical Reviewer recommends that valsartan/amlodipine (Exforge) be approved in the Sponsor's dose range of combination tablets.

### Statistical Review

In her November 3, 2006 review, Dr. Liu concluded the following:

Studies have demonstrated that both valsartan and amlodipine contribute to the overall effect in blood pressure reduction of the combination. The combinations identified to be more effective than their respective components in the reduction of both diastolic and systolic blood pressure from the four studies are: val/aml 40/5 mg, val/aml 80/2.5 mg, val/aml 80/5 mg, val/aml 160/5 mg, val/aml 160/10 mg, val/aml 320/5 mg, val/aml 320/10 mg.

### Clinical Pharmacology Review

In her November 3, 2006 review, Dr. Mishina wrote the following:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 21-990 and finds the clinical pharmacology and biopharmaceutics sections acceptable. The requested biowaivers for the 5/80mg, 5/160mg and 10/320mg dosage strength are granted.

The Agency recommends the following dissolution method and specifications for valsartan:

Apparatus: USP II (paddle)  
Medium: 0.067 M phosphate buffer, pH 6.8, 37°C  
Dissolution Volume: 900 ml  
Rotation Speed: 50 rpm  
Specification: Q = \_\_\_\_\_

And for amlodipine:

Apparatus: USP II (paddle)  
Medium: 0.1N HCL, pH 1.0, 37°C  
Dissolution Volume: 900 ml  
Rotation Speed: 50 rpm  
Specification: Q = \_\_\_\_\_

In a November 13, 2006 teleconference with the sponsor, the Agency proposed that the sponsor use the two dissolution methods above for valsartan and amlodipine in the drug product. The methods are the same as those proposed for the biowaivers. In response, the sponsor had stated that they had not fully evaluated these methods as the release methods. Based on their preliminary data, the solubility of amlodipine is decreased by valsartan in an acidic environment. The sponsor was concerned that they would not be able to meet the specifications since for the 80- and 160-mg combination product strengths, the dissolution specifications "hovered" at Q = \_\_\_\_\_ Therefore, the sponsor had suggested that a specification of Q = \_\_\_\_\_ might be more appropriate. The Agency agreed and the sponsor had confirmed their agreement to accept the following specifications for the actual release methods on an interim basis:

For valsartan:

Medium: pH 6.8, without Tween 80  
Rotation speed: 50 rpm  
Specification: Q = \_\_\_\_\_

For amlodipine:

Medium: pH 1.0, without Tween 80

Rotation speed: 50 rpm

Specification: Q= \_\_\_\_\_

#### **Pharmacology review**

In his November 13, 2006 review, Dr. Jagadeesh recommended that the NDA was "Approvable" and concluded the following:

"....a 16:1 combination of valsartan and amlodipine administered to rats and marmosets had greater adverse effects than treatment with valsartan or amlodipine alone. In spite of this enhancement of toxicity and in spite of the failure to demonstrate a NOAEL for erosive/ulcerative inflammation of the cecum and colon in marmosets, the combination product can still be used safely in humans for the treatment of hypertension as the target organ toxicities are monitorable and attributable to the effects of the individual components of the combination, which have been used, often concomitantly, to treat hypertensive patients since their respective approvals for this indication (1992 for amlodipine besylate and 1996 for valsartan)."

#### **Chemistry review**

In his December 8, 2006 review, Dr. Sarker recommended the following:

This application is recommended for APPROVAL from a chemistry, manufacturing and controls standpoint. Based on drug product stability data including biopharm recommendation on dissolution, shelf-lives of 12 months are recommended for all the strengths, \_\_\_\_\_ 160/5mg, 160/10mg, 320/5mg, 320/10mg, and in all the packaging systems, 30, 90 and 100 count HDPE (90cc and 175cc) bottles; 2 and 14 count HDPE (45cc) bottles, \_\_\_\_\_ blister packs. Applicant noted that drug product strengths, \_\_\_\_\_ will not be marketed at this time.

Tentative shelf-life for drug product has been assigned to 12 months for all the strengths and container/closure systems.

In addition, Dr. Sarker's review recommended the following regarding a post-marketing agreement:

The current dissolution method and the associated acceptance criterion may be considered as interim for one year. During this period, the applicant should generate dissolution test data following current method and the method proposed by the Agency on current drug product stability batches and first three commercial batches. The comparative dissolution test data should be submitted as a supplement by the end of 2007 with proposal for revised expiration date.

#### **Environmental Assessment**

The sponsor submitted an Environmental Assessment (EA) pursuant to 21 CFR Part 25, which was found to be acceptable.

#### **EES Report**

The Office of Compliance provided an overall recommendation of "Acceptable" for the manufacturing sites inspected.

#### **Division of Scientific Investigations**

In his December 13, 2006 review, Dr. Karkowsky wrote that "there were no DSI audits requested. The components of the combination product are approved. The Division considered it unlikely that any

unusual safety concerns would be detected by individual site reviews. Furthermore, the Division considered the likelihood of finding significant deviations from the protocol, which might alter its conclusions as small, since there were a large number of study sites, none of which supplied a significant proportion of the overall population. The yield from inspecting any one or two sites, therefore, appeared minimal.”

#### **Pediatrics**

In her November 1, 2006 review, Dr. Moreschi wrote that “during the pre-NDA meeting for Exforge on April 14, 2005, the Sponsor requested a waiver of the pediatric requirement for the combination product based on the fact that pediatric data was available for amlodipine besylate and that there was an ongoing pediatric program for valsartan. The Agency confirmed at that meeting that a waiver would be granted for the combination product.”

The Acknowledgement Letter to the sponsor dated March 10, 2006 noted that a full waiver was granted.

#### **Labeling**

The original submission contains proposed draft labeling for the package insert (PI), patient package insert (PPI), and container and carton labeling.

DDMAC provided comments on the proposed PI in a review dated August 11, 2006 and to the proposed PPI in a review dated November 13, 2006.

DMETS concluded that the proposed proprietary name “Exforge” was acceptable and provided additional comments on the proposed PI in their final review dated November 6, 2006. DMETS also provided comments on the proposed container and carton label and PI in an earlier review dated July 19, 2006. (The initial tradename review was completed on June 12, 2006.)

DSRCS provided comments on the proposed PPI in a review dated November 28, 2006.

Labeling discussions were held with the sponsor on November 13, and December 7 and 14, 2006. The sponsor’s revised container and carton labeling submitted on December 5, 2006 was found to be acceptable by the chemist. The agreed upon PI and PPI were sent to the sponsor on December 15, 2006.

#### **Pre-Approval Safety Conference**

No Pre-Approval Safety Conference was held because there were no safety issues with this NDA per the primary medical reviewer. This NDA is also a 505(b)(2) application, with both components of the combination product already approved.

#### **User Fee**

The user fee for this application was paid in full (User Fee ID# 3006424).

#### **CSO Summary**

A Tentative Approval letter based on submitted final printed labeling in Structured Product Labeling format will be drafted for Dr. Stockbridge’s signature.

Quynh Nguyen, Pharm.D.  
Regulatory Health Project Manager  
12-15-06

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

/s/

-----  
Quynh Nguyen  
12/21/2006 08:44:26 AM  
CSO

### NDA REGULATORY FILING REVIEW (Including Memo of Filing Meeting)

NDA # 21-990 Supplement # Efficacy Supplement Type SE-

Proprietary Name: amlodipine and valsartan  
Established Name: Exforge  
Strengths: 5/160 mg, 10/160 mg, 5/320 mg, and 10/320 mg

Applicant: Novartis Pharmaceuticals Corporation  
Agent for Applicant (if applicable):

Date of Application: 2/22/06  
Date of Receipt: 2/22/06  
Date clock started after UN: N/A  
Date of Filing Meeting: 4/12/06  
Filing Date: 4/23/06  
Action Goal Date (optional):

User Fee Goal Date: 12/22/06

Indication(s) requested: Treatment of hypertension.

Type of Original NDA: (b)(1)  (b)(2)   
AND (if applicable)  
Type of Supplement: (b)(1)  (b)(2)

**NOTE:**

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

Review Classification: S  P   
Resubmission after withdrawal?  Resubmission after refuse to file?   
Chemical Classification: (1,2,3 etc.) 4  
Other (orphan, OTC, etc.)

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

User Fee Status: Paid  #3006424 Exempt (orphan, government)   
Waived (e.g., small business, public health)

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

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

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

- Does another drug have orphan drug exclusivity for the same indication? YES  NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES  NO

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

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES  NO
- Does the submission contain an accurate comprehensive index? YES  NO   
If no, explain:
- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**
- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as a partial electronic submission).

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

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

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

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

- 1) Table of Contents  
Cover Letter – paper copy also with original signature  
Form FDA 356h – paper copy also with original signature
- 2) Labeling
- 3) Summary
- 4) CMC
- 5) Nonclinical Pharmacology and Toxicology
- 6) Human Pharmacology and Bioavailability/Bioequivalence
- 8) Clinical

- 11) Case Report Tabulations (CRTs)
- 12) Case Report Forms (CRFs)
- 13) Patent Information – paper copy also with original signature
- 14) Patent Certification – paper copy also with original signature
- 16) Debarment Certification – paper copy also with original signature
- 17) Field copy Certification – paper copy also with original signature
- 18) User Fee Cover Sheet – paper copy also with original signature
- 19) Financial Disclosure – paper copy also with original signature
- 20) Other – Statement of Confidentiality

**Additional comments:** One paper archival volume was provided containing documents for which original signatures are required as listed above.

3. This application is an eCTD NDA. YES  NO   
**If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.**

**Additional comments:**

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

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

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES  NO   
**Additional comments:** Division granted waiver of pediatric studies.
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES  NO
- Is this submission a partial or complete response to a pediatric Written Request? YES  NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES  NO   
**(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)**  
*NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section) YES  NO

- PDUFA and Action Goal dates correct in tracking system? YES  NO   
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. YES  NO
- List referenced IND numbers: 65,174
- Are the trade, established/proper, and applicant names correct in COMIS? YES  NO   
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) \_\_\_\_\_ NO   
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 4/14/05 NO   
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) \_\_\_\_\_ NO   
If yes, distribute letter and/or relevant minutes before filing meeting.

**Project Management**

- If Rx, was electronic Content of Labeling submitted in SPL format? YES  NO   
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:  
Was the PI submitted in PLR format? YES  NO

**If no, explain:** *NDA was submitted before 6/30/06.*

Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request: *N/A*

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES  NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES  NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?  
PPI submitted N/A  YES  NO
- Risk Management Plan consulted to OSE/IO? N/A  YES  NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? N/A  YES  NO

**If Rx-to-OTC Switch or OTC application:** *N/A*

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES  NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES  NO

**Clinical**

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

**Chemistry**

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

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** 4/12/06

**NDA #:** 21-990

**DRUG NAMES:** Exforge (amlodipine and valsartan) Tablets

**APPLICANT:** Novartis Pharmaceuticals Corporation

**BACKGROUND:** This NDA provides for Exforge (amlodipine and valsartan) fixed combination tablets for the treatment of hypertension. Amlodipine besylate is a calcium channel blocker and is approved for the treatment of hypertension (Norvasc; NDA 19-787). Valsartan is an angiotensin receptor blocker and is also approved for the treatment of hypertension. (Diovan; NDA 21 -283). This NDA was submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, and contains full reports of safety and effectiveness of the combination drug. However, reference is made to certain information previously submitted to the Agency for Norvasc (amlodipine besylate) Tablets. A paragraph III patent certification is included with the application. The sponsor does not intend to market Exforge until expiration of the pediatric exclusivity for amlodipine besylate.

The development of Exforge was conducted under IND 65,174. Exforge was evaluated in five controlled clinical trials involving over 5,000 patients with hypertension. According to sponsor, the results of the clinical program demonstrate that Exforge provides additional blood pressure reduction beyond each individual component, and is a safe and effective treatment for hypertension.

**ATTENDEES:** Norman Stockbridge, Ellis Unger, Gail Moreschi, Abraham Karkowsky, Kasturi Srinivasachar, Haripada Sarker, Patrick Marroum, Cheryl Ann Borden.

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

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	Gail Moreschi
Secondary Medical:	Abraham Karkowsky
Statistical:	Ququan (Cherry) Liu
Pharmacology:	Gowra Jagadeesh
Statistical Pharmacology:	N/A
Chemistry:	Haripada Sarker
Environmental Assessment (if needed):	
Biopharmaceutical:	Elena Mishina
Microbiology, sterility:	N/A
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	N/A
OPS:	N/A
Regulatory Project Management:	(Cheryl Ann Borden)/Quynh Nguyen
Other Consults:	N/A

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

CLINICAL FILE  REFUSE TO FILE

- Clinical site audit(s) needed? YES  NO   
If no, explain: Per the medical and statistical reviewers, DSI inspections are not needed.
- Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A  YES  NO

CLINICAL MICROBIOLOGY N/A  FILE  REFUSE TO FILE

STATISTICS N/A  FILE  REFUSE TO FILE

BIOPHARMACEUTICS N/A  FILE  REFUSE TO FILE

- Biopharm. study site audits(s) needed? YES  NO

PHARMACOLOGY/TOX N/A  FILE  REFUSE TO FILE

- GLP audit needed? YES  NO

CHEMISTRY FILE  REFUSE TO FILE

- Establishment(s) ready for inspection? N/A  YES  NO
- Sterile product? YES  NO
- If yes, was microbiology consulted for validation of sterilization? YES  NO

**ELECTRONIC SUBMISSION:**  
Any comments:

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

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

**ACTION ITEMS:**

1.  Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2.  If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4.  If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5.  Convey document filing issues/no filing issues to applicant by Day 74.

Quynh Nguyen for Cheryl Ann Borden  
Regulatory Project Manager

## Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

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

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

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

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

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

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

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

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

**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES  NO

*If "No," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):  
NDA 19-787/Norvasc (amlodipine besylate) Tablets

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES  NO

*If "Yes," skip to question 7.*

4. Is this application for a recombinant or biologically-derived product?

YES  NO

*If "Yes" contact your ODE's Office of Regulatory Policy representative.*

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES  NO

*(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))*

*If "No," to (a) skip to question 6. Otherwise, answer part (b) and (c).*

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES  NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)?

YES  NO

*If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.*

*If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.*

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES  NO

(*Pharmaceutical alternatives* are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES  NO

If "Yes," to (c), proceed to question 7.

**NOTE:** If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES  NO

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

This application provides for a fixed dose combination product consisting of two drug substances, amlodipine besylate and valsartan.

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES  NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES  NO

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES  NO
12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES  NO
13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)  
Patent number(s): 4,572,909 and 4,879,303
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)  
Patent number(s):

**NOTE:** IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).  
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.  
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

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

/s/

-----  
Quynh Nguyen  
12/21/2006 08:55:36 AM  
CSO

# MEMORANDUM

**To:** Quynh Nguyen, Pharm. D., RHPM  
Division of Cardiovascular and Renal Products, HFD-110

**From:** Lisa Hubbard, R.Ph., Regulatory Review Officer  
DDMAC, HFD-42

**Date:** August 11, 2006

**Re:** Comments on draft labeling:  
NDA 21-990  
Exforge® (amlodipine besylate/valsartan) Tablets

---

DDMAC has reviewed the proposed package insert for NDA 21-990 Exforge® (amlodipine besylate/valsartan) and offers the following comment with regard to promotional considerations:

## **Description:**

The proposed label contains the following phrase, \_\_\_\_\_ The phrase appears promotional in this section of the package insert. DDMAC recommends deletion. The phrase does not appear in the Description sections of the package inserts of the individual components or combination products such as Lotrel or Caduet.

## **Clinical Pharmacology/Pharmacokinetics/Valsartan**

Please consider confirming the source of the information related to the bioavailability of Valsartan. The proposed label states, \_\_\_\_\_ The approved product label for Diovan® (valsartan) states, "Absolute bioavailability for Diovan® is about 25% (range 10% - 35%)".

## **Clinical Pharmacology/Pharmacokinetics/Special Populations/Heart Failure**

In order to decrease the potential for minimizing risks in promotional materials, DDMAC recommends that you consider incorporating information regarding the \_\_\_\_\_ into the proposed package insert. For example, the approved package insert for Caduet contains the following statement in this section, "*Studies with amlodipine:* In patients with moderate to severe heart failure, the increase in AUC for amlodipine was similar to that seen in the elderly and in patients with hepatic insufficiency." DDMAC notes however, this information is not included in the Lotrel approved labeling.

## **Clinical Pharmacology/Pharmacodynamics/Amlodipine and Valsartan**

The proposed package insert includes the following phrase, \_\_\_\_\_

---

\_\_\_\_\_ DDMAC notes that, although the statement is true, it

does not appear in this section of other approved combination product labels such as Lotrel<sup>®</sup> and Caduet<sup>®</sup>. DDMAC recommends deletion in order to decrease the potential for off label use promotion. Similarly, the same section contains the following statement regarding Valsartan,

\_\_\_\_\_ DDMAC recommends deletion in order to decrease the potential for off label use promotion.

### **Clinical Pharmacology/Pharmacodynamics/Exforge**

The proposed package insert contains the phrase, \_\_\_\_\_  
The phrase appears promotional in tone. DDMAC recommends revision.

### **Clinical Studies**

The proposed package insert contains the phrase, \_\_\_\_\_ The phrase appears promotional in tone. DDMAC recommends stating the actual number of patients studied in each trial or if more appropriate, each treatment group.

The proposed package insert contains information regarding an active control study of 130 hypertensive patients. DDMAC recommends deleting the description, if the study does not represent a portion of the substantial evidence used for regulatory decision making. There is a potential exists for promotional use of the data generated from the smaller study.

### **Warnings/Clinical Laboratory Findings**

The proposed package insert contains the following language, \_\_\_\_\_  
\_\_\_\_\_ The statement appears promotional in tone. In addition, the statement is followed by a list in changes in standard laboratory parameters. DDMAC recommends deleting the language.

### **Post-Marketing Experience**

The following statement from the Diovan<sup>®</sup> label has been omitted from the Exforge label, "**Blood and Lymphatic:** There are very rare reports of thrombocytopenia." DDMAC recommends including the statement in order to prevent minimization of risk in promotional labeling.

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

/s/

-----  
Lisa Hubbard  
8/11/2006 11:46:34 AM  
DDMAC REVIEWER



NDA 21-990

**NDA ACKNOWLEDGMENT**

Novartis Pharmaceuticals Corporation  
Attention: Ms. Donna Vivelo  
One Health Plaza  
East Hanover, New Jersey 07936-1080

Dear Ms. Vivelo:

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

Name of Drug Product: Exforge® (amlodipine besylate/valsartan ) — 5/160,  
10/160, 5/320, and 10/320 mg Tablets

Review Priority Classification: Standard (S)

Date of Application: February 22, 2006

Date of Receipt: February 22, 2006

Our Reference Number: NDA 21-990

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 April 23, 2006, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be December 22, 2006.

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

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We acknowledge receipt of your request for a waiver of pediatric studies for this application. We are waiving the requirement for pediatric studies for this application.

NDA 21-990

Page 2

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

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Cardiovascular and Renal Products, Room 4165  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If you have any questions, please call:

Cheryl Ann Borden, MSN, RN, CCRN, CCNS  
Regulatory Health Project Manager  
(301) 796-1046

Sincerely,

*{See appended electronic signature page}*

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

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS  
FOOD AND DRUG ADMINISTRATION**



**US Mail address:**  
FDA/CDER/HFD-110  
5600 Fishers Lane  
Rockville, MD 20857

Woodmont II  
1451 Rockville Pike  
Rockville, MD 20852

**This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to: CDER, DCRDP (HFD-110); 5600 Fishers Lane; Rockville, MD 20857**

**Transmitted to FAX Number:** 973 781 3590

**Attention:** Donna Vivelo

**Company Name:** Novartis

**Phone:** 862 778 3572

**Subject:** 14 April 2005  
Meeting Minutes  
Pre-NDA 65,174

**Date:** 2005

**Pages including this sheet:**

**From:** Cheryl Ann Borden, MSN, RN, CCRN, CCNS  
LCDR, U.S. Public Health Service  
Regulatory Health Project Manager

**Phone:** 301-594-5312

**Fax:** 301-594-5494

**PLEASE LET ME KNOW YOU RECEIVED THIS. THANK YOU.**

**Meeting Minutes**

**Pre-NDA Meeting between Novartis Pharmaceutical Corporation and the FDA**

**Date:** 14 April 2005

**Sponsor:** Novartis Pharmaceutical Corporation

**Subject:** Diovan® (valsartan) plus amlodipine besylate  
Combination Tablets  
**IND 65,174**

**Type of Meeting:** **Pre NDA**

**FDA Participants:**

Abraham Karkowsky, M.D., Ph.D., HFD-110, Medical Team Leader  
Nhi Beasley, PharmD, HFD-860, Clinical Pharmacology/ Biopharmaceutics Reviewer  
Monica Cooper, PhD., HFD-810, Chemistry Reviewer  
Edward Fromm, R.Ph., HFD-110, Chief, Project Management Staff  
LCDR Cheryl Ann Borden MSN, R.N., HFD-110, Regulatory Health Project Manager

**Sponsor Participants:**

Robert Glazer, MD, Executive Director, Clinical Research and Development  
Joanna Cheng, PhD, Senior Associate Director, Biostatistics  
Joseph Yen, Associate Director, Biostatistics  
Catherine Ford, Associate Director, Global Regulatory CMC  
Gangadhar Sunkara, PhD, Fellow/Lead Pharmacokineticist, Exploratory Development  
Pritam Sahota, PhD, Director of Pathology, Preclinical Safety  
Donna Vivello, Director, Drug Regulatory Affairs

**BACKGROUND:** Novartis plans to submit a New Drug Application for the fixed combination product of valsartan and amlodipine besylate in February 2006. The purpose of this meeting is to review the available clinical data and discuss plans for the content and format of the NDA with the Division.

**DISCUSSION POINTS:**

The meeting was opened by Novartis who briefly described their two factorial studies and the scope of their program which is addressed on pages 5 and 6 of the briefing package. The meeting then progressed to a review of the questions.

**Review of Questions submitted to the Agency by Novartis:**

**Regulatory**

1. Is the Division in agreement with our plans to submit this NDA as a 505(b)(2) application?

**Division response:** We are in agreement with your plan as long as patent certification is included.

2. Is the Division in agreement with our request for a waiver of the pediatric requirement?

**Division response:** The pediatric requirement will be waived for the combination product.

3. The original NDA filing is planned for February 2006 however the bioequivalence study to support the 320/10mg formulation and supporting technical documentation will not be available until June 2006. (All data to support the remaining 5 doses will be submitted with the original filing). Will the Agency accept a submission containing the BE data and supporting technical documentation to support the 320/10mg dosage form in June 2006 as an amendment to the original NDA?

**Division response:** It is acceptable to submit the BE study and the supporting documentation during the course of the standard review.

**Labeling**

4. We will propose draft labeling for the valsartan/amlodipine combination product as noted in Section 3.2. It is proposed that this combination product be used when a patient's blood pressure is not adequately controlled on amlodipine (or another DHP CCB) or valsartan (or another ARB) alone. This labeling is entirely consistent with the labeling for other antihypertensive combination products such as Lotrel® (amlodipine besylate and benazepril HCl) and Lixel® (enalapril maleate/ felodipine ER), see references. Does the Agency have any comments on this proposal?

**Division response:** The labeling will be consistent with the policy in effect at the time of the submission; no additional study is required.

**CMC**

5. Novartis proposes to include an executed batch record for the \_\_\_\_\_ strength and for the 320/5mg strength, only. The \_\_\_\_\_ strength will be representative for four and \_\_\_\_\_ and the 320/5mg will be included as it is a unique formulation and manufacturing process. This will reduce the volume of documentation provided in the regional section (R.1.P.) of the CTD and facilitate review. The \_\_\_\_\_ strength was selected as representative for the four \_\_\_\_\_ due to the fact that the manufacturing process is the same and it contains all of the excipients which are common to the other strengths. All batch records will be available at the site of manufacture for the pre-approval inspection.

Does the Agency agree with this approach?

**Division response:** This approach is acceptable.

6. Novartis proposes providing analytical data for a single representative batch of each excipient used in the above batches in the regional section (R.1.P.) of the CTD.

Diovan®(valsartan) plus amlodipine besylate

Does the Agency agree with this approach?

**Division response:** This approach is acceptable.

Concerning the registration stability protocol submitted to IND 65,174, serial number 035 (14-Jan-2005), the sponsor confirmed that stability testing of physician samples, photostability testing, and microbial limit testing would be performed on a production-scale batch. Also, the missing 9-month and 18-month timepoints were added to the stability test plan for the physician samples.

Regarding the 320/10 mg strength tablet, \_\_\_\_\_

Dr. Cooper asked how much stability data would be available for the 320/10 mg tablet at the time of filing. The sponsor replied that 3 months of stability data on 3 pilot-scale batches would be included in the original filing and a stability update would be provided during the review cycle. The sponsor stated that they would provide as much stability data as possible for the new strength, but understood that a different expiration date may be needed for this strength depending on the data. The sponsor confirmed that CMC information for all -tablet strengths would be included in the original filing.

Dr. Cooper noted that in the drug substance specifications for amlodipine besylate the sponsor should follow ICH guidelines for listing impurities – specified, any individual unspecified, and total.

### **Biopharmaceutics**

7. Does the Division have any comments on our updated biowaiver strategy?

**Division response:** We recommend you submit the BE studies electronically and include the SAS data sets.

### **Clinical/Statistical**

8. Does the Division agree with our proposed pooling strategy for the trials included in the Summary of Clinical Safety and the proposal for the patient narratives?

**Division response:** Patient narratives are acceptable; however, completed case report forms (CRFs) that include hospitalizations, Med Watch forms, etc should be included according to the newly published Guidance.

9. As indicated in Section 3 it is Novartis' intention to provide the results of studies 2305 and 2306 in the original NDA submission. However, enrollment in these studies may be slower than planned and the results may be delayed. As these studies are not required for approval, does the Agency agree that, if delayed, the results can be submitted with the 120-day safety update?

**Division response:** Please include SAS codes and analysis programs when submitting studies 2201 and 2307.

**OTHER:**

As described in the March 18, 2005 pre-NDA briefing book, valsartan/amlodipine 320/10 mg is now being developed as an addition to the originally planned program to provide dosing flexibility. The pilot program for the formulation development of 320/10 mg dose has been recently completed. In this correspondence, we are requesting a biowaiver to conduct a bioequivalence study for the 320/10 mg valsartan/amlodipine fixed combination tablet.

**Division response:** That is acceptable.

**ACTION ITEMS:**

1. The Division requested Novartis submit the SAS codes for studies 2201 and 2307.

**ADDENDUM TO MEETING MINUTES**

After the meeting Dr. Beasley from BioPharmaceutics inquired if the sponsor planned on conducting a food effect study. The sponsor stated they had not planned one. It was then noted the Division would provide direction to the sponsor whether a food effect study was needed.

BioPharmaceutics:

The sponsor is requested to conduct a food effect study with the highest strengths of the two final formulations, i.e, 160/10 and 320/10. The rationale is the new formulation and the described valsartan food effect.

**Signature recorder :** (see appended electronic signature page)  
LCDR Cheryl Ann Borden, MSN, R.N.

**Concurrence, Chair:** (see appended electronic signature page)  
Abraham Karkowsky, M.D., PhD.

**Routed: 29 April 05**

Fromm: 1 May 05

Beasley: 1 May 05

Cooper: 2 May 05

Karkowsky: 5 May 05

**Final: 5 May 05**

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

/s/

-----  
Abraham Karkowsky  
5/6/05 12:50:52 PM