CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 19-787/S30

Administrative/Correspondence

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

DATE: July 15, 2002
FROM: Cheryl Cropp, Pharm.D., BCPS, DDMAC
TO: Denise M. Hinton

SUBJECT: Amlodipine besylate (NDA # 19-787/SE5-030) Labeling Comments

These comments are based on draft labeling from Pfizer Labs received July 2001.

General Comment

Special Studies: Effect of other agents on NORVASC

[redacted]

Appears This Way
On Original

EXCLUSIVITY SUMMARY FOR NDA # 19-787/SE-5 SUPPL #030

Trade Name: Norvasc Generic Name: amlodipine besylate

Applicant Name: Pfizer HFD # 110

Approval Date if known: January 2004

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES / / NO /X/

b) Is it an effectiveness supplement?

YES /X/ NO / / /

If yes, what type? (SE1, SE2, etc.) SE5

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 /X/ 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.

The sponsor submitted a population pharmacokinetic study in response to our Pediatric Written Request.

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 /X/ NO / /

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

4 years

Form OGD-011347 Revised 10/13/98
cc: Original NDA Division File HFD-93 Mary Ann Holovac

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

Yes. Pediatric Exclusivity was granted on November 27, 2001. Patent 4879303 expires on March 25, 2007 and Patent 4572909 expires on July 31, 2006.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES / / NO /X/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 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)

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

YES /___/ NO /___/

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

NDA#_____ _____

NDA#_____ _____

NDA# _____ _____

2. Combination product.

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

YES /___/ NO /___/

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

NDA#_____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S 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 /X/ 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 /X/ 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 /X/

(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 /X/

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 /X/

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:

Protocol A0531018 (PATH-1): Pediatric use of amlodipine in the treatment of hypertension; a randomized, double-blind, placebo-controlled, parallel group dose-ranging study to evaluate the efficacy and safety of amlodipine in the treatment of hypertension in children.

Protocol A0531023 (PATH-II): Pediatric use of amlodipine in the treatment of hypertension; a population pharmacokinetic trial.

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 /X/

Investigation #2 YES /___/ NO /X/

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 /X/

Investigation #2 YES /___/ NO /X/

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"):

Protocol A0531018 (PATH-1)

Protocol A0531023 (PATH-II)

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 # 22.222 YES /X/ NO /___/ Explain:

Investigation #2

IND # 22.222 YES /X/ NO /___/ Explain:

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

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

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

YES /___/ NO /X/

If yes, explain: _____

_____

Signature Denise M. Hinton Date: January 7, 2004
Title: Project Manager

Signature of Office/
Douglas C. Throckmorton Date _____
Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

EXCLUSIVITY SUMMARY FOR NDA # 19-787/SE-5 SUPPL #030

Trade Name: Norvasc Generic Name: amlodipine besylate

Applicant Name: Pfizer HFD # 110

Approval Date if known: N/A

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?
YES / / NO /X/

b) Is it an effectiveness supplement?

YES /X/ NO / / /

If yes, what type? (SE1, SE2, etc.) SE5

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 /X/

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.

The sponsor submitted a population pharmacokinetic study in response to our Pediatric Written Request.

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 /X/ NO / /

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

4 years

Form OGD-011347 Revised 10/13/98
cc: Original NDA Division File HFD-93 Mary Ann Holovac

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

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /X/ NO /___/

If yes, NDA #19-787 Drug Name: Norvasc (amlodipine besylate)

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES /___/ NO /___/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

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

YES /___/ NO /___/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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

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

YES /___/ NO /___/

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

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

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

YES /___/ NO /___/

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

_____

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

YES /___/ NO /___/

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

YES /___/ NO /___/

If yes, explain:

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

YES /___/ NO /___/

If yes, explain:

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

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

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

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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

_____ _____

_____ _____

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

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

Investigation #1

IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

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

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

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

YES /___/ NO /___/

If yes, explain: _____

_____

Signature _____ Date _____
Title: Project Manager

Signature of Office/
Division Director _____ Date _____

cc: Original NDA Division File HFD-93 Mary Ann Holovac

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PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 19-787 Supplement Type (e.g. SE5): SE5 Supplement Number: 030

Stamp Date: October 3, 2003 Action Date: February 6, 2004

HFD: 110 Trade and generic names/dosage form: Norvasc (amlodipine besylate) Tablets 2.5, 5 and 10 mg

Applicant: Pfizer Incorporated Therapeutic Class: Calcium Channel Blocker

Indication(s) previously approved: Hypertension, Chronic Stable Angina, Vasospastic Angina

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Hypertension

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

- ☐ Yes: Please proceed to Section A.
- X No: Please check all that apply: ____Partial Waiver ____Deferred X Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	kg____	mo.____	yr.____	Tanner Stage____
Max____	kg____	mo.____	yr.____	Tanner Stage____

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for deferral:

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

Other:_____

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

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

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	kg 6	mo.6	yr._____	Tanner Stage ≤3 years
Max_____	kg 142	mo. NA	yr. 17	Tanner Stage >3-16 years

Comments:

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Grace Carmouze
(revised 12-22-03)

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

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA #: 19-787 Supplement Type (e.g. SE5): SE5 Supplement Number:030

Stamp Date: September 17, 2001 Action Date: July 17, 2002

HFD 110 Trade and generic names/dosage form: Norvasc (amlodipine besylate) Tablets 2.5, 5, and 10 mg

Applicant: Pfizer Incorporated Therapeutic Class: Calcium Channel Blocker

Indication(s) previously approved: Hypertension, Chronic Stable Angina, Vasospastic Angina

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Hypertension

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

☐ Yes: Please proceed to Section A.

X No: Please check all that apply: ____Partial Waiver ____Deferred XCompleted
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

ction A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

Min ____	kg____	mo.____	yr.____	Tanner Stage____
Max____	kg____	mo.____	yr.____	Tanner Stage____

Reason(s) for deferral:

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

Other:_____

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

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

ction D: Completed Studies

Age/weight range of completed studies:

Min ___	kg 6	mo. 6	yr.____	Tanner Stage ≤ 3 years
Max___	kg 142	mo. NA	yr. 17	Tanner Stage >3-16 years

Comments:

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

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

Attachment A

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

Indication #2: _____

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

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

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

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

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

ction D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

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

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: NDA
HFD-960/ Terrie Crescenzi
(revised 1-18-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
`1-594-7337

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV 2 1999

Four Years from the Date of this Letter 10/7 2003

NDA 19-787

Pfizer Inc.
Attention Jean Lyons, M.S.
235 East 42nd Street
New York, NY 10017-5755

Dear Ms. Lyons:

Reference is made to our February 4, 1999 written request for pediatric studies for Norvasc (amlodipine besylate) Tablets, 2.5, 5 and 10 mg. We have recently reviewed that written request and have decided to amend it. Please note that the following Written Request supercedes that of February 4, 1999, which is no longer valid.

Changes have been made to the following sections:

1. The third bullet under "strategy,"
2. The fourth and fifth bullet under "age groups,"
3. The second sentence under "recruiting,"
4. "Format of Reports," and
5. The date the reports are due
6. Timing of Submission of Reports

Strategy

The requested data will provide guidance for the use of amlodipine besylate to reduce blood pressure in pediatric patients. These data will be derived from

- a dose-ranging trial in hypertensive pediatric patients;
- pharmacokinetic trials in subjects from four pediatric age groups: infants and toddlers, pre-school children, school-age children, and adolescents; and
- safety data derived from the controlled trial, and an open treatment phase following the trial or other comparable database, with a summary of all available information on the safety of the drug in pediatric patients.

Although not a part of this Written Request, we remind you that it may be important to determine the effect of amlodipine besylate on the growth and development of pediatric patients, and we encourage you to perform an active control comparison with diuretic-based therapy.

Appears This Way
On Original

Pediatric Subgroups

Age groups

The five pediatric age groups that we refer to in this document are:

- neonates (age less than one month),
- infants and toddlers (age 1 - 24 months),
- pre-school children (age 2 - 6 years),
- school-age children (age 6 – 12 years or ≤ Tanner Stage 3), preferred group for effectiveness study, and
- adolescents (> 12 years or > Tanner Stage 3 - 16 years).

With respect to effectiveness, studies of antihypertensive drugs should be focused on, and include a reasonable proportion of, pre-pubertal children, as the course of disease and the effects of drugs in adolescents are not likely to differ from the course and effects in adults.

For purposes of antihypertensive drug development, it is useful to divide "children" into "pre-school "and "school-age" children. School-age children (above the age of approximately 6 years)

- are usually able to swallow solid dosage forms,
- may tolerate doses similar to the smallest doses approved for adults, and
- are fairly often diagnosed with hypertension of no specific cause.

Below this age, formulation issues are more important and almost all diagnosed hypertension is attributed to renal disease or other specific causes.

Racial groups

Because response to some therapies in adult hypertension appears to be different in black and non-black populations, your recruitment scheme should be designed to assure a mixture of black and non-black patients.

Formulation Issues

Use age-appropriate formulations in the studies described below. If there is no suspension/solution available, a solid dosage form suspended in food could be used if standardized, palatable, and shown in adults to be of acceptable (similar to the marketed product) bioavailability, or of different but defined bioavailability compared to the marketed product.

Dose-ranging Trial

Trial Design

A trial that would be considered responsive to this request will entail randomized, double-blind observation of parallel dose groups, using a population judged to be of adequate size on the basis of realistic estimates of effect size and the usual statistical calculations. The trial need not be successful (that is, it need not demonstrate that any particular regimen of amlodipine besylate is effective in pediatric patients), but it must be interpretable, as explained in the following discussion of possible study designs.

The most straight-forward, acceptable trial (Trial A), would be one in which each patient is randomized to placebo or to one of three different doses of amlodipine besylate, with the doses chosen to give blood levels in a range from slightly less than those achieved by the lowest approved adult dose to slightly more than those achieved by the

highest approved adult dose.[1] After two weeks of treatment,[2] the trial would be analyzed by looking for a significantly positive slope of the placebo-corrected change in blood pressure from baseline as a function of dose.[3] If the slope of this line were not differentiable from zero, the trial would be unsuccessful by our usual criteria (i.e., it would show not effect), but it would be interpretable.

Although we believe that the hazard associated with two weeks of placebo treatment is likely to be small, we recognize that parents and others may be reluctant to enroll pediatric patients in a traditional placebo-controlled trial. An alternative design (Trial B) would be similar to Trial A, but without the placebo arm.

If analysis of Trial B revealed a significantly positive slope to the dose-response line, the trial would be considered successful by the usual criteria. If, however, Trial B, shows no dose-response, i.e., if the dose-response line is horizontal, the trial will be considered uninterpretable, not merely unsuccessful.[4] In this case, Trial B would then be considered not responsive to this request.

To avoid this possibility, Trial B could be modified to include a randomized withdrawal phase (Trial C). Patients in Trial C would be recruited and treated like those in Trial B. At the end of the 2-week treatment period, patients would be rerandomized in blinded fashion to continue on their assigned treatments or to be withdrawn to placebo, with close follow-up and withdrawal to open-label treatment at the discretion of their physicians. The analysis of Trial C would be a slope analysis for the first phase, but then (if the first phase revealed a flat dose-response curve) an analysis of the second phase would determine whether there was, or was not, a blood pressure effect. This design would allow you to distinguish among a positive dose response (line not flat), doses too low or no effect for some other reason (line flat, withdrawal identical between active treatment and placebo), and doses too high (line flat, withdrawal slower on active treatment). Because this is essentially a placebo-controlled trial, it would be considered interpretable no matter what the outcome so long as the sample size for the withdrawal phase were adequate.

It would be possible to build the entire trial around randomized withdrawal (Trial D). Patients would be force-titrated to maximal tolerated doses of amlodipine besylate and then randomly withdrawn to lower doses (including placebo), with the same close follow-up, discretionary withdrawal to open-label therapy, and analysis as in Trial C.

Recruiting

The trial should be performed in patients of both sexes in one or more of the pediatric age groups defined above, preferably school-age children. If adolescents are included, at least one additional age group must also be included, and at least 50% of the patients in the trial should be 6 – 12 years old or ≤ Tanner Stage 3 or younger. Patients recruited for the trial should be diagnosed as hypertensive according to the standards of local practice, probably by scoring in the highest few percentiles of the age-specific tables of expected blood pressure. They should not be recruited if other interventions likely to affect blood pressure (e.g., repair of arterial anomalies) are likely to occur during the expected course of the trial or if their blood pressures are so high as to need immediate treatment. Patients should be followed weekly, so that unacceptable increases in blood pressure can be detected promptly. Prior treatment with amlodipine besylate or other therapy should be neither required nor disqualifying.

---

[1] Doses would usually be derived from adult doses scaled by body surface area, but there should be, from PK data, assurance that these doses will in fact place patients in the range of blood levels attained in adults.

[2] The study period might need to be somewhat longer if you decide that one or more of the studied doses cannot be used without a period of lower dosing and upward forced titration.

[3] In general, there will be interest in the effect on both systolic and diastolic pressure. Usually, the best measure of blood pressure change will be mmHg, but if pressures vary widely, percent change could be used.

[4] When placebo is included (as in Trial A), a flat dose-response line means simply that all of the doses tested were too low, so they were ineffective, or that the drug does not work in children. Without placebo (as in Trial B), it is alternatively possible that all of the doses tested were too high, and that they were all equally effective.

Eligibility

A recruited patient not receiving antihypertensive therapy should be eligible for randomization if the blood pressure is in the qualifying range on each of two or three occasions of measurement. A recruited patient who is receiving hypertensive therapy should be eligible for randomization if blood pressure becomes elevated during a withdrawal period. Although there may be a placebo group and/or a period of drug withdrawal, the short duration of therapy withdrawal or non-active treatment should pose no risk so long as patients are appropriately monitored.

You should take steps to attempt to obtain a reasonable distribution of age, race, and gender in the trial.

Duration

The study period should generally be of two weeks duration; it may need to be somewhat longer if you decide that one or more of the studied doses cannot be used without a period of lower dosing and upward forced titration.

Statistical considerations

The trial should be designed with at least 80% power to detect a treatment effect of conventional ($P= 0.05$) statistical significance. Please submit your proposed statistical analyses as an amendment to this request, following the procedure described at the end of this letter for submitting proposed changes. It may be useful to make some groups larger to obtain additional safety information, or allow better assessment of subgroups.

Pharmacokinetic Trials

Pharmacokinetic data should be obtained from subjects with grossly normal metabolic function from infants and toddlers, pre-school children, school-age children, and adolescents. You may choose to perform traditional or sparse sampling to estimate pharmacokinetic parameters. You should be aware that a draft guidance document on pediatric pharmacokinetic studies is available [www fda.gov/cder/guidance/index.htm, under Clinical/Pharmacological (Draft)].

In the age group studied in the dose-ranging trial, some or all of the pharmacokinetic data may be obtained from patients in the dose-response trial or from safety studies. Data should be collected with respect to amlodipine besylate and any metabolites that make substantial contributions to its efficacy and/or toxicity. For the parent and each metabolite followed, the data collected should provide estimates of the bioavailability (AUC), half-life, C_{max}, and t_{max} in pediatric subjects of the various age groups.

Format of Reports

Full study reports of the requested trials, including full analysis, assessment, and interpretation, should be submitted in the usual format. You may submit this report with essential data in electronic form, with a case report form annotated with the names of the SAS variables used.

Labeling Changes

The results of the completed studies may be used in the labeling of your drug product to add information allowing proper dosing for the safe and effective use for the reduction of blood pressure in pediatric patients. A new indication will be recognized only if your studies demonstrate safety and efficacy in a population[5] that is distinct, not only in age, but on some other etiologic or diagnostic basis, from the adult population for which your product is approved.

[5] For example, pediatric patients with hypertension secondary to advanced renal disease.

Timing of Submission of Reports

Reports of the above studies must be submitted to the Agency on or before four years from the date of this letter. Please remember that pediatric exclusivity only adds to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to:

Director
Office of Generic Drugs
HFD-600, Metro Park North II
7500 Standish Place
Rockville, MD 20855-2773

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, please contact:

Mr. David Roeder
Regulatory Heath Project Manager
(301) 594-5332

Sincerely yours, 11/6/99

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA 11/2/99. Application Written Request was made to: NDA19-787
Timeframe Noted in Written Request for Submission of Studies 11/2/03.
NDA# 19-787 Supplement #030 Choose one: SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8 SLR
Sponsor: Pfizer Inc.
Generic Name amlodipine besylate Trade Name Norvasc
Strength 2.5, 5, & 10mg (only 2.5 & 5 mg are recommended in peds) Dosage Form/Route tablets oral
Date of Submission of Reports of Studies 9/14/01.
Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) 12/13/01.

Was a formal Written Request made for the pediatric studies submitted?	Y X	N ___
Were the studies submitted after the Written Request?	Y X	N ___
Were the reports submitted as a supplement, amendment to an NDA, or NDA?	Y X	N ___
Was the timeframe noted in the Written Request for submission of studies met?	Y X	N ___
If there was a written agreement, were the studies conducted according to the written agreement? OR If there was no written agreement, were the studies conducted in accord with good scientific principles?	Y X	N ___
Did the studies fairly respond to the Written Request?	Y X	N ___

SIGNED _____ DATE 11/15/01

FORWARD TO THE PEDIATRIC EXCLUSIVITY BOARD, HFD-960.

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity X **Granted** ___ **Denied**

Existing Patent or Exclusivity Protection:

NDA/Product #	Eligible Patents/Exclusivity	Current Expiration Date
19-787	4879303	25-Mar-2007
19-787	4572909	31-Jul-2006

SIGNED _____ DATE 11/27/01

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

/s/

Terrie Crescenzi
11/28/01 04:02:41 PM

ITEM 16.
DEBARMENT CERTIFICATION

Pfizer, Inc. certifies that it is not debarred, and to the best of its knowledge, Pfizer, Inc 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.

Norvasc (amlodipine besylate)
NDA 19-787/S030

FINANCIAL DISCLOSURE COVER NOTE

Section 19.1

There is one covered study for this supplementary NDA, The covered study was not funded via variable compensation and none of the investigators in the study hold any form of propriety interest in Pfizer Inc.

Information regarding Pfizer's efforts to eliminate bias in this study are described in NDA Section 19.2. Pfizer has examined its financial data regarding significant payments of other sorts made to ***all*** investigators in this study and equity information as provided by the investigators, as defined in 21 CFR 54.2. Disclosure: Financial Interests and Arrangements of Clinical Investigators (NDA Section 19.3).

With a total of 186 investigators listed for 51 sites in this multi-centered study, only one of the listed investigators had any financial information to disclose. None of these investigators has equity in Pfizer and only one of the investigators received payments of other sorts. This information is listed in the 3455 forms in this section.

It is important to note that the investigator list for the studies determined by 1572's is not necessarily the same as that for financial disclosure. The FDA criteria for the two lists are not equivalent. Personnel involved with the study but not necessarily with the data are listed on FDA form 1572. There is a complete investigator population list for the covered study attached to this cover note

Pfizer is submitting financial disclosure information on the following covered study:

Protocol: A0531018 entitled: PATH-1 (Pediatric Use of Amlodipine in the Treatment of Hypertension-1). (A Randomized, Double-Blind, Placebo-controlled, Parallel Group Dose-Ranging Study to Evaluate the Efficacy and Safety of Amlodipine in the Treatment of Hypertension in Children).

Each of the investigators listed was sent the Financial Disclosure Form directly or via the principal investigator for their site. For the investigator for which we provided due diligence, we contacted the site by telephone and/or sent 2 separate follow-up letters to the individual who did not return the Financial Disclosure Form. All investigators contacted were reminded to disclose financial information for Warner-Lambert Company and its affiliates including Parke-Davis and Agouron, as they are now wholly owned by Pfizer.

CERTIFICATION

Per Form 3454, certification is provided for 185 of the 186 investigators indicating

1) investigators had nothing to disclose or
2) due diligence in collecting the information on Equity. One of the 186 investigators did not respond or was not reached by our due diligence effort.

Please note that all investigators are assessed for Significant Payments of Other Sorts, Variable Compensation, & Propriety Interest.

DISCLOSURE

In the above covered study only one of the 186 investigators listed had financial information to disclose. A completed Form 3455 is attached for this investigator.

COVERED INVESTIGATOR LIST FOR NDA

Bolded individuals named function as primary investigators.
Other individuals named function as subinvestigators.

AMLODIPINE PROTOCOL # 053:A0531018

SITE ID	INVESTIGATOR NAME
5003	Dr. Stephen Sanders
5003	
5003	
5003	
5003	
5005	Dr. Nancy Drucker
5005	
5005	
5006	Dr. Patrick Brophy
5006	Dr. Joseph T. Flynn
5006	Dr. Albert Rocchini
5006	
5006	
5006	
5006	
5006	
5006	
5007	Dr. Gerald S. Arbus
5007	
5007	
5007	
5008	Dr. Thomas Graham
5008	
5008	
5008	
5008	
5009	Dr. Leland Benson
5009	Dr. Kyong-Jin Lee
5010	Dr. Jane Newburger
5010	
5010	
5010	
5011	Dr. Michael Artman
5011	
5011	
5011	
5012	Dr. Samuel S. Gidding
5012	
5012	
5014	Dr. Abdullah Sakarcan
5014	
5014	

COVERED INVESTIGATOR LIST FOR NDA

Bolded individuals named function as primary investigators.
Other individuals named function as subinvestigators.

AMLODIPINE

PROTOCOL # 053:A0531018

SITE ID	INVESTIGATOR NAME
5014	
5014	
5014	
5014	
5015	**Dr. Bruce S. Alpert**
5015	
5016	**Dr. Douglas Ford**
5016	**Dr. Michael S. Schaffer**
5016	
5016	
5017	**Dr. Robert N. Vincent**
5018	**Dr. Linda J. Addonizio**
5018	**Dr. Thomas Starc**
5018	
5018	
5018	
5019	**Dr. Debbie Gipson**
5019	**Dr. Roberta G. Williams**
5020	**Dr. Nancy D. Bridges**
5020	
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5021	**Dr. Bertrand Ross**
5021	
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5022	**Dr. Steven Kamenir**
5022	
5022	
5023	**Dr. Ronald J. Portman**
5023	
5023	
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5024	**Dr. Robert Cunningham**
5024	
5024	
5024	
5024	

COVERED INVESTIGATOR LIST FOR NDA

Bolded individuals named function as primary investigators.
Other individuals named function as subinvestigators.

AMLODIPINE PROTOCOL # 053:A0531018

SITE ID	INVESTIGATOR NAME
5025	Dr. William B. Strong
5025	
5025	
5025	
5025	
5026	Dr. William C. Kirby
5027	Dr. Jeffrey L. Blumer
5027	
5027	
5027	
5027	
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5028	Dr. Steven N. Weindling
5028	
5028	
5029	Dr. Alan Flint
5030	Dr. John T. Fahey
5030	
5030	
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5030	
5031	Dr. John Mahan
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5032	Dr. Stephen R. Daniels
5033	Dr. Lisa Guay-Woodford
5033	
5034	Dr. Julie Ingelfinger
5034	
5035	Dr. J. Donald Moore
5035	
5035	
5036	Dr. J. Timothy Bricker
5036	

COVERED INVESTIGATOR LIST FOR NDA

Bolded individuals named function as primary investigators.
Other individuals named function as subinvestigators.

AMLODIPINE PROTOCOL # 053:A0531018

SITE ID	INVESTIGATOR NAME
5037	Dr. Ronald J. Hogg
5037	
5037	
5037	
5037	
5037	
5038	Dr. Elaine Urbina
5038	
5039	Dr. Thomas D. Scholz
5039	
5040	Dr. Jacques Lemire
5040	Dr. Dennis Levy
5040	
5040	
5041	Dr. Bonita Falkner
5042	Dr. Alan Sinaiko
5042	
5043	Dr. Kenneth Miller
5044	Dr. Mark C. Johnson
5044	
5044	
5045	Dr. J. Philip Saul
5045	
5045	
5045	
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5046	Dr. Arno R. Hohn
5046	
5047	Dr. Eric Quivers
5049	Dr. Amira Al-Uzri
5049	Dr. Victoria Norwood
5049	
5049	
5050	Dr. Prapti Kanani
5050	
5051	Dr. Steven Lipshultz
5051	
5051	
5052	Dr. Clifford Chin
5052	Dr. Peter Yorgin

COVERED INVESTIGATOR LIST FOR NDA

Bolded individuals named function as primary investigators.
Other individuals named function as subinvestigators.

AMLODIPINE

PROTOCOL # 053:A0531018

SITE ID	INVESTIGATOR NAME
5052	[redacted]
5052	[redacted]
5052	[redacted]
5052	[redacted]
5052	[redacted]
5053	**Dr. David Teitel**
5053	[redacted]
5053	[redacted]
5056	**Dr. Beatriz Grunfeld**
5056	[redacted]
5056	[redacted]
5056	[redacted]
5061	**Dr. Maria Teresa Zanella**
5061	[redacted]
5061	[redacted]
5062	**Dr. Vera Koch**
5062	[redacted]
5062	[redacted]

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Pfizer Inc.
235 East 42nd Street
New York, NY 10017

2. TELEPHONE NUMBER *(Include Area Code)*

(212) 573-7291

3. PRODUCT NAME

Norvasc (amlodipine besylate) Tablets

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____ (APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER

6. LICENSE NUMBER / NDA NUMBER

NDA #19-787

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

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

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO *(See reverse side if answered YES)*

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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.

Please DO NOT RETURN this form to this address.

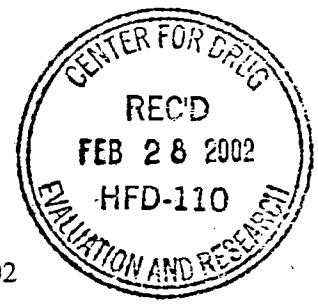
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Signature for R. Wittich 9/14/01	Rita A. Wittich Vice President, Worldwide Regulatory	09/14/01

EF

FORM FDA 3397 (5/98)

ORIGINAL

Pfizer Inc
235 East 42nd Street 150/7/13
New York, NY 10017
Tel 212 733 5999 Fax 212 857 3558
Email jean.lyons@pfizer.com



Pfizer Pharmaceuticals Group

Jean Lyons, MS
Director
Worldwide Regulatory Strategy

February 27, 2002

SUPPL NEW CORRESP
SE5-030(C)

Raymond Lipicky, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
1451 Rockville Pike
Rockville, MD 20852

Re: Norvasc (amlodipine besylate) Tablets, NDA #19-787/S-030
Follow up to Pfizer Telephone Conference With FDA on February 26, 2002 to Discuss Protocol #A0531018 (PATH-1) Study Report.

Dear Dr. Lipicky,

Attached, please find copies of the following two documents:

- minutes from the above telecon held yesterday between Drs. Gobburu, Mishina and Pfizer statisticians.
- follow up note to Drs. Gobburu and Mishina with an explanation from Pam Award detailing the way to identify patients who received the 2.5 mg dose for the first two weeks and then were switched to the 5 mg dose.

These two documents were sent to the Cardio-Renal Division yesterday via e mail. Please include this information in the subject file. Don't hesitate to contact me if you have further questions. Alternatively, Mr. Jim Parker (212-733-5344)'can be contacted if I am not available.

Sincerely,

Jean Lyons

Director, Regulatory Affairs

Cc: Ms. C. LoCicero

Division of Cardio-Renal Drug Products
Norvasc (amlodipine besylate), NDA 19-787/S-030
Telephone Conference Minutes
February 26, 2002

Type of Meeting: Clarify statistical issues concerning patients randomized to 2.5 mg tablets versus those titrated to the 5 mg dose.

FDA Participants:

Dr. Joga Gobburu
Dr. Elena Mishina,

Pfizer Participants:

Ms. Pam Award
Dr. Bill Billing
Dr. Robert Chew
Ms. Jean Lyons

Meeting Objectives: To clarify issues surrounding the pharmacology review of the pediatric clinical data.

Executive Summary:

This telecon is a follow up to a telephone conversation between Dr. Gobburu, Dr. Mishina and J. Lyons on February 25, 2002 concerning the above. Dr. Mishina had previously asked to know which patients were stratified by visit and dose for the first two weeks of the PATH-1 study. On February 25th, Dr. Gobburu further clarified that the reason for the above request was the FDA's need for the name of the variable and the name of the data sets for those patients on the 2.5 mg regimen and those patients titrated to the 5 mg dose. A telecon was arranged between the FDA and Pfizer statisticians to further discuss the question. During the telecon, Dr. Gobburu stated that they were trying to identify the patients who received the 5mg dose during the second two weeks of the study.

Specific Issues Discussed:

- specific file labeled as "raw test drug" contains variables identified as "A/B/C/D"
- these variables contain the descriptor for each of the four patient groups
- how does one match the corresponding letter with its respective patient group?
- a search of the PGRD database enabled Pfizer to identify the groups as follows: "A" are the patients who took the 2.5 mg dose for the first 4 weeks (Phase I of the study) and the 2.5 mg dose for the second 4 weeks (Phase II of the study)

"B" are those patients who took the 2.5 mg dose for the first 4 weeks (Phase I of the study) and a placebo for the second 4 weeks (Phase II of the study)
"C" are the patients who took the 2.5 mg dose for the first 2 weeks and then were given the 5 mg dose for the second 2 week period. They remained on the 5 mg dose for the last 4 weeks of the study (Phase II of the study)
"D" are the patients who took the 2.5 mg dose for the first 2 weeks and then were given the 5 mg dose for the second 2 week period. They were then switched to placebo for the last 4 weeks of the study (Phase II of the study)

Decisions Reached:
Pfizer will forward a set of descriptors to the FDA to help them identify these variables from the data sets previously provided to them.

2/26/02

Lyons, Jean

ım:	Lyons, Jean
ɜnt:	Tuesday, February 26, 2002 3:05 PM
ʻo:	'Dr. Jogarao Gobburu'; 'Dr. Elena Mishina'
Cc:	'Colleen LoCicero'; Audet, Craig; Cropp, Anne B; Award, Pamela L; Billing, Bill; Chew, Robert D; Feldman, Felicia; PPG Regulatory Library Support; Parker, Jim (NYC)
Subject:	FW: Randomization Groups for PATH 1
Importance:	High

Dear Drs. Gobburu and Mishina,

Below is the information promised to you this morning during our telecon. We trust that it will be suitable for your requirements.
I have also attached a copy of the minutes from this morning's discussions. We believe that the minutes capture the essence of our dialogue. However, please advise us if you have any comments/corrections to these minutes.

Thank you very much for giving us the opportunity to address your questions.

Best regards,

Jean

Pediatric telecon minutes2-26-...

Original Message----

m:	Award, Pamela L
ɔent:	Tuesday, February 26, 2002 11:34 AM
To:	Lyons, Jean
Cc:	Chew, Robert D
Subject:	Randomization Groups for PATH 1

Jean,

Two easy ways to identify the patients who received 2.5 mg for 2 weeks then 5 mg for 2 weeks during phase 1 are summarized below.

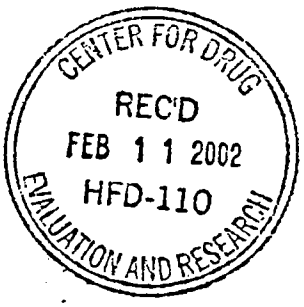
In testdrgj.xpt, patients who received 2.5 mg for 2 weeks then 5 mg for 2 weeks during phase 1 can be distinguished by DRGGROUP = C or D (or RANDTEXT = "Amlodipine 5.0 mg/5.0 mg" or "Amlodipine 5.0 mg/Placebo", respectively.) This information can be merged onto other datasets as needed.

In efficacy.xpt, patients who received 2.5 mg for 2 weeks then 5 mg for 2 weeks can be distinguished by P1TRT = 5.0 (This equates to randomized drug groups of C or D, as above).

Thanks,
Pam.
MS 6025-A4173
Office A4173
^60)732-5928

ORIGINAL

Pfizer Inc
235 East 42nd Street 150/7/13
New York, NY 10017
Tel 212 733 5999 Fax 212 857 3558
Email jean.lyons@pfizer.com



Pfizer Pharmaceuticals Group

Jean Lyons, MS
Director
Worldwide Regulatory Strategy

February 11, 2002

SUPPLEMENT AMENDMENT
SE5-030
(BB)

Raymond Lipicky, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
1451 Rockville Pike
Rockville, MD 20852

Re: Norvasc (amlodipine besylate) Tablets, NDA #19-787/S-030
Response to FDA Question of January 11, 2002.

Dear Dr. Lipicky,

Please refer to our supplemental new drug application (NDA) dated September 14, 2001, for pediatric exclusivity determination. Also, please refer to a telephone request from Dr. Elena Mecina on January 11, 2002. This letter contains our response to the question raised by Dr. Mecina.

FDA Request 1/11/02:

Dr. Mecina would like to see time/dose/plasma concentrations as they relate to the ABPM data for the PATH-2 study (protocol A0531023).

Pfizer Response:

The PATH-2 study (protocol A0531023) was not designed to permit the correlation of ABPM readings with doses so it is not possible to relate the time/dose/plasma concentrations with the ABPM data. ABPM data was collected for 17 subjects in the PATH-2 study. Pfizer has extracted this data and compiled it into one Excel file "TAMBP_FDA-2-11-02". This should help to determine how many ABPM reports were performed around the time of PK sampling. Another Excel file (AMBP_PID-2-11-02) contains the patient ID numbers.

Both of these files are provided electronically on the enclosed diskette (2 diskettes provided). These files are 211 kb in size. The diskettes have been scanned using a virus scan program: McAfee VirusScan w/ SP v4.5.0.534 and are virus-free.

Thank you for the opportunity to address your concerns. Please let us know if you have any additional questions. Please include this information in the subject file.

Sincerely,

Jean Lyons

Director, Regulatory Affairs

Cc: Dr. E. Mecina

Ms. C. LoCicero

Appears This Way
On Original

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

Transmitted to FAX Number:	(212) 857-3558
Attention:	Jean Lyons
Company Name:	Pfizer
Phone:	(212) 573-5999
Subject:	teleconference minutes
Date:	1-15-02
Pages including this sheet:	3
From:	**Colleen LoCicero**
Phone:	**301-594-5332**
Fax:	**301-594-5494**

Dear Jean,

The minutes of our December 19, 2001 teleconference regarding NDA 19-787/S-030 accompany this cover sheet. You are responsible for notifying us of any significant differences in understanding you may have regarding the teleconference outcomes (as reflected in the minutes). Please let me know that you received this fax.

Regards,
Colleen

Minutes of a teleconference

Date of teleconference:	December 19, 2001
Application:	NDA 19-787/S-030
Product:	Norvasc (amlodipine besylate) Tablets
Sponsor:	Pfizer
Purpose:	follow up to request for SAS programs
Teleconference Chair:	James Hung, Ph.D.
Teleconference Recorder:	Colleen LoCicero
Participants:	
FDA	
Jasmine Choi, Ph.D.	Statistician, Division of Biometrics I (HFD-710)
James Hung, Ph.D.	Team Leader, Statistical, HFD-710
Norman Stockbridge, M.D., Ph.D.	Team Leader, Medical, Division of Cardio-Renal Drug Products (HFD-110)
Colleen LoCicero	Regulatory Health Project Manager, HFD-110
Pfizer	
Pamela L. Award, M.S.	Programmer
Robert D. Chew, Ph.D.	Senior Associate Director of Biometrics
Anne B. Cropp, Pharm. D.	Director-Global Team Leader
John R. Haney	Project Manager
Jean Lyons, M.S.	Director, Worldwide Regulatory Strategy

Background

The Sponsor requested this teleconference following a request from the reviewing statistician for the SAS program for the data submitted in support of this pediatric supplemental application.

The teleconference

The Sponsor will be able to provide the SAS program used for the final blood pressure datasets. FDA will have to modify this in order to view it on our system, but this is acceptable provided we can see how and from where the variables were derived. It appears that what Pfizer is proposing will accommodate this.

The Agency explained that the problem is that for race, for example, it appears there were greater than three categories. The same is true for etiologies of hypertension. If this is the case, we need to know these categories so that we can reproduce the Sponsor's analysis. The Sponsor noted that there were not enough subjects in some of the races and etiologies, so these races/etiologies were collapsed together.

The Sponsor agreed to provide the SAS program by mid-January. They agreed to submit another full dataset with the results of the algorithm. If once the Agency receives the submission, we determine it does not meet our needs, another teleconference may be necessary. It will be acceptable for the Sponsor to provide the program on a CD-ROM.

Signature, Teleconference Recorder:_____Colleen LoCicero

Concurrence, Teleconference Chair:_____James Hung, Ph.D.

drafted: January 7, 2002 finaled: January 11, 2002

rd:
J Choi/1/9/02
J Hung/1/9/02
N Stockbridge/1/9/02

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

/s/

Colleen LoCicero
1/15/02 03:35:56 PM
These final minutes were signed by Dr. Hung and faxed to the Sponsor on 1/15/02.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-787/S-030

Pfizer Inc
Attention: Ms. Rita A. Wittich
235 East 42nd Street
New York, NY 10017

Dear Ms. Wittich

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

Name of Drug Product: Norvasc (amlodipine besylate) Tablets

NDA Number: 19-787

Supplement number: S-030

Date of supplement: September 14, 2001

Date of receipt: September 17. 2001

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on November 16, 2001 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please call:

Mr. John Guzman
Regulatory Project Manager
(301) 594-5312

Sincerely yours,

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-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/

Natalia Morgenstern
9/26/01 03:28:49 PM

Douglas C. Throckmorton, M.D.
Division of Cardio-Renal Drug Products, HFD-110

Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
Tel (301) 594-5365, FAX (301) 594-5494

Memorandum

DATE: 7.11.02

FROM: Douglas C. Throckmorton, M.D., Director
Division of Cardio-Renal Drug Products (DCRDP), HFD-110

SUBJECT: Amlodipine Pediatric Labeling
NAME OF DRUG: Amlodipine Besylate (Norvasc)
NDA: 19-787/ SE5-030

SUMMARY
This memorandum is intended to summarize the Divisional views on the Amlodipine pediatric supplement, which is approvable based on the reviews summarized below. The only outstanding issues relate to agreement on the language to be included in the Norvasc labeling. Labeling issues primarily relate to the description of the magnitude of the antihypertensive effect, which is difficult to quantify from the studies, and the description of the pharmacokinetic data in the children <6 years of age.

DOCUMENTS USED FOR MEMO:

1. Approved labeling for Norvasc (Amlodipine Besylate).
2. Sponsor's proposed pediatric labeling for Norvasc.
3. Statistical Review of Norvasc Pediatrics supplement, NDA 19-787, by Jasmine Choi, M.S., dated 5.15.2002.
4. Medical Review of Norvasc Pediatrics supplement, NDA 19-787, by Norman Stockbridge, M.D., Ph.D., dated 11.6.01.
5. Clinical Pharmacology and Biopharmaceutics Review of Norvasc Pediatrics supplement by Elena V. Mishina, Ph.D., dated 4.10.02.
6. Pediatric Written Request initially issued 1.21.2000.

BACKGROUND
The sponsor submitted two trials in support of an indication for the use of Norvasc in children with hypertension:

- PATH-1 (study A0531018), a randomized, double-blind, placebo controlled, parallel-group study in children aged <17 years old.
- PATH-2 (study A0531023), a randomized, open-label study in 70 subjects aged 6 months to 17 years currently on amlodipine.

The sponsors also submitted the published results from 22 additional studies using amlodipine in the treatment of pediatric hypertension. No systematic evaluation of safety or efficacy from these trials or from unpublished sources was conducted.

AMLODIPINE PEDIATRIC TRIAL REVIEWS
Details of the review of these trial are to be found in the review by Drs. Stockbridge, Choi and Mishina. The sections will highlight relevant findings from these reviews. Pediatric Exclusivity was granted to the sponsor based on the submitted trials on 11.27.01.

ANTI-HYPERTENSIVE EFFICACY

I won't summarize the findings from the clinical and statistical reviewers in detail. The following can be drawn from their reviews

1) Amlodipine lowers blood pressure in the population studied at doses of 2.5 mg (unadjusted p-Value around 0.05) and 5.0 mg (p-Value <0.01). Dr. Stockbridge is correct in his observation that the exact magnitude of the mean effect of amlodipine cannot be gauged, given the large reduction in BP from baseline that occurred in both treatment arms and the shortened period of time of follow-up during the withdrawal period. There is a significant influence of gender on the antihypertensive efficacy of amlodipine in children, with the observed reduction in both systolic and diastolic blood pressure in females significantly larger than the reduction in males. This interaction, when modeled by Dr. Choi, was significant for diastolic but not systolic BP. By contrast, race had no significant influence on the derived linear model for changes in systolic or diastolic BP (see Dr. Mishina's review, tables 5 and 11).

2) The Biopharmaceutics reviewer (Dr. Mishina) was able to derive a PK/PD relationship between serum concentration of amlodipine and the mean change in both systolic and diastolic BP, based on the data from study A0531023, further supporting the efficacy of amlodipine in this population.

3) The pharmacokinetics of amlodipine in children >6 years old was quite similar to that of adults. Too few children <6 years of age (11 total) were studied to characterize the pharmacokinetics of amlodipine in this population (which was also not studied in the clinical trial) (see Dr. Mishina's review, pages 3 and 30). As a result, inadequate information is available regarding the effects of amlodipine in these children to inform labeling.

SAFETY

The medical reviewer, Dr. Stockbridge, concluded that there no new safety concerns were identified in the pediatric population relative to the adult population where amlodipine has been used extensively. This conclusion was based on the data from the two clinical trials (PATH-1 and PATH-2) as well as a review of the 22 papers cited by the sponsor and reviewed by Dr. Stockbridge.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

The Biopharmaceutics review by Dr. Mishina is to be referred to for details. Relevant aspects of the pharmacokinetics and the PK/PD modeling performed by Dr. Mishina is included in the Efficacy section above. While Dr. Stockbridge's review concluded that the population <6 years of age had a lower overall clearance rate (approximately 50%) this conclusion was not shared by Dr. Mishina.

CHEMISTRY, PHARMACOLOGY/TOXICOLOGY

There are no issues related to chemistry or pharmacology/ toxicology. The study drug used in the trials was the commercially available 2.5 and 5 mg tablets or matching placebos.

CONCLUSIONS

The antihypertensive efficacy of amlodipine in the pediatric population >6 years of age is adequately demonstrated by the two trials submitted by the sponsor. There are three issues pertinent to the labeling of amlodipine for pediatrics.

Proposed pediatric indication for amlodipine

The sponsor has proposed an indication for the treatment of pediatric hypertension. While the response to amlodipine and other antihypertensives has been somewhat different for pediatric populations when compared with adults, it remains true that the mechanisms of hypertension remain similar in the two populations. The Divisional has not awarded novel indications for new populations when they are studied (*e.g.*, Class II CHF when an existing indication exists for Class IV CHF). Instead, the trial results have been included in the appropriate place in labeling. This is the approach to be taken in this case, as proposed by Dr. Stockbridge.

Inclusion of PK language for children < 6 years of age

In the absence of any clinical data demonstrating the antihypertensive efficacy of amlodipine in children <6 years old, I believe the decision to include this information should be based on two principles: other available data from the trials or other sources regarding antihypertensive efficacy in children <6, and the adequacy of the pharmacokinetic of the drug have been adequately characterized in the children <6. The latter piece is of particular importance if the drug is excreted by the kidneys, as children <1 year of age have significantly different renal function than older children and adults due to incomplete renal maturation. If either piece is missing, the labeling should be silent about the observed pharmacokinetic data. In this case, the inclusion of only 11 children < 6 years of age severely limits the precision of the pharmacokinetic assessment in children <6 years of age, and even though the drug is not renally excreted, these data are of insufficient quality to include in labeling.

Description of the antihypertensive effect of amlodipine

Dr. Stockbridge has proposed language describing the antihypertensive effects of amlodipine observed in study A0531018. This language strikes an appropriate balance between the lack of precise data as to the numerical mean for the antihypertensive effect and the observed dose-dependent effects of amlodipine. That language should be incorporated into labeling. Despite the sponsor's observations regarding the apparent interaction between gender and BP effect for diastolic, the absence of a significant effect with regard to systolic BP in Dr. Choi's review makes this observation suspect and no mention of it in labeling is appropriate.

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/s/

Doug Throckmorton
7/11/02 02:05:04 PM
MEDICAL OFFICER

OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST

NDA: 19-787/S-030 Drug: Norvasc (amlodipine besylate) Tablet 2.5, 5, and 10 mg

Applicant: Pfizer Incorporated Other Type: SE5

CSO/PM: Denise M. Hinton Phone: (301) 594-5312 HFD-110

USER FEE GOAL DATE: July 17, 2002 DATE CHECKLIST COMPLETED: July 2, 2002

Arrange package in the following order (include a completed copy of this CHECKLIST):

		Check or Comment
1.	ACTION LETTER with supervisory signatures Are there any Phase 4 commitments?	Approvable No
2.	Have all disciplines completed their reviews? If no, what reviews are still in draft?	Yes
3.	LABELING (package insert and carton and container labels). (If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.)	Draft
4.	Package inserts of the last 3 drugs approved that are of similar pharmacologic class.	Yes
5.	CLINICAL INVESTIGATOR FINANCIAL DISCLOSURE. (See Medical Review)	Yes
6.	PATENT INFORMATION	N/A
7.	EXCLUSIVITY CHECKLIST	Yes
8.	PEDIATRIC PAGE (all NDAs)	Yes
9.	DEBARMENT CERTIFICATION (Copy of applicant's certification [all NDAs submitted after 1992]).	Yes
10.	Statement on status of DSI's AUDIT OF MAJOR CLINICAL STUDIES If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status. If no audits were requested, include a memo explaining why.	N/A
11.	REVIEWS [If more than 1 review for any 1 discipline, separate reviews with a sheet of: colored paper. Any conflicts between reviews must have resolution documented.]:	
	DIVISION DIRECTOR'S MEMO	July 11, 2002
	GROUP LEADER'S MEMO	N/A
	MEDICAL REVIEW Norman Stockbridge, Ph.D.	6Nov01

	SAFETY UPDATE REVIEW	N/A	
	STATISTICAL REVIEW	Jasmine Chois, M.S.	15May02
	BIOPHARMACEUTICS REVIEW	Elena Mishina, Ph.D.	10Apr02
	PHARMACOLOGY REVIEW (include pertinent IND reviews)		N/A
	Statistical Review of Carcinogenicity Study(ies)		N/A
	CAC Report/Minutes		N/A
	CHEMISTRY REVIEW	(no chemistry issues)	N/A
	Labeling and Nomenclature Committee Review Memorandum		N/A
	Date EER completed (attach signed form or CIRTS printout)		N/A
	FUR needed	FUR requested	N/A
	Have methods been validated?		N/A
	Environmental Assessment Exclusion?		N/A
	If no exclusion, Review/FONSI		
	MICROBIOLOGY REVIEW		
	What is the status of the monograph?		N/A
12.	CORRESPONDENCE and FAXes		Yes
13.	Minutes of Meetings including Telecons and Memoranda		Yes
	Date of End-of-Phase 2 Meeting		N/A
	Date of pre-IND Meeting		N/A
14.	ADVISORY COMMITTEE MEETING MINUTES Minutes		N/A
15.	FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS		
16.	If approval letter, has ADVERTISING MATERIAL been reviewed? An approvable letter has been drafted.		N/A
17.	INTEGRATED SUMMARY OF EFFECTIVENESS (from NDA)		N/A
18.	INTEGRATED SUMMARY OF SAFETY (from NDA)		N/A

RHPM Review of Draft Labeling

Application:	NDAs 19-787/S-030 Norvasc (amlodipine besylate) Tablets 2.5, 5, and 10 mg
Applicant:	Pfizer, Inc.
Document date	October 3, 2003
Receipt date:	October 8, 2003

Background:
On September 14, 2001, Pfizer submitted a supplemental application that provided data from two pediatric studies, submitted in fulfillment of a Written Request from the Agency dated November 2, 1999.

Following the issuance of the approvable letter, the Sponsor submitted draft labeling dated March 21, 2003, which provided for changes in the **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, PRECAUTIONS** and **DOSAGE AND ADMINISTRATION** sections of the labeling.

Electronic final printed labeling dated October 3, 2003 was sent in response to the Division's July 17, 2002 approvable letter and the July 30, 2003 general correspondence letter, which stated that the application was approvable, provided the Sponsor submit final printed labeling revised to reflect the changes listed in the letter.

This supplemental new drug application provided for revised electronic final printed labeling with the following changes:

1. The **CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism, Pediatric Patients** subsection reads as follows:

   Pediatric Patients: Sixty-two hypertensive patients aged greater than 6 years received doses of NORVASC between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

2. Under **CLINICAL PHARMACOLOGY, Effects in Hypertension,**

   a) The first paragraph was placed under the heading "*Adult Patients*".

   b) The **Adolescents and Pediatric Patients Ages 6 to 17 years** subsection was retitled and changed as follows:

   Pediatric Patients: Two-hundred sixty-eight hypertensive patients aged 6 to 17 years were randomized first to NORVASC 2.5 or 5 mg once daily for 4 weeks and then randomized again to the same dose or to placebo for another 4 weeks. Patients receiving 5 mg at the end of 8 weeks had lower

blood pressure than those secondarily randomized to placebo. The magnitude of the treatment effect is difficult to interpret, but it is probably less than 5 mmHg systolic on the 5 mg dose. Adverse events were similar to those seen in adults.

3. The following statement proposed under **INDICATIONS AND USAGE, Hypertension** was deleted:

[redacted]

4. The **PRECAUTIONS, Pediatric Use** reads as follows:

   The effect of Norvasc on blood pressure in patients less than 6 years of age is not known.

5. The **DOSAGE AND ADMINISTRATION, Children** reads as follows:

   The effective antihypertensive oral dose in pediatric patients ages 6-17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients. See **CLINICAL PHARMACOLOGY.**

Evaluation:
I reviewed the October 3, 2003 electronically submitted final printed package insert in its entirety and compared it to the last approved labeling dated May 28, 2002. The Sponsor has revised the label as recommended in the July 30, 2003 letter, excepting the change to the **PRECAUTIONS, Pediatric Use** subsection. The Sponsor has replaced the word [redacted]: as previously agreed upon with the Division.

Action:
An approval letter for this supplement as set forth under 21 CFR 314.70 (a) will be drafted for Dr. Throckmorton's signature.

[redacted]
Ms. Denise M. Hinton
Regulatory Health Project Manager

RHPM Review of Draft Labeling

Application: NDA 19-787/SE5-030
Norvasc (amlodipine besylate) Tablets
2.5, 5, and 10 mg

Applicant: Pfizer, Inc.

Document date March 21, 2003

Receipt date: March 25, 2003

Background: On September 14, 2001, Pfizer submitted a supplemental application which provided data from two pediatric studies, submitted in fulfillment of a Written Request from the Agency dated November 2, 1999.

Based on results of the studies conducted in pediatric patients, the sponsor proposed revisions in the **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, PRECAUTIONS** and **DOSAGE AND ADMINISTRATION** sections of the labeling. On July 17, 2002 we sent an approvable letter indicating that the supplement could be approved once Pfizer submitted final printed labeling with the revisions recommended by the Division.

On March 21, 2003 Pfizer submitted a proposed package insert with the Division's recommendations and one proposal to delete the text [redacted] from the **CLINICAL PHARMACOLOGY, Effects in Hypertension/Pediatric Patients** subsection. In a telephone conversation between Dr. Stockbridge and Alexandra Pearce on April 22, 2003, Dr. Stockbridge agreed with the proposed change to allow the deletion of that text and also to allow the word [redacted] be changed to [redacted] to be consistent with the current approved label.

Review: The sponsor has submitted labeling revised as follows:

1. **CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism, Pediatric** subsection was revised to read as follows:

[redacted]

2. Under **CLINICAL PHARMACOLOGY, Effects in Hypertension,**

a) The first paragraph was placed under the heading "*Adult Patients*".

[redacted]

Pediatric Patients: Two-hundred sixty-eight hypertensive patients aged 6 to 17 years were randomized first to amlodipine 2.5 or 5 mg once daily for 4 weeks and then randomized again to the same dose or to placebo for another 4 weeks. Patients receiving 5 mg at the end of 8 weeks had a lower blood pressure than those secondarily randomized to placebo. The magnitude of the treatment effect is difficult to interpret, but it is probably less than 5 mmHg systolic on the 5 mg dose. Adverse events were similar to those seen in adults.

3. Under **INDICATIONS AND USAGE, Hypertension**, the following text was deleted:

[redacted]

4. **PRECAUTIONS, Pediatric Use** subsection was revised to read as follows:

[redacted]

5. The **DOSAGE AND ADMINISTRATION**, **Children** was revised to read as follows:

The effective antihypertensive oral dose in pediatric patients ages 6-17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients. See **CLINICAL PHARMACOLOGY**.

Comments and recommendation: Pfizer has made the changes as recommended in the July 17, 2002 Approvable Letter. Their proposed changes are acceptable. A letter stating acceptance of the proposed draft package insert will be drafted for Dr. Throckmorton's signature.

Ms. Denise M. Hinton
Regulatory Health Project Manager

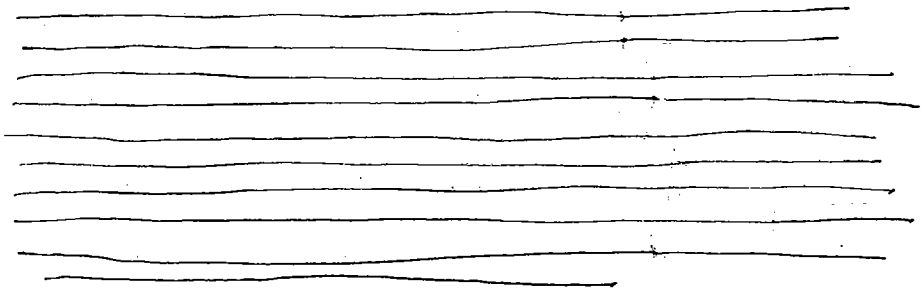
RHPM Review of Draft Labeling

Application:	NDA 19-787/SE5-030 Norvasc (amlodipine besylate) Tablets 2.5, 5, and 10 mg
Applicant:	Pfizer, Inc.
Document date	September 14, 2001
Receipt date:	September 17, 2001

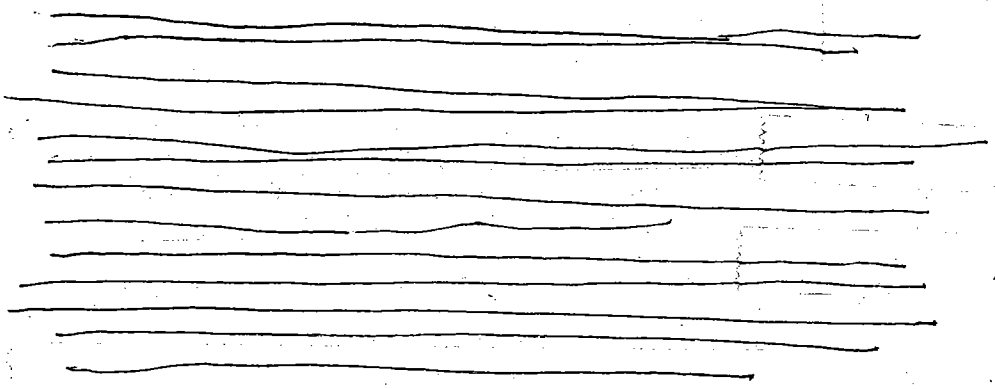
Background: This supplemental application provides data from two pediatric studies, submitted in fulfillment of a Written Request from the Agency dated November 2, 1999. Based on results of the studies conducted in pediatric patients, the sponsor proposes revisions in the **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, PRECAUTIONS** and **DOSAGE AND ADMINISTRATION** sections of the labeling.

Review: The sponsor has submitted draft labeling revised as follows:

1. Under **CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism,** the following subsection has been added:



2. Under **CLINICAL PHARMACOLOGY, Effects in Hypertension**, the following subsection has been added:



3. Under **INDICATIONS AND USAGE, Hypertension**, the following has been added:

Comments/Recommendations: An approvable letter will be drafted for Dr. Throckmorton's signature.

Ms. Denise M. Hinton
Regulatory Health Project Manager

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

/s/

Denise Hinton
7/17/02 02:32:48 PM
CSO

Denise Hinton
7/17/02 02:35:26 PM
CSO

4. Under **PRECAUTIONS,** the **Pediatric Use** subsection has been changed from: Safety and effectiveness of NORVASC in children have not been established.

   to:

   Data establishing efficacy in pediatric patients less than 6 years of age are unavailable. (See Clinical Pharmacology).

5. Under **DOSAGE AND ADMINISTRATION,** the following subsection has been added:

   Children:
   The effective antihypertensive oral dose in pediatric patients ages 6-17 years is 2.5 mg to 5 mg once daily. Doses in excess of 5 mg daily have not been studied in pediatric patients. See CLINICAL PHARMACOLOGY, Clinical Pharmacology in Pediatric Patients.

The medical reviewer recommended the following changes:

1. **CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism,** Pediatric subsection should read as follows:

   Pediatric Patients: [redacted] hypertensive patients aged greater than 6 years received [redacted] doses of [redacted] between 1.25 mg and 20 mg. Weight-adjusted clearance and volume of distribution were similar to values in adults.

2. Under **CLINICAL PHARMACOLOGY, Effects in Hypertension,**

   a) The first paragraph should be placed under the heading "*Adult Patients*".

   b) The **Adolescents and Pediatric Patients Ages 6 to 17** years subsection should be retitled and changed as follows:

   Pediatric Patients: Two-hundred sixty-eight hypertensive patients aged 6 to 17 years were randomized first to [redacted] 2.5 or 5 mg once daily for 4 weeks and then randomized again to the same dose or to placebo for another 4 weeks. Patients receiving 5 mg at the end of 8 weeks had a lower blood pressure than those secondarily randomized to placebo. [redacted] the magnitude of the treatment effect is difficult to interpret, but it is probably less than 5 mmHg systolic on the 5 mg dose. Adverse events were similar to those seen in adults.

3. Under **INDICATIONS AND USAGE,** delete the [redacted]

4. **PRECAUTIONS, Pediatric Use** subsection should read as follows:

   [redacted]

The Biopharmaceutics reviewer suggested the following minor modifications to the **CLINICAL PHARMACOLOGY** section of the labeling:

13 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

X § 552(b)(4) Draft Labeling

18 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling