CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-540

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

Amlodipine/Atorvastatin Tablets

Module 1.3.1
Patent Information on any Patent Which Claims the Drug

Module 1.3.1.1 Patent and Exclusivity Information

13. PATENT AND EXCLUSIVITY INFORMATION FOR (CADUET®)

1.	Active Ingredients:	3-Ethyl 5-methyl 2-[(2-aminoethoxy)methyl)]-4-(2-chlorophenyl)-1, 4-dihydro-6-methyl-3, 5-pyridine-dicarboxylate benzenesulfonate; amlodipine besylate; amlodipine; protonated amlodipine; and [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate; [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1): [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoate anion; [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid; atorvastatin calcium; atorvastatin; atorvastatin anion
2.	Strengths:	amlodipine/atorvastatin: 5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, 5 mg/80 mg, 10 mg/10mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg
3.	Tradename:	CADUET™
4.	Dosage Form / Route of Administration:	Tablets / Oral
5.	Application Firm Name:	CP Pharmaceuticals International
6.	NDA Number:	To Be Assigned
7.	Exclusivity Period:	3 years + 6 months (Pediatric)
8.	Applicable Patent Numbers and Expiration Dates:	6,455,574 August 11, 2018 4,572,909 July 31, 2006 4,572,909 January 31, 2007 (Pediatric) 4,879,303 March 25, 2007 4,879,303 September 25, 2007 (Pediatric) 4,681,893 September 24, 2009 4,681,893 March 24, 2010 (Pediatric) 5,273,995 December 28, 2010 5,273,995 June 28, 2011 (Pediatric)

		5,969,156 July 8, 2016 5,969,156 January 8, 2017 (Pediatric) 5,686,104 November 11, 2014 5,686,104 May 11, 2015 (Pediatric) 6,126,971 January 19, 2013 6,126,971 July 19, 2013 (Pediatric)

APPEARS THIS WAY
ON ORIGINAL

U.S. Patent Number: **6,455,574**

Expiration Date: **August 11, 2018**

Type of Patent – Indicate all that apply:

Drug Substance (Active Ingredient): _____Y __X__ N
Drug Product (Composition/Formulation): _____Y __X__ N
Method of Use: __X__ Y _____ N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by the patent:
Hypertension with Dyslipidemia

Name of Patent Owner: **PFIZER INC.**

==========

A. This information should be submitted for each individual patent submitted.

U.S. Patent Number: **4,572,909**

Expiration Date: **July 31, 2006**
January 31, 2007 (Pediatric)

Type of Patent – Indicate all that apply:

Drug Substance (Active Ingredient): __X__ Y _____ N
Drug Product (Composition/Formulation): __X__ Y _____ N
Method of Use: __X__ Y _____ N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by the patent:
Hypertension and/or Angina

Name of Patent Owner: **PFIZER INC.**

==========

A. This information should be submitted for each individual patent submitted.

U.S. Patent Number: **4,879,303**

Expiration Date: **March 25, 2007**
September 25, 2007 (Pediatric)

Type of Patent – Indicate all that apply:

Drug Substance (Active Ingredient): __X__ Y _____ N
Drug Product (Composition/Formulation): __X__ Y _____ N
Method of Use: _____ Y __X__ N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by the patent:

Name of Patent Owner: **PFIZER INC.**

==========

A. This information should be submitted for each individual patent submitted.

U.S. Patent Number: **4,681,893**

Expiration Date: **September 24, 2009**
March 24, 2010 (Pediatric)

Type of Patent – Indicate all that apply:

Drug Substance (Active Ingredient): __X__ Y _____ N
Drug Product (Composition/Formulation): __X__ Y _____ N
Method of Use: __X__ Y _____ N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by the patent:
Dyslipidemia

Name of Patent Owner: **WARNER-LAMBERT COMPANY LLC a wholly-owned subsidiary of PFIZER INC.**

==========

A. This information should be submitted for each individual patent submitted.

U.S. Patent Number: **5,273,995**

Expiration Date: **December 28, 2010**
June 28, 2011 (Pediatric)

Type of Patent – Indicate all that apply:

Drug Substance (Active Ingredient): __X__ Y _____ N
Drug Product (Composition/Formulation): __X__ Y _____ N
Method of Use: __X__ Y _____ N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by the patent:
Dyslipidemia

Name of Patent Owner: **WARNER-LAMBERT COMPANY LLC a wholly-owned subsidiary of PFIZER INC.**

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A. This information should be submitted for each individual patent submitted.

U.S. Patent Number: **5,969,156**

Expiration Date: **July 8, 2016**
January 8, 2017 (Pediatric)

Type of Patent – Indicate all that apply:

Drug Substance (Active Ingredient): __X__ Y _____ N
Drug Product (Composition/Formulation): _____Y __X__ N
Method of Use: _____ Y __X__ N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by the patent:

Name of Patent Owner: **WARNER-LAMBERT COMPANY LLC a wholly-owned subsidiary of PFIZER INC.**

==========

A. This information should be submitted for each individual patent submitted.

U.S. Patent Number: **5,686,104**

Expiration Date: **November 11, 2014**
May 11, 2015 (Pediatric)

Type of Patent – Indicate all that apply:

Drug Substance (Active Ingredient): _____Y __X__ N
Drug Product (Composition/Formulation): __X__ Y _____ N
Method of Use: __X__ Y _____ N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by the patent:
Dyslipidemia

Name of Patent Owner: **WARNER-LAMBERT COMPANY LLC a wholly-owned subsidiary of PFIZER INC.**

==========

A. This information should be submitted for each individual patent submitted.

U.S. Patent Number: **6,126,971**

Expiration Date: **January 19, 2013**
July 19, 2013 (Pediatric)

Type of Patent – Indicate all that apply:

Drug Substance (Active Ingredient): _____Y __X__ N
Drug Product (Composition/Formulation): __X__ Y _____ N
Method of Use: _____ Y __X__ N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by the patent:

Name of Patent Owner: **WARNER-LAMBERT COMPANY LLC a wholly-owned subsidiary of PFIZER INC.**

Amlodipine/Atorvastatin Tablets

Module 1.3.1
Patent Information on any Patent Which Claims the Drug

Module 1.3.1.1 Patent and Exclusivity Information

13. PATENT AND EXCLUSIVITY INFORMATION FOR (CADUET™)

1.	Active Ingredients:	3-Ethyl 5-methyl 2-[(2-aminoethoxy)methyl)]-4-(2-chlorophenyl)-1, 4-dihydro-6-methyl-3, 5-pyridine-dicarboxylate benzenesulfonate; amlodipine besylate; amlodipine; protonated amlodipine; and [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate; [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1); [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoate anion; [R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid; atorvastatin calcium; atorvastatin; atorvastatin anion
2.	Strengths:	amlodipine/atorvastatin: 5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, 5 mg/80 mg, 10 mg/10mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg
3.	Tradename:	CADUET™
4.	Dosage Form / Route of Administration:	Tablets / Oral
5.	Application Firm Name:	CP Pharmaceuticals International
6.	NDA Number:	To Be Assigned
7.	Exclusivity Period:	3 years
8.	Applicable Patent Numbers and Expiration Dates:	6,455,574 August 11, 2018 4,572,909 July 31, 2006 4,572,909 January 31, 2007 (Pediatric) 4,879,303 March 25, 2007 4,879,303 September 25, 2007 (Pediatric) 4,681,893 September 24, 2009 4,681,893 March 24, 2010 (Pediatric) 5,273,995 December 28, 2010 5,273,995 June 28, 2011 (Pediatric) 5,969,156 July 8, 2016 5,969,156 January 8, 2017 (Pediatric) 5,686,104 November 11, 2014 5,686,104 May 11, 2015 (Pediatric) 6,126,971 January 19, 2013 6,126,971 July 19, 2013 (Pediatric)

U.S. Patent Number: **6,455,574**

Expiration Date: **August 11, 2018**

Type of Patent – Indicate all that apply:

Drug Substance (Active Ingredient): _____Y __X__ N
Drug Product (Composition/Formulation): _____Y __X__ N
Method of Use: __X__ Y _____ N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by the patent:
Concomitant Hypertension and Dyslipidemia

Name of Patent Owner: **PFIZER INC.**

A. This information should be submitted for each individual patent submitted.

U.S. Patent Number: **4,572,909**

Expiration Date: **July 31, 2006**
January 31, 2007 (Pediatric)

Type of Patent – Indicate all that apply:

Drug Substance (Active Ingredient): __X__ Y _____ N
Drug Product (Composition/Formulation): __X__ Y _____ N
Method of Use: __X__ Y _____ N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by the patent:
Hypertension and/or Angina

Name of Patent Owner: **PFIZER INC.**

A. This information should be submitted for each individual patent submitted.

U.S. Patent Number: **4,879,303**

Expiration Date: **March 25, 2007**
September 25, 2007 (Pediatric)

Type of Patent – Indicate all that apply:

Drug Substance (Active Ingredient): **X** Y _____ N
Drug Product (Composition/Formulation): **X** Y _____ N
Method of Use: _____ Y **X** N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by the patent:

Name of Patent Owner: **PFIZER INC.**

A. This information should be submitted for each individual patent submitted.

U.S. Patent Number: **4,681,893**

Expiration Date: **September 24, 2009**
March 24, 2010 (Pediatric)

Type of Patent – Indicate all that apply:

Drug Substance (Active Ingredient): **X** Y _____ N
Drug Product (Composition/Formulation): **X** Y _____ N
Method of Use: **X** Y _____ N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by the patent:
Dyslipidemia

Name of Patent Owner: **WARNER-LAMBERT COMPANY LLC a wholly-owned subsidiary of PFIZER INC.**

A. This information should be submitted for each individual patent submitted.

U.S. Patent Number: **5,273,995**

Expiration Date: **December 28, 2010**
June 28, 2011 (Pediatric)

Type of Patent – Indicate all that apply:

Drug Substance (Active Ingredient): __X__ Y _____ N
Drug Product (Composition/Formulation): __X__ Y _____ N
Method of Use: __X__ Y _____ N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by the patent:
Dyslipidemia

Name of Patent Owner: **WARNER-LAMBERT COMPANY LLC a wholly-owned subsidiary of PFIZER INC.**

A. This information should be submitted for each individual patent submitted.

U.S. Patent Number: **5,969,156**

Expiration Date: **July 8, 2016**
January 8, 2017 (Pediatric)

Type of Patent – Indicate all that apply:

Drug Substance (Active Ingredient): __X__ Y _____ N
Drug Product (Composition/Formulation): _____ Y __X__ N
Method of Use: _____ Y __X__ N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by the patent:

Name of Patent Owner: **WARNER-LAMBERT COMPANY LLC a wholly-owned subsidiary of PFIZER INC.**

A. This information should be submitted for each individual patent submitted.

U.S. Patent Number: **5,686,104**

Expiration Date: **November 11, 2014**
May 11, 2015 (Pediatric)

Type of Patent – Indicate all that apply:

Drug Substance (Active Ingredient): _____Y __X__ N
Drug Product (Composition/Formulation): __X__ Y _____ N
Method of Use: __X__ Y _____ N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by the patent:
Dyslipidemia

Name of Patent Owner: **WARNER-LAMBERT COMPANY LLC a wholly-owned subsidiary of PFIZER INC.**

A. This information should be submitted for each individual patent submitted.

U.S. Patent Number: **6,126,971**

Expiration Date: **January 19, 2013**
July 19, 2013 (Pediatric)

Type of Patent – Indicate all that apply:

Drug Substance (Active Ingredient): _____Y __X__ N
Drug Product (Composition/Formulation): __X__ Y _____ N
Method of Use: _____ Y __X__ N

a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by the patent:

Name of Patent Owner: **WARNER-LAMBERT COMPANY LLC a wholly-owned subsidiary of PFIZER INC.**

Module 1.3.1.2 Patent Certification

APPEARS THIS WAY
ON ORIGINAL

14. PATENT CERTIFICATION

The undersigned declares that the above stated United States Patent Numbers 6,455,574; 4,572,909; 4,879,303; 4,681,893; 5,273,995; 5,969,156; 5,686,104; 6,126,971 cover the active ingredient, composition, formulation and/or method of use of CADUET™. This product is the subject of this application for which approval is being sought.

Signed: _____
Jeffrey B. Chasnow

Date: March 13, 2003

Title (optional): Senior Corporate Counsel

Telephone Number (optional): (212) 733-5225

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY for NDA # 21-540

Trade Name: CADUET
Generic Name: amlodipine besylate and atorvastain calcium
Applicant Name: Pfizer, Inc.

Division: HFD-110
Approval Date: January 30, 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 questions about the submission.

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

   b) Is it an effectiveness supplement? YES /___/ NO /X/

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

   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.

      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?

3 years + 6 months (pediatric)

e) Has pediatric exclusivity been granted for this Active Moiety? YES /X/ NO /___/

Pediatric exclusivity was granted for Norvasc and Lipitor.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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 9 (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 /X/ NO /___/

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

NDA # 19-787 Norvasc (amlodipine besylate)

NDA # 20-702 Lipitor (atorvastin calcium)

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 9:**

(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 /___/

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:

Investigation #1, Study #A3841001 AVALON

Investigation #2, Study #A3841003 RESPOND

Investigation #3, Study #A3841009 Pivotal BE Study

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/
Investigation #3	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:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(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/

Investigation #3 YES /___/ NO /X/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(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"):

Investigation #1, Study #A3841001 AVALON

Investigation #2, Study #A3841003 RESPOND

Investigation #3, Study #A3841009 BE Study

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 # 59,585 YES /X/ NO /___/ Explain:

Investigation #2

IND # 59,585 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: _____

Denise M. Hinton
Regulatory Health Project Manager January 27, 2004

Douglas C. Throckmorton, M.D.
Division Director, HFD-110

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Doug Throckmorton
2/3/04 10:04:39 AM

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ON ORIGINAL

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA #: 21-540 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: April 1, 2003 Action Date: February 1, 2004

HFD: 110 Trade and generic names/dosage form: CADUET (amlodipine besylate and atorvastatin calcium)

Applicant: Pfizer Inc. Therapeutic Class: Standard

Indication(s) previously approved: NDA 19-787 Norvasc (Hypertension, angina)
NDA 20-702 Lipitor (Treatment of Hypercholesterolemia)

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

Number of indications for this application(s): 2

Indication #1: Hypertension/angina

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: Both amlodipine besylate and atorvastatin calcium have conducted studies and have been approved for indications in the pediatric population.

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

Comments:

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

This page was completed by:

{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

Attachment A

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

Indication #2: Dyslipidemia

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

X 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: Both amlodipine besylate and atorvastatin calcium have conducted studies and have been approved for indications in the pediatric population.

X 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.

ection 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/Grace Carmouze
revised 10-14-03)

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

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: NDA 19-787
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: /S/ 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

APPEARS THIS WAY
ON ORIGINAL

Module 1.3.6.2 FDA Action on Request for Partial Waiver to 21 CFR 314.55 (Pediatric Use information) for children (children) 1-15 years of age

Pfizer have formally requested a Partial Waiver to 21 CFR 314.55 (Pediatric Use information) for children (children) 1-15 years of age at the time of the pre-NDA meeting (March 12, 2003). The FDA advised that due to the stay on the pediatric rule at this point in time they could not provide advice to sponsors on waiver requests.

Both amlodipine besylate and atorvastatin calcium have conducted studies in the pediatric population. Based on these studies an indication in the pediatric population was approved for atorvastatin and amlodipine is negotiating the addition of information to the amlodipine label on pediatric use. Pediatric information from both atorvastatin and amlodipine labels will be incorporated in the Caduet label.

NDA 21540
Amlodipine/Atorvastatin Tablets

DEBARMENT CERTIFICATION
[FD&C Act 306(k)(l)]

Pfizer hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

N. Tenzell 2/21/03

Signature of Company Representative Date

APPEARS THIS WAY
ON ORIGINAL

RHPM Overview

NDA:	**21-540**
Drug:	**CADUET (amlodipine besylate/atorvastatin calcium) Tablets**
Sponsor:	Pfizer Inc.
Classification:	4S
Date of Application:	March 31, 2003
Date of Receipt:	April 1, 2003
User Fee Goal Date:	February 1, 2004
RHPM Review Date:	January 1 and 30, 2004

Background:
Amlodipine is a calcium channel blocker approved for use in the treatment of hypertension, chronic stable angina, and confirmed or suspected vasospastic angina. Norvasc (amlodipine besylate) was initially approved in 1992 and in 1997 additional safety claims were approved for the administration of amlodipine in patients with moderate to severe congestive heart failure.

Atorvastatin is a synthetic inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, approved for use as an adjunct to diet to reduce elevated total cholesterol, low-density lipoprotein cholesterol, apolipoprotein B, and triglycerides, and to increase high-density lipoprotein cholesterol in patients with primary hypercholesterolemia and mixed dyslipidemia. Approval for Lipitor (atorvastatin calcium) was granted in 2002.

CADUET is a combination product containing both amlodipine and atorvastatin formulated for once daily oral administration in eight respective dose combinations: 5/10, 5/20, 5/40, 5/80, 10/10, 10/20, 10/40 and 10/80 mg. Pfizer is seeking approval to market the eight fixed-dose combination tablets for the treatment of [redacted]

Pfizer plans to use a package insert that combines the essential elements of the current Norvasc and Lipitor inserts.

Review

Medical Review

Reviewer:	Akinwole Williams, M.D. (HFD-110)
Labeling:	See page 73 Of Dr. William's December 5, 2003 review
Conclusion:	Dr. William's recommended that CADUET be approved subject to the [redacted] amlodipine dose combined with atorvastatin and revisions to the label as recommended by the Division.

Statistical Review:

Reviewer:	Jasmine Choi, M.S. (HFD-710)
Labeling:	None
Conclusion:	The studies, AVALON (Phase 3, double-blind, placebo-controlled and open-label phases, randomized, North-America, multi-center study) and RESPOND

(Phase 3. double-blind. placebo-controlled and open-label phases, randomized, open-label multi-national study) were evaluated for safety and efficacy of the dual therapy of atorvastatin calcium and amlodipine besylate in the simultaneous treatment of coexisting hyperlipidemia and hypertension. Ms. Choi concluded that the two studies showed that the combination treatment had the significantly better effect than atorvastatin on hypertension and significantly better effect than amlodipine on hyperlipidemia. Neither amlodipine nor atorvastatin modifies the treatment effect of the other when both are administered in combination.

Chemistry Review

Reviewer: Ramsharan Mittal, Ph.D.

Labeling: The labels and package insert are satisfactory. (See page 106 of the December 22, 2003 review).

Conclusion: The Office of Compliance found all facilities inspected to be adequate. Dr. Mittal recommended approval of the 5 mg amlodipine besylate/atorvastain calcium combinations and recommended an expiration date of 18 months for the CADUET Tablets packaged in container/closure configurations of foil/foil blisters and HDPE bottles of 30 tablets. Further extension of the expiry date and use of additional packaging configuration should be based on the analysis of real time stability data of CADUET Tablets manufactured [redacted] as per the post-approval stability protocol.

Pfizer will have [redacted]

[redacted]

Pharmacology Review:

Reviewer: Charles Resnick, Ph.D.

Labeling: Pfizer used the language from the individual labels of Norvasc and Lipitor for the sections of labeling that address nonclinical evaluations of the toxicity of amlodipine and atorvastatin. Dr. Resnick stated that the labeling was adequate for the CADUET insert subject to minor revisions to the PRECAUTIONS and OVERDOSAGE sections of the label. Dr. Resnick also recommended that Pfizer identify the specific salt form (base, maleate or besylate) used in the studies. See Dr. Resnick's review of labeling dated September 9, 2003.

Conclusion: A formal pharmacology/toxicology review was not conducted, as the sponsor relied on data contained in their NDA's for Norvasc (NDA 19-787) and Lipitor (NDA 20-702) as documentation of safety.

Biopharmaceutics Review:

Reviewer: Atul Bhattaram, Ph.D.

Labeling: See Dr. Bhattaram's review dated December 17, 2003.

Dr. Bhattarum reviewed the pharmacokinetic study at the highest and lowest strengths (5/10 and 10/80) in healthy subjects, food effect study and dissolution study of the CADUET formulation and found them to be acceptable. A biowaiver for the intermediate strengths was granted based on the dissolution data at pH 1.2, 4.5 and 6.8. Dr. Bhattaram recommended that the sponsor change the proposed dissolution media for both ingredients (amlodipine besylate and atorvastatin calcium) to pH 6.8, volume to 900 ml, paddle speed to 75 rpm and specifications to [redacted] in 15 minutes.

[redacted]

Safety Update:	No significant safety concerns identified. See page 61 of Dr. Williams' review dated December 5, 2003.
Patent Information:	Included in package
Pediatric Information:	Studies were conducted and an indication was approved for amlodipine besylate and atorvastatin calcium in the pediatric population. Pediatric information from both atorvastatin and amlodipine labels were incorporated in the CADUET label.
EER:	The overall EER recommendation is acceptable as of January 30, 2004.
DSI:	Inspections conducted at four different sites for Protocol A3841003 were uneventful. Data were acceptable and no follow up was indicated.
Debarrment Certification:	Included in package
ODS Tradename Review:	The Office of Drug Safety, Division of Medication Errors and Technical Support have no objection to the use of the tradename CADUET (see reviews dated April 2 and December 24, 2003).
Labeling:	The Sponsor submitted electronic draft labeling inclusive of the Agency's recommendations on January 16 with a final draft on January 30, 2004. Copies of the revised labeling are included in the action package.
Advisory Committee Meeting:	No meeting held.

Project Manager's Summary:
To my knowledge, there are no issues that may prevent action on this NDA.

Denise M. Hinton
Regulatory Health Project Manager
Division of Cardio-Renal Drug Products, HFD-110

APPEARS THIS WAY
ON ORIGINAL

G

Number of Pages Redacted 124

Draft Labeling
(not releasable,

124 (G)

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) 594-5327, FAX (301) 594-5494

Memorandum

DATE: 2.10.04

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

SUBJECT: NDA 21-540,
NAME OF DRUG: Amlodipine/Atorvastatin (Caduet)
SPONSOR: Pfizer Inc.

DOCUMENTS USED FOR MEMO:

1) Project Management summary by Denise Hinton, dated 1.04.
2) Patent information from section 1.3.1 of submission.
3) DSI Inspection reports, from Robert Shibuya (signed by Sherry George, 11.24.03), Joseph Salewski (11.24.03), and Leslie Bell (12.16.03).
4) Medical Review by A.O. Williams, M.D., Ph.D., dated 12.5.03.
5) Statistical Review by Jasmine Choi, Ph.D., dated 12.17.03.
6) Chemistry Review by Ramsharam Mittal, dated 12.23.03.
7) Clinical Pharmacology and Biopharmaceutics Review, by Atul Bhattaram, Ph.D., dated 11.7.03 and 12.17.03.
8) Pharmacology Review by C.A. Resnick, Ph.D., dated 9.9.03.
9) DMETS review by Tia Harper-Velazquez, Pharm.D., 5.6.03 and 1.8.04.
10) DDMAC review by Andy Haffer, dated 1.6.04.
11) Environmental Assessment by Nancy Sager, dated 12.5.03.
12) Financial Disclosure, module 1.3.5.1, from sponsor.
13) FDA minutes of meetings with sponsor.
14) Email from Michael Johnston regarding hepatic injury in post-marketing use of atorvastatin and amlodipine, dated 1.06.04.

CONCLUSIONS

This memorandum constitutes the Divisional decision of approval for the proposed marketing of the Caduet product. The sponsor is [redacted]

BACKGROUND

This product has been discussed in a number of meetings with the Agency dating back to 1999. The overarching theme of the development was to assure the Agency that there using the two products (amlodipine and atorvastatin) together does not result in an (unanticipated) loss of efficacy for either of the products, as measured by changes in blood pressure and LDL cholesterol.

CHEMISTRY

For the doses to be marketed at this time, no outstanding issues remain. The sponsor is [redacted]

The environmental assessment concluded that the product can be used and disposed of without any expected adverse environmental effects.

The site inspections (conducted on the action date!), found all facilities inspected to be adequate.

PHARMACOLOGY TOXICOLOGY

The Pharmacology reviewer identified a need for greater consistency in the use of the salt forms of amlodipine and atorvastatin in the labeling. In particular, the Carcinogenicity and Teratology sections of amlodipine did not identify the salt form used in the studies. This is relevant as the sections report adverse effects in mgs of drug substance/ kg animal weight. Were individuals interested in better understanding these calculations, it would be necessary to know the salt for used (*e.g.*, maleate, besylate, free base). I also noted that the atorvastatin labeling reported the salt (calcium in this case) more consistently. The sponsor and Dr. Resnick were able to agree on a standard reporting format and the labeling was adjusted accordingly.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

The sponsor submitted a study testing bioequivalence of the Caduet 10/80 and the individual components (amlodipine 10 and atorvastatin 80), protocol Z 3841009. Bioequivalence was demonstrated (see Dr. Bhattaram's review, page 93). They also applied for, and were granted biowaivers for the 5 and 10 mg amlodipine combinations with atorvastatin 10, 20, 40 and 80 mg, based on in vitro dissolution testing (see Dr. Bhattaram's review, page 96-118).

The sponsor has also developed a dissolution methodology, reviewed and found acceptable by Dr. Bhattaram in his submission dated 11.7.03.

MEDICAL/STATISTICAL REVIEW

Efficacy

The sponsor submitted two trials looking at the potential interactions between atorvastatin and amlodipine on blood pressure and on lipid lowering (AVALON and RESPOND). The details of these studies can be found in the relevant reviews. In short, no evidence of such an interaction was found over the range of doses to be marketed (see Dr. Choi's review, table 2 page 5 for the best summary). While differences exist in the changes in BP and LDL lowering within groups (as noted by the Medical Reviewer on page 23 of his review), the totality of the data is quite clear: the use of the two drugs together does not lead to the loss of efficacy for either of the monotherapies (as marked by the changes in the surrogates used for their initial approvals, BP and LDL lowering). The elegant additional analyses by Dr. Choi (for instance, see Figure 1 in her review on page 51) serve to reinforce this conclusion.

The Medical Reviewer correctly points out that these data do not directly inform the potential for an interaction with the angina component of the effects of amlodipine. He questions whether this product should receive the antianginal claims without conducting trials looking for an interaction between the two products on the 6- minute walk test. I do not agree with his concern, primarily because the pharmacodynamic effect that is responsible for the blood pressure lowering and the antianginal activity is the same (*i.e.*, calcium channel blockade). Were this not the case, I would agree that additional trialing is needed. Here, that the pharmacodynamic effects of amlodipine persist when taken in combination with atorvastatin is sufficient to merit both claims.

Safety

The safety of this combination product has been evaluated quite fully by the sponsor, and they should be congratulated on the size of the safety database here. There are, of course, limitations, and rare interactions cannot expect to be seen in a database available prior to approval. The adverse events reported with the combination were the same adverse events reported for one or both of the monotherapies. One set of them merits comment, as the Medical Reviewer has conducted extensive, and somewhat confusing, analyses of them: the changes in LFTs.

Changes in Liver Function Tests

Dr. Williams looked at the change from baseline to last measured LFTs, and has identified a trend towards higher mean values for some (AST, ALT) liver function tests in patients taking the combination when compared with

patients taking either of the two monotherapies (see table 64 in his review for summary). In truth, the comparison is between the combination (atorvastatin and amlodipine) and atorvastatin alone (which is labeled as causing increases in AST/ALT). In this comparison, however, the combination is not worse than the atorvastatin for mean changes in Alk Phos, GGT, or Total Bilirubin, suggesting that the small differences between Caduet and atorvastatin are the play of chance and do not represent any synergism as regards hepatic toxicity. It goes without saying there were no cases of clinical hepatic injury (one patient was discontinued for elevated LFTs). While I cannot find a discussion of it in his review, Dr. Williams was also asked about differences in the incidence of 3X or greater increases in AST or ALT (alone or in association with an increased Total Bilirubin), as such differences might signal a toxicity: apparently, no difference exists in the database. Finally, as summarized on page 61 of his review, the AERS database was examined for evidence of an interaction between the two products and liver injury. As reflected in the email from Michael Johnston, in the Office of Drug Safety, no signal for an interaction resulting in increased numbers of liver injuries is evident in the available postmarketing data.

Dr. Williams has also conducted analyses suggesting that the higher the dose of Caduet have larger mean changes than lower doses. Again, I believe this is relevant only if you conclude that the use of amlodipine is 'enhancing' the labeled effects of atorvastatin on liver enzyme, something I see no evidence for in his review.

To conclude, the available data suggest that the known effects of atorvastatin on the liver, as reflected by small mean changes in liver enzyme levels, are also seen when the drug is taken with amlodipine. No evidence for synergistic effects on the liver, and no evidence for clinical toxicity exists.

SUMMARY

The data demonstrate that taking amlodipine and atorvastatin together does not have a substantial adverse effect on the individual's effects of the two monotherapies. In fact, the studies reveal no evidence for any relevant attenuation of the lipid lowering effects of atorvastatin or the blood pressure lowering effects of amlodipine when the combination is used. The labeling has been agreed to by the Agency and sponsor (see below) and the product can be approved.

LABELING

The critical theme of the labeling for this, and other, so-called 'combinations of convenience' is to emphasize that they are not 'more' than the sum of the two drugs taken separately. The labeling, as agreed to by the Agency and the sponsor, reflects this, focusing the reader on the appropriate sections of the monotherapy labels. Reflecting this principle, the indications section leads with a simple statement that this product is intended for use in patients taking both products, followed by a 'cut and paste' from the relevant monotherapy Indications sections. Also reflecting this principle, the Dosage and Administration section starts with the individual entities before discussing the use of Caduet. As noted by several of the reviewers, including the reviewer from DDMAC, the inclusion of the [redacted] the labeling is not consistent with this principle, and is removed, as is the use of [redacted] ' in the proposed indications section.

As discussed above, some of the sections reflecting animal testing have been updated to mention the salt used for the relevant studies.

The labeling at present is explicit about the inability to use this product when the patient requires the 2.5 mg dose of amlodipine. [redacted] . The sponsor has provided sufficient rationale that the Division of Metabolic and Endocrine Drug Products is satisfied that patients taking the higher dose of atorvastatin combined with the low dose of amlodipine would be taken care of by specialists who would be quite familiar with the use of the individual products.

PEDIATRICS

Both products have pediatric labeling. and the use of combination products like this are not typically appropriate for fragile populations like the children who might require both of these medications. The requirement for pediatric testing is waived.

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

/s/

Doug Throckmorton
2/10/04 10:25:16 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

Amlodipine/Atorvastatin Tablets

Module 1.3.5.1
Financial Disclosure Cover Note

Module 1.3.5.1 Financial Disclosure Cover Note

All three studies identified as covered studies were carried out at the Pfizer Ann Arbor, Michigan Phase 1 unit. There were no independent investigators participating in these studies.

The clinical investigators participating in these studies for this program were all employees of Pfizer Inc. Therefore, as defined in 21 CFR 54.4, certification regarding the financial interests of these investigators is not required.

Information regarding Pfizer efforts to eliminate bias in these studies are described in NDA Module 1.3.5.3.

The studies are:

Protocol A3841007	A Comparative Bioavailability Study of Amlodipine (10 mg)/Atorvastatin (80 mg) Combination Tablet Following a Single Dose Under Fed and Fasted Conditions
Protocol A3841009	A single dose bioequivalence study comparing a 10 mg amlodipine/80 mg atorvastatin combination tablet to coadministration of 10 mg amlodipine and 80 mg atorvastatin tablets.
Protocol A3841010	A Single Dose Bioequivalence Study comparing a 5-mg Amlodipine/10-mg Atorvastatin Combination Tablet to Coadministration of 5-mg Amlodipine and 10-mg Atorvastatin Tablets

Module 1.3.5.2 List of Covered Investigators

Three of the four studies were identified as covered and they were carried out at the Pfizer Ann Arbor, Michigan Phase 1 unit. There were no independent investigators participating in these studies Protocols A3841007, A3841009 and A3841010.

The clinical investigators participating in these studies for this program were all employees of Pfizer Inc. Therefore, as defined in 21 CFR Part 54.4, certification regarding the financial interests of these investigators is not required.

The fourth study, Protocol A0531029, was run by [redacted]. This study is not considered a covered study because as this Phase 1 study will not be relied on to establish that the product is effective or to demonstrate safety. Thus, certification regarding the financial interests of investigators in this study is not required.

Steps Taken to Minimize the Potential for Bias

Protocol # A3841007

Study Title: A Comparative Bioavailability Study of Amlodipine (10 mg)/Atorvastain (80 mg) Combination Tablet Following a Single Dose Under Fed and Fasted Conditions

The above referenced trial was randomized and conducted according to ICH Good Clinical Practices by appropriately qualified investigators at the Pfizer Research Clinic in Ann Arbor, MI. The study protocol was filed to IND-59, 585 and provided for informed consent consistent with the requirements of 21 CFR Part 50. Further, the study protocol was the subject of review and approval by an Institutional Review Board, in accordance with 21 CFR Part 56.

During the course of processing, analyzing and reporting data from clinical trials the Pfizer Development Operations Department applies many procedures designed to ensure that errors are eliminated. Some of these procedures and their results may indicate aberrant data.

Our standard operating procedure is to follow the current ICH Good Clinical Practices. And, we always check the current FDA listing:

"DISQUALIFIED/RESTRICTED/ASSURANCES LIST FOR CLINICAL INVESTIGATORS"
http://www.fda.gov/ora/compliance_ref/bimo/dis_res_assur.htm

Other processes we use to minimize potential bias are as follows:

DATA VALIDATION/QUALITY ASSURANCE

Prior to the initiation of the study the clinical staff received instructions on proper protocol interpretation, specific clinical procedures, drug utilization, proper handling of biological specimens for assay and case report form (CRF) completion. Individuals performing the safety evaluations were determined to be acceptable based on historical performance, qualifications and credentials.

DATA PROCESSING

During the course of processing, analyzing and reporting data from clinical trials the Pfizer Biometrics Department applies procedures designed to ensure that errors are eliminated. Some of these procedures and their results may have identified inconsistent data that was clarified through consultation with the site staff.

Paper CRFs were completed for all subjects ECG data. All other data for all subjects were collected in PIMS (Phase 1 Management System). PIMS is a validated, electronic data capturing system. PIMS data was downloaded into Ann Arbor's Oracle clinical

database, tables were run and data was then transferred into the Groton Oracle database for final reporting. PIMS queries erroneous data as it is entered. The clinical principle investigator signed a 'memo to file' stating that each adverse event and study completion status were reviewed and approved.

Data from paper CRFs were data entered twice into the Oracle clinical and verified against the CRFs. Discrepancies or clarifications were addressed using data clarification forms. All corrections on the CRFs were made in a way as not to obscure the original entry. Corrected data was inserted, initialed and dated by the study site clinical team. The principle investigator attested to the accuracy and completeness of all data by signing the final page of each case report form.

A database of study information was created. The data was checked by Ann Arbor data management team and then transferred to Groton for final reporting. The report of study A3841007 including data listings and all tabular presentations of data derived from the database, were reviewed by data processing, medical and regulatory affairs personnel prior to issue.

DATA ANALYSIS

Assumptions and adequacy of the model were examined to support the validity of the findings.

Steps Taken to Minimize the Potential for Bias

Protocol # AA3841009

Study Title: A Single Dose Bioequivalence Study Comparing a 10 mg Amlodipine/80 mg Atorvastatin Combination Tablet to Coadministration of 10 mg Amlodipine and 80 mg Atorvastatin Tablets

The above referenced trial was randomized and conducted according to ICH Good Clinical Practices by appropriately qualified investigators at the Pfizer Research Clinic in Ann Arbor, MI. The study protocol was filed to IND-59,585 and provided for informed consent consistent with the requirements of 21 CFR Part 50. Further, the study protocol was the subject of review and approval by an Institutional Review Board, in accordance with 21 CFR Part 56.

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During the course of processing, analyzing and reporting data from clinical trials the Pfizer Biometrics Department applies procedures designed to ensure that errors are eliminated. Some of these procedures and their results may have identified inconsistent data that was clarified through consultation with the site staff.

Paper CRFs were completed for all subjects ECG data. All other data for all subjects were collected in PIMS (Phase 1 Management System). PIMS is a validated, electronic

data capturing system. PIMS data was downloaded into Ann Arbor's Oracle clinical database. tables were run and data was then transferred into the Groton Oracle database for final reporting. PIMS queries erroneous data as it is entered. The clinical principle investigator signed a 'memo to file' stating that each adverse event and study completion status were reviewed and approved.

Data from paper CRFs were data entered twice into the Oracle clinical and verified against the CRFs. Discrepancies or clarifications were addressed using data clarification forms. All corrections on the CRFs were made in a way as not to obscure the original entry. Corrected data was inserted, initialed and dated by the study site clinical team. The principle investigator attested to the accuracy and completeness of all data by signing the final page of each case report form.

A database of study information was created. The data was checked by Ann Arbor data management team and then transferred to Groton for final reporting. The report of study A3841009 including data listings and all tabular presentations of data derived from the database, were reviewed by data processing, medical and regulatory affairs personnel prior to issue.

DATA ANALYSIS

Assumptions and adequacy of the model were examined to support the validity of the findings.

Steps Taken to Minimize the Potential for Bias

Protocol # A3841010

Study Title: A Single Dose Bioequivalence Study Comparing a 5 mg Amlodipine/10 mg Atorvastatin Combination Tablet to Coadministration of 5 mg Amlodipine and 10 mg Atorvastatin Tablets

The above referenced trial was randomized and conducted according to ICH Good Clinical Practices by appropriately qualified investigators at the Pfizer Research Clinic in Ann Arbor, MI. The study protocol was filed to IND-59,585 and provided for informed consent consistent with the requirements of 21 CFR Part 50. Further, the study protocol was the subject of review and approval by an Institutional Review Board, in accordance with 21 CFR Part 56.

During the course of processing, analyzing and reporting data from clinical trials the Pfizer Development Operations Department applies many procedures designed to ensure that errors are eliminated. Some of these procedures and their results may indicate aberrant data.

Our standard operating procedure is to follow the current ICH Good Clinical Practices. And, we always check the current FDA listing:

"DISQUALIFIED/RESTRICTED/ASSURANCES LIST FOR CLINICAL INVESTIGATORS"
http://www.fda.gov/ora/compliance_ref/bimo/dis_res_assur.htm

Other processes we use to minimize potential bias are as follows:

DATA VALIDATION/QUALITY ASSURANCE

Prior to the initiation of the study the clinical staff received instructions on proper protocol interpretation, specific clinical procedures, drug utilization, proper handling of biological specimens for assay and case report form (CRF) completion. Individuals performing the safety evaluations were determined to be acceptable based on historical performance, qualifications and credentials.

DATA PROCESSING

During the course of processing, analyzing and reporting data from clinical trials the Pfizer Biometrics Department applies procedures designed to ensure that errors are eliminated. Some of these procedures and their results may have identified inconsistent data that was clarified through consultation with the site staff.

Paper CRFs were completed for all subjects ECG data. All other data for all subjects were collected in PIMS (Phase 1 Management System). PIMS is a validated, electronic

data capturing system. PIMS data was downloaded into Ann Arbor's Oracle clinical database, tables were run and data was then transferred into the Groton Oracle database for final reporting. PIMS queries erroneous data as it is entered. The clinical principle investigator signed a 'memo to file' stating that each adverse event and study completion status were reviewed and approved.

Data from paper CRFs were data entered twice into the Oracle clinical and verified against the CRFs. Discrepancies or clarifications were addressed using data clarification forms. All corrections on the CRFs were made in a way as not to obscure the original entry. Corrected data was inserted, initialed and dated by the study site clinical team. The principle investigator attested to the accuracy and completeness of all data by signing the final page of each case report form.

A database of study information was created. The data was checked by Ann Arbor data management team and then transferred to Groton for final reporting. The report of study A3841010 including data listings and all tabular presentations of data derived from the database, were reviewed by data processing, medical and regulatory affairs personnel prior to issue.

DATA ANALYSIS

Assumptions and adequacy of the model were examined to support the validity of the findings.

Module 1.3.5.5 US FDA Certification Form 3455

Three of the four studies were identified as covered and they were carried out at the Pfizer Ann Arbor, Michigan Phase 1 unit. There were no independent investigators participating in these studies Protocols A3841007, A3841009 and A3841010.

The clinical investigators participating in these studies for this program were all employees of Pfizer Inc. Therefore, as defined in 21 CFR Part 54.4, certification regarding the financial interests of these investigators is not required.

The fourth study, Protocol A0531029, was run by [redacted]. This study is not considered a covered study because as this Phase 1 study will not be relied on to establish that the product is effective or to demonstrate safety. Thus, certification regarding the financial interests of investigators in this study is not required.

MODULE 1.3.5.1 FINANCIAL DISCLOSURE COVER NOTE

There is one covered study for this submission. The covered study was not funded via variable compensation and none of the investigators in either study hold any form of propriety interest in Caduet.

Information regarding Pfizer efforts to eliminate bias in the study is described in NDA Module 1.3.5.3. 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 Module 1.3.5.5).

With a total of 849 investigators listed in the multi-centered study, 32 of the listed investigators had financial information to disclose. Eight of these investigators have equity in Pfizer Inc. and 24 of the investigators received significant payments of other sorts. This information is listed in the 3455 forms in this item.

It is important to note that the investigator list for the study determined by 1572s 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 (NDA Module 1.3.5.2).

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

Protocol # A3841001
Study Title: A Multi-center, randomized, double-blind, placebo-controlled and open-label evaluation of the safety and efficacy of dual therapy with atorvastatin plus amlodipine when compared to either therapy alone in the treatment of patients with simultaneous hyperlipidemia and hypertension (the AVALON Study).

A complete list of all investigators is attached. Each of the individual investigators listed was sent the Financial Disclosure Form directly or via the principal investigator for their site. In addition, if necessary we contacted the site by telephone and/or sent 2 separate follow-up letters to those individuals 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.
It was not possible to obtain a completed Financial Disclosure form for five investigators on protocol A3841001.

Per Form 3454, certification is provided for 817 of the 849 investigators indicating

- Certified investigators (A total of 812 of the 849 investigators are certified as having no Financial Arrangement as defined in 21 CFR 54.2)
- Due diligence in collecting the information on Equity. (A total of 5 of the 849 investigators did not respond or could not be reached by our due diligence effort.)

Note that all investigators are assessed for Equity, Significant Payments of Other Sorts, Variable Compensation, & Propriety Interest. With the exception of Equity, all other financial arrangements are checked via internal Pfizer system.

In the covered study, 32 of the 849 investigators listed had financial information to disclose. One of the 32 investigators disclosed both equity & significant payments of other sorts. A completed Form 3455 is attached for these investigators.
All Independent Grants associated with our investigators are paid directly to the Institution rather than to the individual investigator.

APPEARS THIS WAY
ON ORIGINAL

Module 1.3.5.4 US FDA Certification Form 3454

Three of the four l studies were identified as covered and they were carried out at the Pfizer Ann Arbor, Michigan Phase 1 unit. There were no independent investigators participating in these studies Protocols A3841007, A3841009 and A3841010.

The clinical investigators participating in these studies for this program were all employees of Pfizer Inc. Therefore, as defined in 21 CFR Part 54.4, certification regarding the financial interests of these investigators is not required.

The fourth study, Protocol A0531029, was run by [redacted] This study is not considered a covered study because as this Phase 1 study will not be relied on to establish that the product is effective or to demonstrate safety. Thus, certification regarding the financial interests of investigators in this study is not required.

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 2, 2003

IND NUMBER: 59,585

NAME OF DRUG: **Caduet**
(Amlodipine Besylate and Atorvastatin Calcium Tablets)
5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, 5 mg/80 mg, 10 mg/10 mg, 10 mg/40 mg, and 10 mg/80 mg

IND SPONSOR: Pfizer Pharmaceuticals

I. INTRODUCTION

This consult was written in response to a request from the Division of Cardio-Renal Drug Products, for an assessment of the proprietary name "Caduet" regarding potential name confusion with other proprietary or established drug names. The draft container labels, carton labels, and package insert labeling for Caduet were not submitted for review and comment.

PRODUCT INFORMATION

Caduet is the proposed proprietary name for a combination product consisting of amlodipine besylate and atorvastatin calcium tablets. The amlodipine component of the combination is a calcium ion antagonist and slow-channel blocker, indicated for the treatment of hypertension and/or angina. The atorvastatin calcium component of the combination is an HMG-CoA reductase inhibitor, indicated for the treatment of dyslipidemia. The dosage and administration of the combination product is in accordance with the approved dosage and administration of the individual components, amlodipine and atorvastatin (Norvasc® and Lipitor® respectively). The usual initial dose of Norvasc® is 5 mg once daily with a maximum dose of 10 mg once daily. The recommended starting dose of Lipitor® is 10 mg or 20 mg once daily.

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[i,ii] as well as several FDA databases[iii] for existing drug names which sound alike or look alike to "Caduet" to a degree where potential confusion between drug names could occur under

[i] MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[ii] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[iii] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[iv] and the data provided by Thomson & Thomson's SAEGIS™ Online Service[v] were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

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

1. DDMAC did not have any concerns with Caduet in regard to promotional claims.

2. The Expert Panel identified four medication names that have potential for confusion with Caduet. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual FDA-approved dosage.

[iv] WWW location http://www.uspto.gov.

[v] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

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

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Caduet	**Amlodipine Besylate and Atorvastatin Calcium Tablets 5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, 5 mg/80 mg, 10 mg/10 mg, 10 mg/40 mg, and 10 mg/80 mg**	**One tablet daily.**	
Adalat (Rx)	Nifedipine Capsules 10 mg and 20 mg	10 mg to 20 mg three times a day.	**S/A
Aldomet (Rx)	Methyldopa Tablets: 125 mg, 250 mg, and 500 mg Oral Suspension: 50 mg/mL Injection: 50 mg/mL	Initial: 250 mg two to three times daily in the first 48 hours. Adjust dosage at intervals of ≥ 2 days until an adequate response is achieved. Maintenance: 500 mg to 2 grams daily in two to four divided doses.	**L/A
Caverject (Rx)	Alprostadil Powder for Injection 5 mcg/mL, 10 mcg/mL, 20 mcg/mL, and 40 mcg/mL.	Initial dose is 2.5 mcg. If there is a partial response, the dose may be increased by 2.5 mcg, depending on response. If there is no response, the second dose may be increased to 7.5 mcg, followed by increments of 5 mcg to 10 mcg.	**S/A
Calcet (OTC)	Calcium and Vitamin D Tablets 300 mg/200 IU	Take 2 tablets in the morning and 2 tablets at bedtime. Do not exceed 4 tablets a day.	**L/A

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Caduet with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 105 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Caduet (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

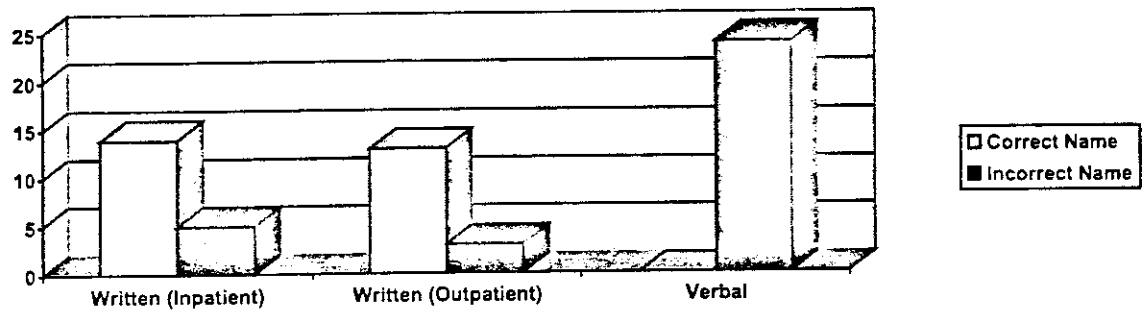
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Caduet 5 mg/20 mg 1 po qd #30	Caduet 5 mg/20 mg, take 1 by mouth daily, dispense #30.
Inpatient RX: Caduet 5mg/20mg 1 po QD	

2. Results:

The results are summarized in Table 2.

Table 2

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%)	Incorrectly Interpreted (%)
Written Inpatient	35	19 (54%)	14 (74%)	5 (26%)
Written Outpatient	31	16 (52%)	13 (81%)	3 (19%)
Verbal	39	24 (62%)	0 (0%)	24 (100%)
Total	105	59 (56%)	27 (46%)	32 (54%)



Among the verbal prescription study participants for Caduet, 24 of 24 (100%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of "Caduet". The incorrect responses were *Gayderet (1), K?? (1), K Duet (1), Kaduet (2), Kaydrel (1), Kayduet (1), Kaydret (1), Kdret (2), Kdurret (1), K-Duet (5), Kduett (1), Kduette (1), K-durect (1), Kduret (1), K-duret (1), and K-Durette (3).* None of the interpretations are similar to a marketed drug product.

Among the written prescription study participants for Caduet, 8 of 35 (23%) of the participants interpreted the name incorrectly. The majority of the responses were misspelled variations of "Caduet". The incorrect responses were *Cadmet (3), Cadnet (2), Cadvet (2), and Caudet (1).* None of the interpretations are similar to a marketed drug product.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Caduet", the primary concerns raised were related to four look-alike and/or sound-alike names that are currently available in the U.S. marketplace: Adalat, Aldomet, Caverject, and Calcet.

We conducted prescription studies to simulate the prescription ordering process. Our study did not confirm confusion between Adalat, Aldomet, Caverject, or Calcet. The majority of the incorrect interpretations of the written and verbal studies were misspelled/phonetic variations of the proposed name, Caduet. However, a negative finding does not discount the potential for name confusion given the limited predictive value of these studies, primarily due to the sample size.

Adalat was identified to have sound-alike potential with the proposed name, Caduet. Adalat contains nifedipine, and is indicated for the treatment of hypertension alone or in combination with other hypertensive agents. Adalat and Caduet have sound-alike similarities in that each name has three syllables, and the beginning of each name differs by only one letter ("Ad" vs. "Cad"). However, the suffix of each is name distinguishable when spoken ("dalat" vs. "duet"). Both drugs share overlapping indications (hypertension), routes of administration (oral), as well as have overlapping numerals in their strengths (10 mg and 20 mg vs. 5 mg/10 mg, 10 mg/10 mg, 10 mg/40 mg, and 10 mg/80 mg). However, Adalat is a single strength product whereas Caduet is a combination drug product with two strengths indicated. Additionally, Adalat and Caduet differ in dosing regimen (three times a day vs. once daily). Despite the similarities, the lack of convincing sound-alike similarities in addition to the differences in dosing regimen, minimize the potential for confusion between the two drugs. Adalat and Caduet will also not be stored in close proximity to one another on pharmacy shelves, further decreasing the potential for confusion between the products.

Aldomet has look-alike similarities to Caduet. Aldomet contains methyldopa, and is indicated for the treatment of hypertension. When scripted (see page 7), each name contains similar looking prefixes ("Ald" vs. "Cad") as well as suffixes ("met" vs. "uet"). Besides the look-alike characteristics, both drugs share overlapping routes of administration (oral), indication (hypertension), and have overlapping numerals in their strengths (500 mg and 50 mg/mL vs. 5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, and 5 mg/80 mg). However, because Caduet will be available in combination strengths, a prescription would need to contain the strength of both active ingredients before it could be dispensed. Therefore, although Aldomet and Caduet share overlapping numerals in their strength, it would not be likely that these products would be confused for each other. The drugs also differ in dosing regimen (2 to 4 times daily vs. once daily). Furthermore, Aldomet and Caduet will not be stored near each other on pharmacy shelves, further decreasing the potential for confusion between the two products.

Aldomet **Caduet**

Caverject was identified to have sound-alike similarities to Caduet. Caverject contains alprostadil, and is indicated for the treatment of erectile dysfunction. Both drugs contain the same number of syllables (three), and the prefixes of each name differ by only letter ("Cav" vs. "Cad"). However, the suffix of each name ("ject" vs. "duet") are distinguishable when pronounced. Caduet is a combination drug product with the strength of each ingredient indicated, there is overlap in the strengths of the two products (5 mcg/mL, 10 mcg/mL, 20 mcg/mL and 40 mcg/mL vs. 5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, 5 mg/80 mg, 10 mg/10 mg, 10 mg/40 mg, and 10 mg/80 mg). Caverject and Caduet differ in dosage form (powder for injection vs. tablet), and route of administration (intracavernous vs. oral). Additionally, Caverject doses are individualized for initially for each patient by careful titration under the supervision by the physician. Therefore, despite the similarities in the sound-alike characteristics of the name and the overlap in strengths, the differences in the dosage form, route of administration, and the increased monitoring process required for optimal Caverject dosing, minimize the risk of confusion between the two products. Also, the use of Caverject is limited to a specific patient population, which further minimizes the risk of confusion.

Calcet has look-alike similarities to Caduet (see below). Calcet is an over-the-counter vitamin supplement containing 300 mg of calcium and 200 international units of Vitamin D. The beginning of each name differ by only one letter ("Cal" vs. "Cad"). Additionally, the ending of each name contains similar upstroke letters ("cet" vs. "uet"). Besides the look-alike similarities, Calcet and Caduet share an overlapping dosage form (tablet) and route of administration (oral). However, the drugs differ in dosing regimen (twice daily vs. once daily). Additionally, Calcet is a single strength product, whereas Caduet is a combination product that will be available in multiple strengths. Also, because Calcet is available over-the-counter, it will not be stored on pharmacy shelves with prescription drug products. While there are similarities in the look-alike characteristics in addition to the overlapping dosage form and route of administration, the differences in the dosing regimen, strengths, and storage location makes the potential for error low between Calcet and Caduet.

Calcet **Caduet**

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

A. Please submit for evaluation.

B. [redacted]

IV. RECOMMENDATIONS

A. DMETS has no objections to the use of the proprietary name "Caduet". Additionally, see Section III above regarding the label and labeling. DMETS decision is tentative. The firm should be notified that this name with its associated labels and labeling must be re-evaluated upon submission of the NDA and 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

B. DDMAC finds the name Caduet acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

Tia M. Harper-Velazquez, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Tia Harper-Velazquez
5/6/03 03:16:59 PM
PHARMACIST

Alina Mahmud
5/6/03 03:18:58 PM
PHARMACIST

Carol Holquist
5/6/03 03:56:51 PM
PHARMACIST

Jerry Phillips
5/8/03 11:15:59 AM
DIRECTOR

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION RESPONSE

Division of Medication Errors and Technical Support
Office of Drug Safety
(DMETS; HFD-420)

DATE RECEIVED: Feb. 18, 2003	DUE DATE: April 18, 2003	ODS CONSULT #: 03-0071

TO: Douglas Throckmorton, MD
Director, Division of Cardio-Renal Drug Products
HFD-110

THROUGH: Denise Hinton
Project Manager
HFD-110

PRODUCT NAME:	SPONSOR: Pfizer Pharmaceuticals
Caduet (Amlodipine Besylate and Atorvastatin Calcium Tablets) 5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, 5 mg/80 mg, 10 mg/10 mg, 10 mg/40 mg, and 10 mg/80 mg IND #: 59,585	

SAFETY EVALUATOR: Tia M. Harper-Velazquez, Pharm.D.

SUMMARY: In response to a consult from the Division of Cardio-Renal Drug Products, the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Caduet" to determine the potential for confusion with approved proprietary and established names as well as pending names.

RECOMMENDATIONS:

1. DMETS has no objection to the use of the proprietary name "Caduet". DMETS decision is tentative. The firm should be notified that this name with its associated labels and labeling must be re-evaluated upon submission of the NDA and 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward.

2. DDMAC finds the name "Caduet" acceptable from a promotional perspective.

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

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Number of Pages Redacted 4

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(H)

CONSULTATION RESPONSE

Division of Medication Errors and Technical Support
Office of Drug Safety
(DMETS; HFD-420)

DATE RECEIVED: Dec. 11, 2003	DUE DATE: Jan 9, 2004	ODS CONSULT #: 03-0071-1

TO: Douglas Throckmorton, MD
Director, Division of Cardio-Renal Drug Products
HFD-110

THROUGH: Denise Hinton
Project Manager
HFD-110

PRODUCT NAME:	SPONSOR: Pfizer Pharmaceuticals
Caduet (Amlodipine Besylate and Atorvastatin Calcium Tablets) 5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, 5 mg/80 mg, 10 mg/10 mg, 10 mg/40 mg, and 10 mg/80 mg NDA #: 21-540	

SAFETY EVALUATOR: Tia M. Harper-Velazquez, Pharm.D.

RECOMMENDATIONS:

1. DMETS has not identified any additional proprietary or established names that have the potential for confusion with Caduet since we conducted our initial review on April 2, 2003, (ODS consult # 03-0071) that would render the name objectionable. Therefore, we have no objections to the use of this proprietary name. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the labeling revisions outlined in Section II of this review to minimize potential errors with the use of this product.

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: December 24, 2003

NDA NUMBER: 21-540

NAME OF DRUG: **Caduet**
(Amlodipine Besylate and Atorvastatin Calcium Tablets)
5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, 5 mg/80 mg, 10 mg/10 mg, 10 mg/40 mg, and 10 mg/80 mg

NDA SPONSOR: Pfizer Pharmaceuticals

I. INTRODUCTION

This consult was written in response to a request from the Division of Cardio-Renal Drug Products, for an re-review of the proprietary name "Caduet" regarding potential name confusion with other proprietary or established drug names. The proposed name "Caduet" was previously reviewed by DMETS and found acceptable (ODS consult # 03-0071, dated April 2, 2003). The container labels, carton and insert labeling for Caduet were provided for review and comment.

PRODUCT INFORMATION

Caduet is the proposed proprietary name for a combination product consisting of amlodipine besylate and atorvastatin calcium tablets. The amlodipine component of the combination is a calcium ion antagonist and slow-channel blocker, indicated for the treatment of [redacted]. The atorvastatin calcium component of the combination is an HMG-CoA reductase inhibitor, indicated for the [redacted] The dosage and administration of the combination product is in accordance with the approved dosage and administration of the individual components, amlodipine and atorvastatin (Norvasc® and Lipitor® respectively). The usual initial dose of Norvasc® is 5 mg once daily with a maximum dose of 10 mg once daily. The recommended starting dose of Lipitor® is 10 mg or 20 mg once daily.

II. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

In review of the container labels, carton and insert labeling of Caduet, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified areas of possible improvement, which might minimize potential user error.

A. BLISTER FOIL LABEL (Professional Samples)

1. We recommend including the [redacted] in the established name.

2. Consider including the product strength on the random foil print size. Currently the strength appears only once on the front side of the random foil. This may be obscured when a prescription label is attached.

3. In order to differentiate strength, please use contrasting colors, boxing or some other means.

B. BLISTER LABEL (Hospital Unit Dose)

See comments A-3.

C. CONTAINER LABELS [redacted] t and 30 count)

1. We recommend including the dosage form "tablets" in the established name.

2. Please remove the [redacted]

3. [redacted] ɔn

4. We note that the [redacted]. Please adjust the colors so that the different strengths are clearly differentiated from one another.

D. CONTAINER LABELS (30 count [redacted]

1. See comments C-1, C-2, and C-4.

2. We note that the labels do not have Child Resistant Closure (CRC). Please adjust accordingly.

E. CARTON LABELING [redacted]

See comments C-1, C-2, and C-4..

F. CARTON LABELING [redacted]

See comments C-1, C-2, and C-4.

G. PACKAGE INSERT LABELING

[redacted]

IV. RECOMMENDATIONS

A. DMETS has not identified any additional proprietary or established names that have the potential for confusion with Caduet since we conducted our initial review on April 2, 2003, (ODS consult # 03-0071) that would render the name objectionable. Therefore, we have no objections to the use of this proprietary name. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document

B. DMETS recommends implementation of the labeling revisions outlined in Section II of this review to minimize potential errors with the use of this product.

DMETS would appreciate feedback of the final outcome of this consult (e.g., copy of revised labels/labeling). We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam at 301-827-3242.

Tia M. Harper-Velazquez, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

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/s/

Tia Harper-Velazquez
1/8/04 12:26:48 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
1/8/04 02:15:19 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
1/8/04 02:22:59 PM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
1/9/04 01:50:35 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-540

Pfizer Inc.
Attention: Ms. Natalie Touzell
235 East 42nd Street
New York, NY 10017

Dear Ms. Touzell:

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

Name of Drug Product: Caduet (amlodipine besylate/ atorvastatin calcium)
5/10, 10/10, 5/20, 10/20, 5/40, 10/40, 5/80, 10/80 mg Tablets.

Review Priority Classification: Standard (S)

Date of Application: March 31, 2003

Date of Receipt: April 1, 2003

Our Reference Number: NDA 21-540

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 31, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be February 1, 2004.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products HFD-110
Attention: Division Document Room, 5002
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: Document Room 5002
1451 Rockville Pike, Woodmont II
Rockville, Maryland 20852

If you have any questions, please call:

Ms. Denise Hinton
Regulatory Project Manager
(301) 594-5333

Sincerely,

{See appended electronic signature page}

Zelda McDonald
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Zelda McDonald
4/14/03 09:57:54 AM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING REVIEW LETTER

NDA 21-540

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

Dear Ms. Wittich:

Please refer to your March 31, 2003 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Caduet (amlodipine besylate/atorvastatin calcium) 5/10, 10/10, 5/20, 10/20, 5/40, 10/40, 5/80 and 10/80 mg Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b)1 of the Act on May 31, 2003 in accordance with 21 CFR 314.101(a).

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

1. Additional comparative dissolution profile data in two other media (pH 1.2, and 4.5) are necessary to support your bio-waiver request. Water may be used as the additional medium. The dissolution profiles should be generated using 12 units/lot of the test, reference products and the same dissolution conditions (i.e., USP II, paddles and rotation speed of 75 rpm). Individual and mean dissolution data, dissolution profiles, and similarity factors (f2) need to be provided.

2. The full report for the RESPOND study has not been submitted. This is highly relevant to understanding the interaction between atorvastatin and amlodipine in a hypertensive/hyperlipidemic population.

3. Outcome data have not been submitted to support the use of amlodipine and atorvastatin as a combination product. While the approval can be based on the pharmacokinetic and pharmacodynamic interactions from the AVALON and RESPOND studies, any additional information relative to the interaction of atorvastatin and amlodipine on clinical events would also be relevant, including information derived from meta-analysis from previous studies.

4. The pharmacodynamic interaction data that you proposed for submission in support of CADUET's approval reflects only the interaction between atorvastatin and amlodipine in a population with hypertension and hyperlipidemia. Data on the use of the combination derived from trials for other currently approved indications for either drug (i.e., angina for amlodipine or familial hyperlipidemias for atorvastatin) have not been submitted in the filing.

We note that the ongoing efficacy and safety study, DUAAL, that will evaluate the effect of the combination of amlodipine and atorvastatin on exercise tolerance in 360 patients with CAD and stable angina pectoris, will add critical additional data to support the anti-anginal claim in the proposed label. Whether such interaction data are needed to support claims for the combination in those disease areas will be a review issue.

5. The current application contains safety information for the combination product or concurrent administration of atorvastatin and amlodipine for the lowest combination (5 mg amlodipine /10 mg atorvastatin) in 207 patients treated for only 8 weeks. This database is considered, on its own, to be inadequate to evaluate the safety of the combination product. Additional safety data from the ongoing RESPOND study is critical for assessment of safety. You need to provide any other available data on the safety of the combination of atorvastatin and amlodipine from previous studies for which patients were randomized to one component and were concurrently treated with the other product.

6. The pharmacodynamic results of the AVALON and RESPOND trials have not been fully incorporated into the clinical pharmacology section of your proposed label.

7. The administration of the combination product, including timing and dosing, has not been described in the proposed label.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

You are encouraged to submit additional materials responding to the above comments and requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, please call:

Ms. Denise M. Hinton
Regulatory Health Project Manager
(301) 594-5333

Sincerely,

{See appended electronic signature page}

Douglas C. Throckmorton, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Doug Throckmorton
6/13/03 03:51:27 PM

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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:	212-573-1563
Attention:	Rita Wittich
Company Name:	Pfizer
Phone:	212-573-7291
Subject:	Minutes of the August 18, 1999 meeting
Date:	9/15/99
Pages including this sheet:	6

From: David Roeder
Phone: 301-594-5313
Fax: 301-594-5494

YOU ARE RESPONSIBLE FOR NOTIFYING US OF ANY SIGNIFICANT DIFFERENCES IN UNDERSTANDING YOU MAY HAVE REGARDING THE MEETING OUTCOMES (AS REFLECTED IN THE MINUTES).

cc: Orig
HFD-110
HFD-110/DRoeder/SMatthews

Minutes of a Meeting between Pfizer, Parke-Davis and the FDA

SEP 15 1999

Date of Meeting: August 18, 1999
2:30 p.m.

Sponsors: Pfizer and Parke-Davis

Type of Meeting: Guidance

Purpose of Meeting: To discuss the development of a fixed combination product containing amlodipine and atorvastatin

Meeting Participants:

FDA

Murray Lumpkin, M.D., HFD-2, Deputy Center Director, CDER
Robert Temple, M.D., HFD-101, Director, Office of Drug Evaluation I
John Jenkins, M.D., HFD-102, Director, Office of Drug Evaluation II
Solomon Sobel, M.D., HFD-510, Division Director
Leah Ripper, HFD-102, Associate Director for Regulatory Affairs, ODE II
Norman Drezin, R.Ph., J.D., HFD-40, Acting Director, DDMAC
Patrick Marroum, Ph.D., HFD-860, Clinical Pharmacology/Biopharmaceutics Team Leader
Kasturi Srinivasachar, Ph.D., HFD-110, Chemistry Team Leader
Norman Stockbridge, M.D., Ph.D., HFD-110, Medical Team Leader
Natalia Morgenstern, HFD-110, Chief, Project Management Staff
Stephen K. Moore, Ph.D., HFD-510, Chemistry Team Leader
Charles Hoiberg, Ph.D., HFD-800, Acting Deputy Director, ONDC
Xavier Ysern, Ph.D., HFD-820, Chemist
Mary Parks, M.D., HFD-510, Medical Officer
Karen Lechter, Ph.D., J.D., HFD-40, Social Science Analyst
Iris Masucci, Pharm.D., HFD-40, Regulatory Reviewer
Hae Young Ahn, Ph.D., HFD-870, Clinical Pharmacology/Biopharmaceutics Team Leader
David Roeder, HFD-110, Regulatory Health Project Manager

Pfizer

Rob Scott, M.D., Medical
Rita Wittich, Regulatory
Laurie Olson, Marketing
Marie-Caroline Sainpy, CV Team Leader

Parke-Davis

Stephanie Kafonek, M.D., Medical
Byron Scott, Regulatory
Adele Gulfo, Marketing
Michael Tayor, Drug Development

Background

Lipitor (atorvastatin) is currently marketed as a lipid-lowering agent; the NDA is owned by Parke-Davis. Norvasc (amlodipine) is currently marketed for the treatment of angina and hypertension; the NDA is owned by Pfizer. Parke-Davis and Pfizer requested a meeting with the Agency to discuss the possibility of developing a fixed combination product containing both amlodipine and atorvastatin.

Meeting

Regulatory Considerations

The sponsor presented justification for the development of a fixed combination product containing amlodipine and atorvastatine. It would be marketed for use by patients with hypertension/angina and hypercholesterolemia for whom the two drugs would be appropriate. FDA representatives agreed with the sponsor that such a product is consistent with the regulations concerning fixed combinations (21 CFR 300.50) and would not need a new efficacy study. A multifactorial study would not be necessary since the two drugs are used to treat different diseases. The firms stated that they plan to continue marketing the single entity products if the combination is approved.

Promotion Issues

The sponsor is not planning to demonstrate that this combination product improves patient compliance, but they believed that a case could be made for greater convenience. FDA representatives said that it would be difficult to make a case for compliance claim and that such a claim would have to be supported with data. FDA agreed, however, that a claim of convenience would be easier to justify.

Dr. Lumpkin noted that the firms would not be allowed to imply that [redacted]

Proposed Dose Formulation Strategy

Atorvastatin is currently marketed in 10, 20 and 40 mg tablets. The recommended dose range is 10 to 80 mg. The sponsor proposed a formulation strategy that would make 10 and 80 mg strengths available in combination with 5 or 10 mg amlodipine. Amlodipine is currently marketed in 2.5, 5 and 10 mg tablets. The 2.5 mg dose is recommended for use only in the small, fragile, elderly or hepatically impaired.

FDA representatives noted that the proposed formulations would require patients titrating upward on atorvastatin to go directly from 10 mg to 80 mg, and this is not the recommended approach to dosing atorvastatin. A fixed combination product should not be formulated in a way that forces patients into taking doses that they would normally not take. They recommended that

more doses of atorvastatin be made available in the combination. If the sponsor wishes to continue with the current proposal, they need to convince us that the absence of intermediate atorvastatin doses would not expose patients to unnecessary risk. It was agreed that the 2.5 mg amlodipine strength would not have to be included in the combination product.

Chemistry, Manufacturing and Controls

Parke-Davis is currently developing an 80 mg atorvastatin tablet for the single entity product. They haven't yet begun formulating a combination tablet, but they will probably use the atorvastatin tablet as the starting point. The company is investigating whether there is any interference of one drug product and impurities with the other in the chemical assays.

Bioequivalence studies

The sponsor proposed a bracketing approach to the bioequivalence program in which one intermediate and the high and low and combinations would be tested against the individual components. FDA representatives agreed that this approach could be acceptable to gain approval for all dose combinations within the bracket, but that would depend on the formulation.

Clinical Considerations

FDA representatives agreed that clinical efficacy studies would not be necessary. They noted, however, that this combination treating two distinct conditions was unusual for prescription drugs. We might bring such an application to a public advisory committee to get feedback from the medical community on the wisdom of combining prescription drugs that are approved for different indications.

Dr. Ahn was concerned about possible interactions between atorvastatin and amlodipine since the two drug substances are metabolized by the same cytochrome P450 enzyme, and she suggested that the companies submit their data for the Agency's review. It was decided, however, that the FDA would discuss these concerns internally and get back to the sponsor at a later date if necessary.

Pediatric Rule

Since both companies are conducting pediatric studies with the individual components, the requirement for pediatric studies with the combination NDA could be waived, especially since it is expected that very few pediatric patients would have both diseases covered by the combination. This would depend, however, on the progress of the studies with the single entity products.

Administrative

Dr. Lumpkin stated that Parke-Davis and Pfizer will have to decide who will be the lead sponsor.

This would determine the lead review division at the FDA. Both companies agreed that Pfizer would be the applicant of the NDA. This would make HFD-110 the lead review division.

[redacted]

Labeling and Nomenclature

The package insert will be constructed with each section divided into information on the separate components.

The product should have a unique trade name, and the dosage strengths should be included as part of the name.

Post marketing adverse reactions will not be attributed to the combination if the reaction has already been seen in one of the components. If it is a new event, it might be attributed to the combination. The sponsor should consider this and make a proposal on how to approach this issue.

Conclusion

The sponsor will follow up with the review divisions as the program develops.

Minutes Preparation: /S/
David Roeder

Concurrence Chair: /S/
Murray Lumpkin, M.D.

dr/8-24-99/9-2-99/9-14-99

RD: RTemple
JJenkins
SSobel
LRipper
NDrezin
PMarroum
NStockbridge
SMoore
CHoiberg
XXsern

MParks
KLechter
IMasucci
HYAhn
DRoeder
MLumpkin

cc: Orig NDA
HFD-110
HFD-110/Project Manager/SMatthews
MLumpkin/HFD-2
RTemple/ HFD-101
JJenkins/HFD-102
SSobel/HFD-510
LRipper/HFD-102
NDrezin/ HFD-40
PMarroum/ HFD-860
KSrinivasachar/HFD-110
SMoore/ HFD-510
CHoiberg/HFD-800
XYsern/ HFD-820
MParks/ HFD-510
KLechter/ HFD-40
IMasucci/HFD-40
HYoung Ahn/ HFD-870
MSimoneau/HFD-510

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THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

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Minutes of a meeting between Pfizer and the FDA Division of Cardio-Renal Drug Products

Sponsor:	Pfizer, Inc.
NDA:	21-540
Date request received:	July 18, 2003
Date of confirmation:	July 30, 2003
Date of meeting:	September 9, 2003
Type:	B
Classification:	90 Day Conference
Meeting chair:	Douglas C. Throckmorton, M.D.
Meeting recorder:	Denise Hinton

FDA attendees:

Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products
Abraham Karkowsky, M.D., Ph.D.	Medical Officer Team Leader
Akinwole Williams, M.D.	Medical Officer
Ramsharan Mittal, Ph.D.	Chemist
Patrick Marroum, Ph.D.	Biopharmaceutical Team Leader
Atul Bhattaram, Ph.D.	Clinical Pharmacologist and Biopharmaceutist
James Hung, Ph.D.	Statistical Team Leader
Jasmine Choi, Ph.D.	Statistician
Denise M. Hinton	Regulatory Health Project Manager

Pfizer attendees:

Natalie Touzell	Director, Regulatory
Paul Nitschmann	Director, Regulatory
Beth-Anne Piper	Worldwide Medical Team Leader
Gary Palmer	Vice President, US Medical
Craig Hopkinson	Sr. Director/Group Leader, US Medical
Eric Gibson	Biometrics Team Leader
Deanna Murden	Regulatory CMC
Tamie Bergtsrom	Director, Scientific Development
Patrick Holmes	Vice President, US Marketing
Kipp Kreutzberg	Caduet Team Leader

Background:
On March 31, 2003, Pfizer submitted a NDA for Caduet (amlodipine besylate/atorvastatin calcium) 5/10, 10/10, 5/20, 10/20, 5/40, 10/40, 5/80 and 10/80 mg Tablets. On June 13, 2003, the Division issued a 74 day filing letter to communicate seven potential review issues.

Pfizer requested this meeting to gain the Division's endorsement of their proposals written to address the potential review issues communicated in the 74 day filing letter.

Discussions:
After introductions, Pfizer presented proposals of each issue raised in the 74 day filing letter. The Division responded to each as follows:

1. **Comparative dissolution profile data necessary to support the bio-waiver**
   The Pfizer communicated with the biopharmaceutics and chemistry reviewer regarding the necessary requirements to support a bio-waiver. The Division stated that it would be acceptable for Pfizer to gather additional dissolution data and provide it by the end of October 2003.

2. **Provision of the full study report for Respond**
   Pfizer submitted the data and data sets from Respond as an executive summary of the primary efficacy analyses. The Division stated it would be acceptable for the full study report and data sets to be provided in October 2003, as sufficient data has been submitted for the assessment of the pharmacodynamic profile and safety.

   In regard to the short-term safety data, the Division agreed that the study would assess the short-term safety of the combination product. The Division asked Pfizer to provide rationale for not submitting any meta analyses of data for concomitant use from other clinical trials and data bases would not be needed.

   Per the Advisory Committee, while it is not necessary, clinical outcome data that address a potential for drug interactions are in many ways more robust than data looking at PK/PD.

3. **Availability of additional information relative to interaction of atorvastatin and amlodipine on clinical events relevant to the combination product**
   The Division agreed, in principle, with Pfizer's proposal of migrating the outcome data from the parent compound labels into the Caduet label and will speak with the Division of Metabolic and Endocrine regarding the Ascot study which will be filed with the Lipitor application.

4. **Requirements to support claims for the combination in the indications of angina for amlodipine or familial hyperlipidemia for atorvastatin.**
   Pfizer explained that they believed the angina and familial hyperlipidemia indications were appropriate since the combination does not modify the blood pressure and lipid effects of the components. [redacted] Pfizer was asked to provide any additional rationale for why they felt they could extrapolate from an interaction study measuring hypertension to support the claim for the angina indication. Such an argument might be that the hypertensive effect measures a 'vascular' activity that is relevant, but the sponsor needs to make that case in writing.

The Division consulted with Dr. Mary Parks of the Division of Metabolic and Endocrine and she stated that the familial hyperlipidemia indication should not be an issue since the mechanism of action is identical.

The Division recommended that Pfizer refer to the language used in the indication section of the Pravagard label as a guide in writing their label. Language stating that the combination is indicated for patients in whom treatment with the components is appropriate should be clearly stated in the label.

5. **Safety data available for assessment of safety**
The Division commented that the concomitant use data was limited. The Division is looking for rare, unanticipated, unexpected adverse events or well-characterized databases. The Division would not comment on their proposal, as it is a review issue, however Pfizer should present a formal position as to why the Division should not be concerned over recurrent, unanticipated events (as discussed above).

6. **Inclusion of AVALON and Respond PD data in the proposed label**

Pfizer proposed to include a description of the AVALON and Respond study in the pharmacodynamic section of the label and commented that they believed the results should be described in the clinical trial section. Other details of the trials would need to be discussed after review.

Pfizer also proposed to

The Division agreed that the data from AVALON and Respond studies could be described in the label; however disagreed with Pfizer's proposal An alternative would be to say that no adverse events were seen with the combination therapy during short-term use that differed from those in the individual components, then they could be listed and described in line fashion. Pfizer was advised to use the Losartan label as an example. Labeling will be addressed in more detail after future discussions.

The description of administration, including timing and dosing in the proposed label

The Division stated that the proposed dosage and administration section, on its face, appears adequate. The revised language proposed by the Sponsor is more clearly written and the population and dosing are appropriate. The special population and considerations should be described earlier in the label and the table should be deleted. Pfizer was advised to use the Pravagard label as a guide. DDMAC will also review and comment on the label.

[redacted]

At the close of the meeting, the Division asked Pfizer to act on the following:

- Resubmit a revised version of the adverse event section of the label
- Make a case [redacted]
- Discuss the need for formal assessment of long-term use of the combination of amlodipine and atorvastatin
- Make a case for [redacted]
  Further discussions with the Agency [redacted]

Pfizer agreed to provide annotated labeling with rationale for all revisions made in the label and to submit revisions made to the PD, Clinical Trials, Adverse Events, Dosage and Administration section of the label.

Meeting recorder: _____
Denise M. Hinton

Meeting concurrence: _____
Douglas C. Throckmorton, M.D.

Draft: 17Sep03
Final: 7Oct03

RD:
Throckmorton 7Oct03
Karkowsky 7Oct03
Williams 3Oct03
Marroum 2Oct03
Bhattaram 1Oct03
Hung 6Oct03

Attachments:
Pfizer slides

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/s/

Denise Hinton
10/7/03 06:08:24 PM

Doug Throckmorton
10/8/03 10:40:14 AM

(J)

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19 pages

(J)

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: November 24, 2003

TO: Denise Hinton, Regulatory Project Manager
Akinwole Williams, M.D., Medical Officer
Division of Cardio-Renal Drug Products, HFD-110

THROUGH: Joseph Salewski, Acting Director
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Robert Shibuya

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-540

APPLICANT: Pfizer

DRUG: Caduet (amlodipine besylate/atorvastatin calcium)

CHEMICAL CLASSIFICATION: 6

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: [redacted]

CONSULTATION REQUEST DATE: August 18, 2003

ACTION GOAL DATE: December 1, 2003

I. BACKGROUND:

These were routine data verification inspections performed to validate data submitted in support of NDA 21-540. Caduet is the trade name for a new combination of amlodipine besylate and atorvastatin calcium. This protocol was inspected at the request of HFD-110. The study was a double-blind, full factorial design comparing several doses (and placebo) of amlodipine and atorvastatin in combination. The endpoints were blood pressure and LDL-cholesterol after 8 weeks of double blind therapy.

II. RESULTS (by protocol/site):

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Harvey	Addlestone	UK	9/11/03	pending	NAI*
Cheung	Long Beach	CA	9/11/03	10/15/03	VAI
Dykstra	Bartlesville	OK	9/11/03	11/13/03	VAI*
Preston	Miami	FL	9/11/03	pending	VAI*

*Pending formal review of completed EIR. DSI will notify HFD-110 if review significantly changes conclusions.

A. Protocol # A3841003

1. Site #1 (Peter Harvey, M.D., Addlestone, UK) Acceptable

a. Inspected were sponsor and IRB correspondence, drug accountability, subject records, informed consents, and case report forms. Records for 29 subjects were inspected in detail.

b. There were no limitations to the inspection. The inspection only covered the referenced protocol.

c. This site enrolled 38 subjects. All subjects underwent an appropriate consent procedure. No regulatory violations were noted. Data appear acceptable. DSI has not received this inspection report at the time of this memo. Should our review of the report change our conclusion, DSI will notify HFD-110 immediately.

2. Site #2 (Deanna Cheung, M.D., Long Beach, CA) Acceptable

a. Inspected were sponsor and IRB correspondence, drug accountability, subject records, informed consents, and case report forms. Records for eight subjects were inspected in detail.

b. There were no limitations to the inspection. The inspection only covered the referenced protocol.

c. This site enrolled 15 subjects. All subjects underwent an appropriate consent procedure. One subject was enrolled who did not meet the inclusion criteria. Data appear acceptable.

3. Site #3 (Gary Dykstra, D.O., Bartlesville, OK) Acceptable

a. Inspected were sponsor and IRB correspondence, drug accountability, subject records, informed consents, and case report forms.

b. There were no limitations to the inspection. The inspection only covered the referenced protocol.

c. This site screened 35 subjects, randomized 21, and completed 18. All subjects underwent an appropriate consent procedure. Protocol violations and a minor issue with the IRB (the site collected urine on one subject without IRB approval) were documented. Data appear acceptable. DSI has not completed our review of the inspection report at the time of this memo. Should our review of the report change our conclusion, DSI will notify HFD-110 immediately.

4. Site #4 (Richard Preston, M.D., Miami, FL) Acceptable

a. Inspected were sponsor and IRB correspondence, drug accountability, subject records, informed consents, and case report forms. Records for ten subjects were inspected in detail.

b. There were no limitations to the inspection. The inspection only covered the referenced protocol.

c. This site randomized 16 subjects, dropped 3, and completed 13. All subjects underwent an appropriate consent procedure. Protocol violations, deficiencies in study records, and a minor issue with the IRB were documented. Data appear acceptable. DSI has not received this inspection report at the time of this memo. Should our review of the report change our conclusion, DSI will notify HFD-110 immediately.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The inspections revealed nothing that would be expected to impact the validity of the data submitted for the four sites inspected.

No follow up is indicated.

Data appear acceptable.

Robert B. Shibuya
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments

Joseph P. Salewski
Acting Director
Good Clinical Practice Branch II
Division of Scientific Investigations

DISTRIBUTION:
NDA 21-540
DISTRIBUTION:
NDA 21-399
HFD-45 Division File / Reading File
HFD-45 Program Management Staff (electronic copy)
HFD-47/JS/RS
HFD-47/Balser GCPB2 Files # 11026; # 11044; and pending x 2.

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

/s/

Sherry George
11/24/03 04:21:00 PM
TECHNICAL

APPEARS THIS WAY
ON ORIGINAL

DSI CONSULT: Request for Clinical Inspections

Date: August 27, 2003

To: Joseph P. Salewski, Acting Director, Good Clinical Practice Branch II, HFD-47

Through: Joanne L. Rhoads, M.D., MPH, Director, Division of Scientific Investigations, HFD-45
Douglas Throckmorton, M.D., Director, HFD-110

From: Denise Hinton, Regulatory Project Manager
Division of Cardio-Renal Drug Products, HFD-110

Subject: Request for Clinical Inspections
NDA 21-540
Pfizer
Caduet (amlodipine besylate/atorvastatin calcium)

Protocol/Site Identification:

As discussed with DSI, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Indication	Protocol #	Site (Name and Address)
Data Audit	A3841003 (RESPOND)	Peter Harvey Addleston, UK
Data Audit	A3841003 (RESPOND)	Deanna Cheung Long Beach, CA
Data Audit	A3841003 (RESPOND)	Gary Dykstra Bartlesville, OK
Data Audit	A3841003 (RESPOND)	Richard Preston Miami, FL

Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.

ADD THE FOLLOWING SECTION IF THERE ARE ANY FOREIGN SITES IN THE ABOVE LISTED SITES REQUESTED TO BE INSPECTED:

International Inspections:

We have requested inspections because (please check appropriate statements):

_X_ There are insufficient domestic data (80 domestic and 200 foreign)

___ Only foreign data are submitted to support an application

___ Domestic and foreign data show conflicting results pertinent to decision-making

___ There is a serious issue to resolve, e.g. suspicion of fraud, scientific misconduct, or significant human subject protection violations

___ Other

ADD THE FOLLOWING SECTION IF THERE ARE FIVE OR MORE SITES TO BE INSPECTED:

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by **December 1, 2003.** We intend to issue an action letter on this application by **February 1, 2004. Please expedite your inspection scheduling and review for internal divisional decision making processes.**

Should you require any additional information, please contact Ms. Denise M. Hinton, Regulatory Project Manager at (301) 594-5333.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Deanna Cheung, M.D.
Memorial Research Medical Clinic
2865 Atlantic Avenue, Suite 227
Long Beach, California 90806

NOV 18 2003

Dear Dr. Cheung:

Between October 7 and 10, 2003, Mr. Allen Hall, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation (protocol # A3841003 entitled: "A Multi-National, Prospective, Randomized, Double-Blind, Multi-Center, Placebo-Controlled Study to Evaluate Efficacy and Safety of a Fixed Combination Therapy of Amlodipine and Atorvastatin in the Treatment of Concurrent Hypertension and Hyperlipidemia") of the investigational drug Caduet (amlodipine besylate/atorvastatin calcium), performed for Pfizer. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Mr. Hall presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

You did not conduct the investigation in accordance with the protocol (21 CFR 312.60) in that subject 159 was enrolled in the study despite not meeting inclusion criteria. Criteria for inclusion into Group I were an LDL-cholesterol of 190-250 mg/dL inclusive, blood pressure of 140-179/90-109 inclusive, and no risk factors. Criteria for inclusion into Group II were a LDL-cholesterol of 160-250 mg/dL inclusive, blood pressure of 140-179/90-109 inclusive, and one risk factor. If HDL-cholesterol exceeded 59 mg/dL, an additional risk factor was required for Group II. Criteria had to be met on both run-in visits.

This subject had LDL-cholesterol levels of 182 and 210 mg/dL and HDL-cholesterol levels of 90 and 95 mg/dL on her two run-in visits and one risk factor. As such, she did not meet inclusion criteria into either Group I or II. You originally enrolled her into Group II then changed her to Group I.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Hall during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

/S/

Joseph P. Salewski
Acting Director
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

APPEARS THIS WAY
ON ORIGINAL

FEI: 3004152365
Field Classification: VAI
Headquarters Classification:
_____1)NAI
___X_2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

Deficiencies noted:
__X_failure to adhere to protocol (05)
Deficiency Codes: **5**

cc:
HFA-224
HFD-110 Doc.Rm. NDA# 21-540
HFD-110 Review Div.Dir. Throckmorton
HFD-110 MO Williams
HFD-110 PM Hinton
HFD-47c/r/s/ GCP File # 11026
HFD-47 Shibuya
HFR-PA-252 DIB Tucker
HFR-PA-2565 Bimo Monitor Koller
HFR-PA-250 Field Investigator Hall
GCF-1 Seth Ray

r/d: (RS:10/29/03)
reviewed:JPS: 10/30/03
f/t:ml: 10/29/03

o:\RS\NDA 21-540\Cheung.doc

Reviewer Note to Rev. Div. M.O.
- This site enrolled 15 subjects.
- All subjects consented to the trial.
- Records for eight subjects were inspected in detail.
- One subject was enrolled who did not meet the inclusion criteria.
- Data appear acceptable.

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

/s/

Joseph Salewski
11/24/03 11:18:30 AM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Gary T. Dykstra, D.O.
BlueStem Cardiology
3400 SE Frank Phillips, Suite 502
Bartlesville, Oklahoma 74006

DEC 16 2003

Dear Dr. Dykstra:

Between October 20 and 24, 2003, Ms. Janice Hickok, representing the Food and Drug Administration (FDA), conducted an investigation to review your conduct of a clinical investigation (protocol # A3841003 entitled: "A Multi-National, Prospective, Randomized, Double-Blind, Multi-Center, Placebo-Controlled Study to Evaluate Efficacy and Safety of a Fixed Combination Therapy of Amlodipine and Atorvastatin in the Treatment of Concurrent Hypertension and Hyperlipidemia") of the investigational drug Caduet (amlodipine besylate/atorvastatin calcium), performed for Pfizer. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Hickok presented and discussed with you Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You did not adhere to the approved protocol (21 CFR 312.60).

   a. Subject 322 was enrolled despite not meeting the inclusion criterion of an LDL-cholesterol ≥ 130 mg/dL on both Run-In visits. This subject's LDL-cholesterol value was 115 mg/dL on the second Run-In visit.

   b. Subject 324 took pentoxifylline and subjects 034 and 328 took cilostazol while on the study. These drugs were prohibited by the protocol.

   c. You did not follow the procedure for breaking the blind specified by the protocol for subject 006.

2. You made changes to the research without prior approval of your Institutional Review Board (IRB) (21 CFR 312.66).

   Amendment 2 of the protocol varied from Amendment 1 in that it required you to store serum and urine specimens for possible later analysis. You collected urine to be stored for future assays on subjects 002 and 004 prior to obtaining approval by your IRB.

We acknowledge receipt of your letter dated November 4, 2003 and trust that your corrective actions will assure that the findings noted above are not repeated in any ongoing or future studies Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Hall during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

/S/

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II, HFD-47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3004152344
Field Classification: VAI
Headquarters Classification:
_____1)NAI
___X_2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

Deficiencies noted:
__X_failure to adhere to protocol (05)
__X_failure to obtain or document IRB approval (14)
Deficiency Codes: **5, 14**

cc:
HFA-224
HFD-110 Doc.Rm. NDA# 21-540
HFD-110 Review Div.Dir. Throckmorton
HFD-110 MO Williams
HFD-110 PM Hinton
HFD-47c/r/s/ GCP File # 11044
HFD-47 Shibuya
HFR-SW-150 DIB Thornburg
HFR-SW-1540 Bimo Monitor Martinez
HFR-SW-1535 Field Investigator Hickok
GCF-1 Seth Ray

r/d: (RS:11/26/03)
reviewed:LKB: 12/2/03
f/t:ml: 12/8/03

o:**RS\NDA 21-540\Dykstra.doc**

<u>Reviewer Note to Rev. Div. M.O.</u>
- This site enrolled 15 subjects.
- All subjects consented to the trial.
- Records for eight subjects were inspected in detail.
- One subject was enrolled who did not meet the inclusion criteria.
- Data appear acceptable.

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

/s/

Leslie Ball

12/16/03 05:58:51 PM

APPEARS THIS WAY
ON ORIGINAL

NDA 21-540
CADUET (amlodipine besylate and atorvastatin calcium)
Pfizer Inc.

NA

LAST PAGE
OF
Approval pkg.