CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-540

CHEMISTRY REVIEW(S)

NDA 21-540

CADUET

Tablets

Pfizer Inc.

Ramsharan D. Mittal

Division of Cardio-Renal Drug Products

Chemistry Review Data Sheet

1. **NDA** 21-540
2. **REVIEW #:** 1
3. **REVIEW DATE:** 12-22-2003
4. **REVIEWER:** Ramsharan D. Mittal
5. **PREVIOUS DOCUMENTS:** None
6. **SUBMISSION(S) BEING REVIEWED:**

Submission(s) Reviewed	Document Date
N000 (BZ)	12-NOV-2003
N000 (BC)	12-NOV-2003
N000 (BL)	10-NOV-2003
N000 (BZ)	05-NOV-2003
N000 (BC)	08-JUL-2003
N000	31-MAR-2003

7. **NAME & ADDRESS OF APPLICANT:**
   Name: Pfizer Inc.
   Address: 235 East 42nd Street
   New York, NY 10017

8. **DRUG PRODUCT NAME/CODE/TYPE:**
   a) Proprietary Name: CADUET
   b) Non-Proprietary Name (USAN): Amlodipine Besylate/Atorvastatin calcium
   c) Code Name/#
      - Chem. Type: 4
      - Submission Priority: S
9. **LEGAL BASIS FOR SUBMISSION:** N/A
10. **PHARMACOL. CATEGORY:**

    Calcium Channel Blocker (antihypertensive/antianginal) and antidyslipidemic

11. **DOSAGE FORM:** Tablets
12. **STRENGTH/POTENCY:** 5/10, 5/20, 5/40, 5/80, 10/10, 10/20, 10/40 and 10/80 mg
13. **ROUTE OF ADMINISTRATION:** Oral
14. **Rx/OTC DISPENSED:** _x_ **Rx** ___ **OTC**
15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

    _____SPOTS product – Form Completed
    __x__Not a SPOTS product

16. CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT, STRUCTURAL FORMULA:

AMLODIPINE BESYLATE:

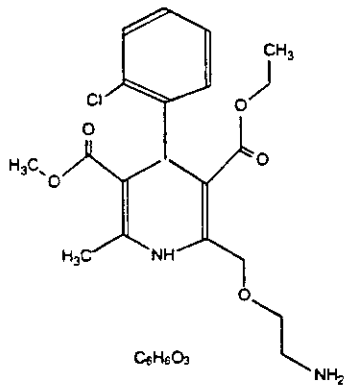
Chemical Name:

(R.S.) 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)- (2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate benzenesulphonate

Molecular Formula: $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$

Molecular Weight: 567.1

Structural Formula:



ATORVASTATIN CALCIUM:

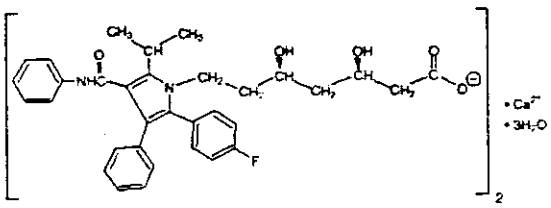
Chemical Name:

[R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate.

Molecular Formula: $(C_{33}H_{34}FN_2O_5)_2Ca \cdot$

Molecular Weight: 1209.42

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: Raw Materials

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	4	Adequate	This review	[redacted]
	II			4	Adequate	This review	
	II			4	Adequate	This review	

B. DMFs: Packaging Material

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]	[redacted]	7	Adequate	Sep. 27, 2000 Dec. 27, 2002	Reviewed by Donald Klein
	III			7	Adequate	July 31, 1996 July 24, 1999 March 14, 2000 May 27, 2003	Resign reviewed for similar applications
	III			7	Adequate	March 16, 2001	Reviewed by S. Prasad
	III			7	Adequate	April 30, 2002 April 15, 2003	B. Roggers S. Markofsky
	III			7	Adequate	Sep. 9, 1999 Nov. 1, 1999	[redacted]
	III			7	Adequate	Sep. 1, 2003	Reviewed by E. Jao
	III			7	Adequate	Sep. 2, 2003	Reviewed by Bing Wu
	III			7	Adequate	March 13, 1996	Reviewed by Craig Berta
	III			7	Adequate	January 1, 1999 July 3, 2000	Not Reviewed for updates
	III			7	Adequate	September 03, 1998	Not Reviewed for updates
	III			7	Adequate	September 22, 1999	Not Reviewed for updates

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

C. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	59,585	Amlodipine besylate/atorvastatin calcium IND for 5 /10 mg, 10/10 mg, 5 /20 mg, 10 /20 mg, 5 /40 mg, 10 /40 mg, 5 /80 mg and 10/80 mg tablets
NDA	19,787	Norvasc, immediate release 2.5, 5, and 10 mg tablets
NDA	20,702	Lipitor, immediate release 10, 20, 40, and 80 mg tablets

18. STATUS:

B. ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	Acceptable	September 9, 2003	Charles Resnick
Biopharm	Proposed Change in dissolution specifications	December 17, 2003	Atul Bhattaram
LNC	N/A		
Methods Validation	To be submitted		
DMETS	CADUET - Acceptable /IND 59,585	April 2, 2003	Tia M. Haeper-Velazquer
EA	EA Acceptable	December 7, 2003	Florian Zieliniski
Microbiology	N/A		

The Chemistry Review for NDA 21-540

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The chemistry section is deficient in some areas of manufacturing and controls. The resolution of these deficiencies should be relatively straight forward since most of them involve inadequate documentation by the applicant. A list of deficiencies has been sent to the applicant by Fax and e-mail on December 22, 2003 and applicant will be responding to these deficiencies shortly. The July 8, 2003 amendment provided [redacted] from CADUET tablets. The preliminary data from CADUET tablets made [redacted] shows no difference in tablet performance. The applicant plans to submit 6 weeks stability data for the tablets [redacted] before the end of December 2003 and 3 months data in early part of February 2004. Approval of the CADUET tablets without [redacted] and their expiration date are contingent upon the satisfactory review and length of stability data of the CADUET tablets manufactured [redacted] The cGMP status of one of the facilities submitted for inspection is pending. A recommendation of approvability can not be given at this time because an overall recommendation from Office of Compliance regarding cGMP status of one of the facility submitted for inspection is pending

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

The drug product is a combination of two active ingredients, amlodipine besylate and atorvastatin calcium. Amlodipine besylate/atorvastatin calcium dual therapy (angina and hyperlipidemia) immediate release tablets are presented as film coated tablets in 8 different dose-strength combinations. These formulations contain amlodipine besylate (equivalent to labeled quantity of free base) and atorvastatin calcium (equivalent to labeled quantity of anhydrous free acid) as follows: 5 /10 mg, 10 /10 mg, 5 /20 mg, 10 /20 mg, 5 /40 mg, 10 /40 mg, 5 /80 mg and 10 /80 mg amlodipine besylate and atorvastatin calcium respectively.

Five formulations of different ratios of amlodipine/atorvastatin have been manufactured. These are **1:1** (10/10 mg), **1:2** (5/10 and 10/20 mg), **1:4** (5/20 and 10/40

mg), **1:8** (5/40 and 10/80 mg), and **1:16** (5/80 mg) of amlodipine/atorvastatin respectively. Atorvastatin [redacted] is common to all 8 strengths of the CADUET tablets. The amount of atorvastatin [redacted] used in each tablet is proportional to the strength of atorvastatin in the tablet.

For information regarding the characterization, physical and chemical properties, stability, method of manufacture, and specification of drug substance, amlodipine besylate and atorvastatin calcium, reference was made to currently approved NDAs Norvasc (NDA 19-787) and Lipitor (NDA 20-702) respectively.

Amlodipine besylate is a salt of amine and atorvastatin calcium is a salt of carboxylic acid and both have polar groups such as ether, amide, carboxyl and hydroxyl etc. There is a possibility of interaction between the two drug substances. To investigate the interaction between them, applicant did various studies under different conditions, which showed them to be stable except that amlodipine besylate degrades in presence of moisture and heat. Amlodipine besylate was therefore included in the combination product as a [redacted]

Atorvastatin calcium present in CADUET tablets is an enantiomer with two chiral center. [redacted]

[redacted] of atorvastatin in CADUET tablets were observed.

Amlodipine besylate, present in CADUET tablets is a racemate, synthesized [redacted] product may change the ratio of amlodipine besylate enantiomers. Development studies and stability studies [redacted] have shown that the ratio of amlodipine enantiomers is unaffected by the tablet formulation.

CADUET tablets are manufactured by [redacted]

The CADUET tablets are oval shaped and come in two colors and four sizes. The

tablets containing 5 mg and 10 mg amlodipine are film coated white and blue respectively. The tablets containing 10 mg, 20 mg, 40 mg and 80 mg atorvastatin

calcium have a total weight of 100 mg, 200 mg, 400 mg, and 800 mg respectively. CADUET tablets are debossed with "Pfizer" on one side and "CDT" and code number on the other side. The 8 strengths of tablets can be differentiated from one another by size, film coat color and debossing.

The NDA provided test methods for identity, potency, purity, and dissolution. The July amendment revised these methods with new regulatory analytical procedures, while maintaining the original methods as alternative procedures. The analytical procedures are validated in accordance with ICH Q2 guidelines.

The CADUET tablets of each strength are packaged and different closure combinations of in counts of 30 (all strengths), . The Bottles are closures containing . Each bottle contains one 1-gm desiccant. The 30 and configurations with Child Resistant Squeeze-n-Turn (SNT) Closure are intended for patient distribution and

The original NDA provided 6 months long-term and accelerated stability data for CADUET tablets. The July amendment updated this stability data to 12 months, which also provided statistical analysis of the data through 12 months. The amendment of November 12, 2003, provided Certificate of Analysis on four batches of CADUET tablets (5/20, 5/40, 5/80 and 10/10 mg) without Based on the above data, the applicant proposes an expiry date for CADUET Tablets. The applicant has not provided any stability data for tablets . A minimum of 3 months stability data for tablets is needed for review and to assign a meaningful expiration date.

The amendment of July 8, 2003 . This This

FDA that will submit

B. Description of How the Drug Product is Intended to be Used

CADUET is a combination product containing both amlodipine and atorvastatin formulated as a once a day tablet for oral use in eight respective dose combinations: 5/10, 5/20, 5/40, 5/80, 10/10, 10/20, 10/40 and 10/80 mg. Amlodipine is 1,4-dihydropyridine structural class of calcium channel blockers that inhibits the trans-membrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Atorvastatin is a selective, competitive inhibitor of HMG CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutary-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. The product is proposed to be used for

the treatment of r

[redacted]

C. Basis for Approvability or Not-Approval Recommendation

A list of the deficiencies which should be addressed is attached at the end of this review. A copy of the deficiencies from this review #1 was sent to the applicant by Fax and e-mail on December 23, 2003. The applicant will be responding to these deficiencies shortly. A final recommendation can not be given at this time since an overall recommendation from Office of Compliance has not been issued pending cGMP inspection of one of the facility.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

C. CC Block

(A)

THIS SECTION WAS DETERMINED NOT TO BE RELEASABLE

97 pages (A)

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

/s/

Ramsharan Mittal
12/23/03 02:55:35 PM
CHEMIST

Kasturi Srinivasachar
12/23/03 03:07:06 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

NDA 21-540

CADUET

Tablets

Pfizer Inc.

Ramsharan D. Mittal

Division of Cardio-Renal Drug Products

Chemistry Review Data Sheet

1. NDA 21-540
2. REVIEW #: 2
3. REVIEW DATE: 01-30-2004
4. REVIEWER: Ramsharan D. Mittal

1. PREVIOUS DOCUMENTS

Submission(s) Reviewed	Document Date
N000 (BZ)	12-NOV-2003
N000 (BC)	12-NOV-2003
N000 (BL)	10-NOV-2003
N000 (BZ)	05-NOV-2003
N000 (BC)	08-JUL-2003
N000	31-MAR-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
N000 (BC)	28-JAN-2004
N000 (BZ)	21-JAN-2004
N000 (BC)	20-JAN-2004
N000 (BL)	16-JAN-2004
N000 (BC)	19-DEC-2003
N000 (BC)	12-DEC-2003

7. NAME & ADDRESS OF APPLICANT:

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

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: CADUET
b) Non-Proprietary Name (USAN): Amlodipine Besylate/Atorvastatin calcium
c) Code Name/#
- Chem. Type: 4
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY:

Calcium Channel Blocker (antihypertensive/antianginal) and antidyslipidemic

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 5/10, 5/20, 5/40, 5/80,
10/10, 10/20, 10/40 and 10/80 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed
__x__Not a SPOTS product

16. CHEMICAL NAME, MOLECULAR FORMULA, MOLECULAR WEIGHT, STRUCTURAL FORMULA:

AMLODIPINE BESYLATE:

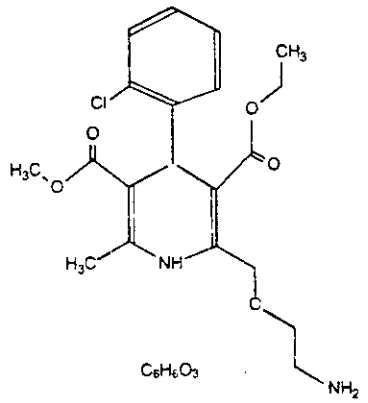
Chemical Name

3-Ethyl 5-methyl (±) -2-[(2-aminoethoxym)ethyl]-4-(o-chlorophenyl) -1,4-dihydro-6-methyl-3,5-pyridinedicarboxylate, monobenzenesulphonate

Molecular Formula: $C_{20}H_{25}ClN_2O_5 \cdot C_6H_6O_3S$

Molecular Weight: 567.1

Structural Formula:



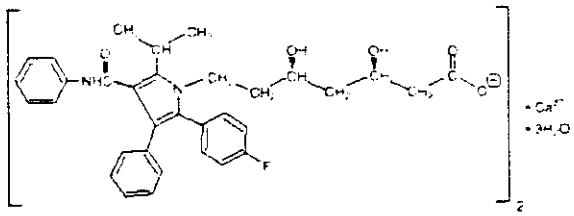
ATORVASTATIN CALCIUM:

Chemical Name: [R-(R*, R*)]-2-(4-fluorophenyl)-ß, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) trihydrate.

Molecular Formula: $(C_{33}H_{34}FN_2O_5)_2Ca \cdot$

Molecular Weight: 1209.42

Structural Formula:



APPEARS THIS WAY
ON ORIGINAL

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: Raw Materials

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	II	[redacted]	[redacted]	4	Adequate	This review	[redacted]
	II			4	Adequate	This review	
	II			4	Adequate	This review	

B. DMFs: Packaging Material

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	III	[redacted]		7	Adequate	Sep. 27, 2000 Dec. 27, 2002	Reviewed by Donald Klein
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	III			7	Adequate	March 16, 2001	Reviewed by S. Prasad
	III			7	Adequate	April 30, 2002 April 15, 2003	B. Roggers S. Markofsky
	III			7	Adequate	Sep. 9, 1999 Nov. 1, 1999	[redacted]
	III			7	Adequate	Sep. 1, 2003	Reviewed by E. Jao
	III			7	Adequate	Sep. 2, 2003	Reviewed by Bing Wu
	III			7	Adequate	March 13, 1996	Reviewed by Craig Berta
	III			7	Adequate	January 1, 1999 July 3, 2000	Not Reviewed for updates
	III			7	Adequate	September 03, 1998	Not Reviewed for updates
	III			7	Adequate	September 22, 1999	Not Reviewed for updates

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

C. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	59,585	Amlodipine besylate/atorvastatin calcium IND for 5 /10 mg, 10 10 mg, 5 /20 mg, 10 /20 mg, 5 /40 mg, 10 /40 mg, 5 /80 mg and 10 /80 mg tablets
NDA	19,787	Norvasc, immediate release 2.5, 5, and 10 mg tablets
NDA	20,702	Lipitor, immediate release 10, 20, 40, and 80 mg tablets

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	January 28, 2004	Office of Compliance
Pharm/Tox	Acceptable	September 9, 2003	Charles Resnick
Biopharm	Proposed Change in dissolution specifications	December 17, 2003	Atul Bhattaram
LNC	N/A		
Methods Validation	To be submitted		
DMETS	CADUET is ACCEPTABLE	January 8, 2004	Tia M. Haeper-Velazquer
EA	EA Acceptable	December 7, 2003	Florian Zieliniski
Microbiology	N/A		

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-540

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

An acceptable cGMP status of all facilities has been received from the Office of Compliance. All other pending CMC issues have been resolved. The application may be approved from a chemistry standpoint and the action letter should include the following statements:

> An expiration date of 18 months is granted for CADUET tablets 5/10, 5/20, 5/40, 5/80, 10/10, 10/20, 10/40 and 10/80 mg, packaged in foil/foil blisters and HDPE bottles of 30 tablets. Any extension of the expiration date beyond 18 months should be based on real time stability data generated according to the amended post-approval stability protocol submitted on January 28, 2004.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable. N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

The drug product is a combination of two active ingredients, amlodipine besylate and atorvastatin calcium. In the original NDA the amlodipine besylate/atorvastatin calcium dual therapy (angina and hyperlipidemia) immediate release tablets were presented as film coated tablets in 8 different dose-strength combinations. The applicant has added [redacted] combinations containing [redacted] amlodipine. The [redacted] of 5/20 mg, 5/40 mg, and 5/80 mg tablets. There is no change in the manufacture and controls of tablets containing [redacted] mg vs. 5 mg amlodipine, except the [redacted]. These [redacted] combinations of CADUET tablets now contain amlodipine besylate (equivalent to labeled quantity of free base) and atorvastatin calcium (equivalent to labeled quantity of anhydrous free acid) as follow: [redacted] 5 /10 mg, 10 /10 mg, [redacted] 5 /20 mg, 10 /20 mg, [redacted] 5 /40 mg, 10 /40 mg, 5 /80 mg and 10 /80 mg amlodipine besylate and atorvastatin calcium respectively.

The detail information for the description, characterization, physical and chemical properties, stability, method of manufacture, and specification amlodipine besylate and atorvastatin calcium of drug substances and similar information related to CADUET drug product were provided in CMC review # 1. Five formulations of different ratios of amlodipine/atorvastatin have been discussed in CMC review # 1. These are **1:1** (10/10 mg), **1:2** (5/10 and 10/20 mg), **1:4** [redacted] 5/20 and 10/40 mg), **1:8** [redacted] 5/40 and 10/80 mg), and **1:16** [redacted] and 5/80 mg) of amlodipine/atorvastatin respectively. Atorvastatin [redacted] is common to [redacted] strengths of the CADUET tablets. The amount of atorvastatin [redacted] used in each tablet is proportional to the

strength of atorvastatin in the tablet.

The CADUET tablets containing [redacted] 15 mg amlodipine are film-coated white and tablets containing 10 mg amlodipine are film-coated blue. The CADUET tablets containing [redacted] amlodipine are [redacted] The tablets containing 5 mg and 10 mg amlodipine are oval shaped and come in four sizes depending on the weight of atorvastatin. The tablets containing 10 mg, 20 mg, 40 mg and 80 mg atorvastatin calcium have a total weight of [redacted] respectively. The CADUET tablets are debossed with "Pfizer" on one side and "CDT" and code number on the other side. The [redacted] combinations of CADUET tablets can be differentiated from one another by color, size, shape and debossing.

The CADUET tablets of all strengths containing 5 and 10 mg amlodipine with [redacted] were packaged in foil/foil blisters and different HDPE bottle/closure combinations in various counts (see CMC review # 1). All strengths of CADUET tablets [redacted] will be marketed in [redacted] bottles of [redacted], in counts of 30.

The CMC review # 1, covered 12 months long-term and 6 months accelerated stability data for CADUET tablets with [redacted] and statistical analysis of the data through 12 months. The review # 1 included only Certificate of Analysis on four batches of CADUET tablets (5/20, 5/40, 5/80 and 10/10 mg) [redacted] and no stability data was provided. The applicant has updated stability data for tablets [redacted] to 18 months and also provided 6 weeks accelerated and long-term conditions stability data for tablets [redacted] in blisters and HDPE bottles of size [redacted] containing [redacted] (5/20, 5/40, 5/80 and 10/10 mg). This review also covers release data (Certificate of Analysis) of CADUET tablets containing [redacted] amlodipine [redacted]

Based on the above data, the applicant proposes an expiry date [redacted] for all combinations of CADUET Tablets [redacted] in all container closure configurations covered in original NDA [redacted]

The 6 weeks long-term and accelerated stability data of four strengths of CADUET tablets made [redacted] and packaged in blisters and HDPE bottles of [redacted] tablets show no difference in tablet performance. The monotherapy amlodipine tablets (Norvasc) are manufactured [redacted] and the stability of Norvasc can be used to support the performance of CADUET tablets [redacted]

B. Description of How the Drug Product is Intended to be Used

CADUET is a combination product containing both amlodipine and atorvastatin formulated as a once a day tablet for oral use in eight respective dose combinations:

5/10, 5/20, 5/40, 5/80, 10/10, 10/20, 10/40 and 10/80 mg . Amlodipine is 1,4-dihydropyridine structural class of calcium channel blockers that inhibits the trans-membrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Atorvastatin is a selective, competitive inhibitor of HMG CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutary-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. The product is proposed to be used for

C. Basis for Approvability or Not-Approval Recommendation

The applicant has responded satisfactorily to most of the deficiencies sent on December 22, 2003. The response to some of the deficiencies such as explanation of the use of ranges for during manufacture of CADUET tablets and assay results of atorvastatin require further clarifications. The applicant commits to respond to these issues post-approval of this NDA.

The applicant added three additional strengths of CADUET tablets containing of amlodipine) and provided release data of one batch each for new strengths. The stability data of the CADUET tablets is limited with respect to coverage of all strengths, length of data and container/closure configurations. The stability data of CADUET tablets is considered as a supporting data, which along with limited data for the tablets can not be considered to extend expiration date beyond 18 months and cover all container closure configurations except foil/foil blister and HDPE bottles containing 30 CADUET tablets of all strengths. The applicant has agreed to revise their post-approval stability protocol for coverage of other container/closure configurations and extension of expiry date. The applicant is required to periodically submit stability data of all batches made covering a period of at least up to 18 months for various container/closure configurations that may be agreed under post-approval stability protocol. The applicant commits to revise CMC information related to CADUET tablets containing amlodipine.

An acceptable cGMP status of all facilities has been received from the Office of Compliance (copy attached at the end of this review). All other pending CMC issues have been resolved. The application may be approved from a chemistry standpoint.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

C. CC Block

B

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

20 pages

(B)

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

/s/

Ramsharan Mittal
1/30/04 09:24:31 AM
CHEMIST

Kasturi Srinivasachar
1/30/04 09:33:53 AM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21540/000
Org Code : 110
Priority : S

Sponsor: PFIZER
235 EAST 42ND ST
NEW YORK, NY 10017

Stamp Date : 01-APR-2003
PDUFA Date : 01-FEB-2004
Action Goal :
District Goal: 03-DEC-2003

Brand Name : CADUET(AMLODIPINE BESYLATE/ATORVASTATIN
Estab. Name:
Generic Name: AMLODIPINE BESYLATE/ATORVASTATIN CALCIUM
Dosage Form: (TABLET)
Strength : 5/10,10/10,5/20,10/20

FDA Contacts:	D. HINTON	Project Manager (HFD-110)	301-594-5300
	R. MITTAL	Review Chemist (HFD-110)	301-594-5353
	K. SRINIVASACHAR	Team Leader (HFD-110)	301-594-5376

Overall Recommendation: ACCEPTABLE on 29-JAN-2004by S. ADAMS (HFD-322) 301-827-9051

Establishment :

[redacted]

DMF No:

AADA:

Responsibilities:

[redacted]

Profile : TCM
Last Milestone: OC RECOMMENDATION
Milestone Date: 29-JAN-04

OAI Status: NONE

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Responsibilities: FINISHED DOSAGE PACKAGER

Profile : TCM OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 03-OCT-03

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

APPEARS THIS WAY
ON ORIGINAL

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 2210721 FEI : 2210721

PFIZER INC

182 TABOR RD

MORRIS PLAINS, NJ 07950

DMF No: AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 03-OCT-03

Decision : ACCEPTABLE

Reason : BASED ON PROFILE

Establishment : CFN : 2410924 FEI : 2410924

PFIZER INC

630 FLUSHING AVE

BROOKLYN, NY 11206

DMF No: AADA: