# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-269**

## CHEMISTRY REVIEW(S)

**NDA 21-269**

# Cardura XL

(doxazosin mesylate extended release tablets)

**Pfizer Inc.**

**Rajiv Agarwal**

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

**Chemistry Review Data Sheet**

1. NDA 21-269
2. REVIEW # 3
3. REVIEW DATE: 22-FEB-2005
4. REVIEWER: Rajiv Agarwal
5. PREVIOUS DOCUMENTS:

| Submission (s) Reviewed | Document date |
|---|---|
| ORIGINAL | 02-APR-2001 |
| AMENDMENT | 13-FEB-2002 |
| AMENDMENT | 17-DEC-2003 |
| AMENDMENT | 04-MAY-2004 |
| AMENDMENT | 10-MAY-2004 |
| AMENDMENT | 13-MAY-2004 |
| AMENDMENT | 14-MAY-2004 |
| AMENDMENT | 26-MAY-2004 |
| AMENDMENT | 28-MAY-2004 |
| AMENDMENT | 07-JUN-2004 |
| AMENDMENT | 09-JUN-2004 |
| AMENDMENT | 16-JUN-2004 |
| AMENDMENT | 20-AUG-2004 |
| AMENDMENT | 22-NOV-2004 |
| AMENDMENT | 24-NOV-2004 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| AMENDMENT | 20-AUG-2004 |
| AMENDMENT | 22-NOV-2004 |
| AMENDMENT | 24-NOV-2004 |
| AMENDMENT | 25-NOV-2004 |
| AMENDMENT | 02-DEC-2004 |
| AMENDMENT | 18-FEB-2005 |

7. NAME & ADDRESS OF APPLICANT:

Name: Pfizer, Inc.

Address: 235 E 42nd Street, New York, NY 10017

Chemistry Review Data Sheet

Representative: Mr. Alan J Dunbar

Telephone: 212-733-4126

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Cardura XL
b) Non-Proprietary Name (USAN): Doxazosin mesylate extended release tablets
c) Code Name/# (ONDC only): None
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: For the treatment of benign prostatic hyperplasia

11. DOSAGE FORM: Extended Release tablets (GITS formulation)

12. STRENGTH/POTENCY: 4 mg and 8 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

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

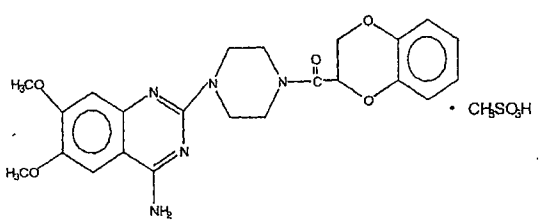
_____SPOTS product – Form Completed

____x__Not a SPOTS product

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

**Chemical Name:** 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(1,4-benzodioxan-2-ylcarbonyl) piperazine methanesulfonate

**Structural formula:**




**Molecular Formula**: $C_{23}H_{25}N_5O_5$ $CH_3O_3S$

**Molecular weight**: 547.6

17. RELATED/SUPPORTING DOCUMENTS:

- EES inspection report: Acceptable 20-APR-2004 (see the attached EER report; Appendix -1)
- Chemistry Review # 1 of NDA 19-668 (Cardura IR) dated 8-MAY-1987
- [redacted]
- [redacted]
- Chemistry Review # 1 of NDA 21-269 dated 21-FEB-2002 and Addendum to Chemistry Review # 1 dated 22-FEB-2002
- Chemistry Review # 2 of NDA 21-269 dated 17-JUN-2004
- Meeting minutes dated 3-FEB-2004 (Teleconference between the Cardio-Renal and Pfizer regarding the proposal to deal with the issue of [redacted] in doxazosin mesylate)
- Meeting minutes dated 14-MAY-2004
- Meeting minutes dated 16-JUN-2004
- Approvable letter dated 17-JUN-2004
- Teleconference dated 18-NOV-2004
- Teleconference dated 08-DEC-2004
- Teleconference dated 17-FEB-2005

18. STATUS:

**ONDC:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| EES | **Acceptable** | 20-APR-2004 | Ms. Janine Ambrogio |
| DDMAC | **Acceptable*** | 24-JAN-2005 | Ms. Corrinne Kulick |
| DMETS | **Acceptable** | 16-DEC-2004 | Linda Kim-Jung |
| Biopharmaceutics | **Approval** | 17-JUN-2004 | Dr. Stephan Ortiz |
| Pharm./Tox. | **Approval** | 11-NOV-2004 | Dr. Lynnda Reid |

*DDMAC recommended [redacted] from the trade name (Cardura XL) on 24-JAN-2005. The recommendation was communicated to the applicant via a t-con held on 26-JAN-2005. The applicant satisfactorily revised the container/closure labels as requested via amendment dated 18-FEB-2005.

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**The Chemistry Review for NDA 21-269**

**The Executive Summary**

***I. Recommendations***

***A. Recommendation and Conclusion on Approvability:***

This NDA is recommended for **approval** from the CMC stand point.

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

None

***II. Summary of Chemistry Assessments***

***A. Description of the Drug Product(s) and Drug Substance(s)***

**Drug Product:**

Cardura XL, extented release tablet, utilizes the Gastrointestinal Therapeutic System (**GITS**), which is designed to provide a controlled rate of delivery of doxazosin into the gastrointestinal lumen. The tablet consists of an osmotically active drug core surrounded by semi-permeable membrane. The core is divided into an active layer containing the drug and a push layer containing osmotically active components. The membrane surrounding the tablet is permeable to water but not to drug or osmotic excipients. Water from the GI tract enters the tablet, the pressure increases in the osmotic layer which pushes against the drug layer and resulting in the release of drug through a small, laser drilled orifice in the membrane on the drug side of the tablet.

The **active ingredient** is **doxazosin mesylate** and inactive excipients are polyethylene oxide, sodium chloride, [redacted], red ferric oxide, titanium dioxide, magnesium stearate, cellulose acetate, Macrogol, pharmaceutical glaze and black iron oxide. A 5% overage of drug substance is included in the drug product at manufacturing. [redacted]

[redacted] The bio-lots (N5214-QC2021 and N5215-QC2023) also have this overage.

It is recognized that during the manufacturing of Cardura XL, there is a potential for having [redacted] impurities in the drug product either due to a possible reaction between [redacted] doxazosin mesylate or due to a potential for carry over of the impurities from the drug substance.

The applicant was asked to address the issue by providing the results of analysis to eliminate the concern. The applicant proposed that 12 batches each of Cardura, Cardura IR and Cardura XL be analyzed to demonstrate the amount of [redacted]

***The applicant has provided the data, and the results demonstrated that the [redacted] impurities in these products were [redacted]***

The drug product is manufactured at Pfizer Inc. in Brooklyn, NY and the facility is **in compliance with cGMP**. The **EER** was forwarded to the Office of Compliance on 05-JAN-2004 for NDA 21-269. An **acceptable** recommendation was issued on 20-APR-2004 (**see Appendix 1**).

Based on the available data, a **24 month expiry date** can be granted for the product packaged in [redacted] **bottles,** [redacted]

The trade name and graphics of **Cardura XL** was accepted by **DMETS** on 09-APR-2004. The consult was submitted to DDMAC to comment on the [redacted] DDMAC recommended [redacted] (Cardura XL) on 24-JAN-2005. The recommendation was communicated to the applicant via a t-con held on 26-JAN-2005. The applicant satisfactorily revised the container/closure labels as requested via amendment dated 18-FEB-2005.

[redacted] ***Also, please refer to Chemistry review # 1, addendum to review # 1 and Chemistry review # 2 of NDA 21-269 dated 21-FEB-2002, 22-FEB-2002, and 17-JUN-2004, respectively.***

**Drug Substance:**

Doxazosin mesylate is a quinazoline compound and is a selective inhibitor of the alpha$_1$ subtype of alpha adrenergic receptors. Drug substance is manufactured at three different sites (Pfizer Inc. in Groton, CT, USA; Pfizer Inc. in Barceloneta, Puerto Rico; and Pfizer Inc. in Ringaskiddy, Cork, IRL).

The major concern with the drug substance was the possibility of formation of [redacted] impurities during drug substance synthesis. There is a potential for the formation of [redacted] impurities either during the synthesis where [redacted] These impurities could also be present as process impurities in [redacted] The applicant was asked to address the issue by providing the results of analysis to eliminate the concern.

To address this issue, the applicant proposed that12 batches of doxazosinn mesylate be analyzed to demonstrate the amount of [redacted] with the lower limit of detection of the validated analytical method at [redacted]

The applicant withdrew the Kent (UK) site from this submission via an amendment. All three remaining facilities are **in compliance with cGMP.**

***Please refer to Chemistry Review # 1 of NDA 19-668 (8-MAY-1987)*** [redacted]

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

Cardura XL is formulated as a once-a-day controlled release tablet for oral use and is designed to deliver 4 or 8 mg of doxazosin as the free base.

***C. Basis for Approvability or Not-Approval Recommendation:***

- The applicant has responded satisfactorily (via amendments dated 24-NOV-2004 and 25-NOV-2004) to the CMC issues on [redacted] delineated in the approvable letter dated 17-JUN-2004. The provided data indicate that the drug substance and the drug product contain [redacted]

- DDMAC recommended to [redacted] (Cardura XL) on 24-JAN-2005. The recommendation was communicated to the applicant via a t-con held on 26-JAN-2005. The applicant satisfactorily revised the container/closure labels as requested via amendment dated 18-FEB-2005.

- DMETS recommended to [redacted]

The recommendations were communicated to the applicant via a t-con held on 26-JAN-2005. The applicant satisfactorily revised the container/closure labels as requested via amendment dated 18-FEB-2005.

## *III. Administrative*

### *A. Reviewer's Signature*

***Electronically captured in DFS***

### *B. Endorsement Block*

Rajiv Agarwal/Moo-Jhong Rhee/Jennifer Mercier/MKaufman: Date 22-FEB-2005

### *C. CC Block*

HFD-580/Division File/NDA 21-269

10 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Chemistry-1*

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/s/

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Rajiv Agarwal
2/22/05 03:03:20 PM
CHEMIST

Moo-Jhong Rhee
2/22/05 03:35:43 PM
CHEMIST
I concur

**NDA 21-269**

**Cardura XL**
(doxazosin mesylate extended release tablets)

**Pfizer Inc.**

**Rajiv Agarwal**

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

**Chemistry Review Data Sheet**

1. NDA 21-269
2. REVIEW # 2
3. REVIEW DATE: 15-JUN-2004
4. REVIEWER: Rajiv Agarwal
5. PREVIOUS DOCUMENTS:

| Submission (s) Reviewed | Document date |
|---|---|
| Original | 02-APR-2001 |
| AMENDMENT | 13-FEB-2002 |
| CMC Review # 1 | 21-FEB-2002 |
| Addendum to CMC Review #1 | 22-FEB-2002 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| ORIGINAL | 17-DEC-2003 |
| AMENDMENT | 04-MAY-2004 |
| AMENDMENT | 10-MAY-2004 |
| AMENDMENT | 13-MAY-2004 |
| AMENDMENT | 14-MAY-2004 |
| AMENDMENT | 26-MAY-2004 |
| AMENDMENT | 28-MAY-2004 |
| AMENDMENT | 07-JUN-2004 |
| AMENDMENT | 09-JUN-2004 |
| AMENDMENT | 16-JUN-2004 |

7. NAME & ADDRESS OF APPLICANT:

Name: Pfizer, Inc.

Address: 235 E 42nd Street, New York, NY 10017

Representative: Mr. Alan J Dunbar

Telephone: 212-733-4126

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Cardura XL
b) Non-Proprietary Name (USAN): Doxazosin mesylate extended release tablets

Chemistry Review Data Sheet

c) Code Name/# (ONDC only): None
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: For the treatment of benign prostatic hyperplasia

11. DOSAGE FORM: Extended Release tablets (GITS formulation)

12. STRENGTH/POTENCY: 4 mg and 8 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

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

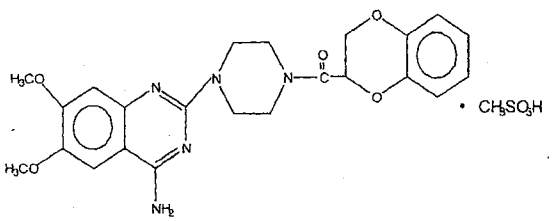
_____SPOTS product – Form Completed

____x__Not a SPOTS product

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

**Chemical Name:** 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(1,4-benzodioxan-2-ylcarbonyl) piperazine methanesulfonate

**Structural formula:**




**Molecular Formula**: $C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$

**Molecular weight**: 547.6

17. RELATED/SUPPORTING DOCUMENTS:

- EES inspection report: Acceptable 20-APR-2004 (see the attached EER report; Appendix -1)
- Chemistry Review # 1 of NDA 19-668 dated 8-MAY-1987

- [redacted]
- Chemistry Review #1 of NDA 21-269 dated 21-FEB-2002 and Addendum to Chemistry Review # 1 dated 22-FEB-2002
- [redacted]
- Meeting minutes dated 3-FEB-2004 (Teleconference between the Cardio-Renal and Pfizer regarding the proposal to deal with the issue of [redacted] in doxazosin mesylate)
- Meeting minutes dated 14-MAY-2004
- Meeting minutes dated 16-JUN-2004

18. STATUS:

**ONDC:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| EES | **Acceptable** | 20-APR-2004 | Ms. Janine Ambrogio |
| DMET | **Acceptable** | 09-APR-2004 | Ms. Kristina Arnwine |
| Biopharmaceutics | **Approval** | 17-JUN-2004 | Dr. Stephan Ortiz |
| Pharm./Tox. | **Approvable** | 10-JUN-2004 | Dr. Suzanne Thornton-Jones |

Chemistry Review Data Sheet

**The NDA 21-269 is amended (Via E-mails) by the following amendments during this review cycle.**

**04-MAY-2004:** A 5% overage for Cardura XL is provided via this amendment.
**10-MAY-2004:** The applicant states that there is no [redacted] bottle and the [redacted] bottles [redacted]
**13-MAY-2004:** Stability information of 4 mg tablets [redacted]
**14-MAY-2004:** Method validation (drug substance and drug product) and COAs of Cardura XL is provided.
**26-MAY-2004**: COAs for lots N9123, N9123, N9124 and N9125 are provided.
**28-MAY-2004:** Interim analysis of the [redacted] impurity in drug substance and literature reference to calculate its formation is provided.
**07-JUN-2004:** Drug product manufacturing information is provided.
**09-JUN-2004:** Color mock-ups (draft) of container closure labels are provided.
**16-JUN-2004:** Finalized Dissolution Specifications for Cardura XL (4 and 8 mg) are provided.

**The Chemistry Review for NDA 21-269**

**The Executive Summary**

*I. Recommendations*

*A. Recommendation and Conclusion on Approvability:*

This NDA is recommended for **approvable** because data is not available for addressing issues on the [redacted] impurities in the drug substance and drug product.

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

None

*II. Summary of Chemistry Assessments*

*A. Description of the Drug Product(s) and Drug Substance(s)*

**Drug Product:**

Cardura XL, extented release tablet, utilizes the Gastrointestinal Therapeutic System (**GITS**), which is designed to provide a controlled rate of delivery of doxazosin into the gastrointestinal lumen. The tablet consists of an osmotically active drug core surrounded by semi-permeable membrane. The core is further divided into an active layer containing the drug and a push layer containing osmotically active components. The membrane surrounding the tablet is permeable to water but not to drug or osmotic excipients. Water from the GI tract enters the tablet, the pressure increases in the osmotic layer which pushes against the drug layer and resulting in the release of drug through a small, laser drilled orifice in the membrane on the drug side of the tablet.

The **active ingredient** is **doxazosin mesylate** and inactive excipients are polyethylene oxide, sodium chloride, [redacted] red ferric oxide, titanium dioxide, magnesium stearate, cellulose acetate, Macrogol, pharmaceutical glaze and black iron oxide. A 5% overage of drug substance is included in the drug product at manufacturing.

[redacted] The bio-lots (N5214-QC2021 and N5215-QC2023) also have this overage.

It is recognized that during the manufacturing of Cardura XL, there is a potential for having [redacted] impurities in the drug product due to a possible reaction between [redacted] in doxazosin mesylate or a potential for carrying over the impurities from the drug substance. The applicant was asked to address the issue by providing the results of analysis to eliminate the concern. To address this issue, the applicant proposed that 12 batches of each Cardura and Cardura XL will be analyzed to demonstrate the amount of [redacted]. The lower limit of detection of the validated analytical method will be [redacted]

The drug product is manufactured at Pfizer Inc. in Brooklyn, NY and the facility is **in compliance with cGMP**. The **EER** was forwarded to the Office of Compliance on 05-JAN-2004 for NDA 21-269. An **acceptable** recommendation was issued on 20-APR-2004 (**see Appendix 1**).

Based on the available data **24 month expiry date** can be granted for the product packaged in [redacted] **bottles,** [redacted] Drug product packaged in [redacted] bottle is intended for commercial launch. [redacted]

The trade name **Cardura XL** was accepted by **DMETS** on 09-APR-2004.

[redacted] ***Also, please refer to Chemistry review # 1 and addendum to review # 1 of NDA 21-269 dated 21-FEB-2002 and 22-FEB-2002, respectively.***

**Drug Substance:**

Doxazosin mesylate is a quinazoline compound and is a selective inhibitor of the $alpha_1$ subtype of alpha adrenergic receptors. Drug substance is manufactured at three different sites (Pfizer Inc. in Groton, CT, USA; Pfizer Inc. in Barceloneta, Puerto Rico; and Pfizer Inc. in Ringaskiddy, Cork, IRL).

During the synthesis of doxazosin mesylate, there is a potential for the formation of [redacted] impurities either during the synthesis, where [redacted] or these impurities can be present as process impurities in [redacted] The applicant was asked to address the issue by providing the results of analysis to eliminate the concern.
To address this issue, the applicant proposed that12 batches of doxazosin mesylate will be analyzed to demonstrate the amount of [redacted] The lower limit of detection of the validated analytical method will be [redacted]

Applicant withdrew the Kent (UK) site from this submission via an amendment.
All three remaining facilities are **in compliance with cGMP.**

***Please refer to Chemistry Review # 1 of NDA 19-668 (8-MAY-1987)*** [redacted]

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

Cardura XL is formulated as a once-a-day controlled release tablet for oral use and is designed to deliver 4 or 8 mg of doxazosin as the free base.

*C. Basis for Approvability or Not-Approval Recommendation:*

1. Although the applicant has made argument that under the manufacturing conditions, it is not expected to produce significant amount of [redacted] impurities, until it is demonstrated with validated analytical data from a statistically significant number of batches of drug substance and drug product, no assurance has been established.
2. The final color lay outs of the container labels with indicated changes are not provided.
3. There is a discrepancy in the NDC # provided on the container labels and insert. The NDC # on all the labels should be identical.

*III. Administrative*

*A. Reviewer's Signature*

*Electronically captured in DFS*

*B. Endorsement Block*

Rajiv Agarwal/Moo-Jhong Rhee/Jennifer Mercier/MKaufman: Date 17-JUN-2004

*C. CC Block*

HFD-580/Division File/NDA 21-269

24 Page(s) Withheld

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_____ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Chemistry-*2

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/s/

Rajiv Agarwal
6/17/04 02:43:36 PM
CHEMIST

Moo-Jhong Rhee
6/17/04 02:50:05 PM
CHEMIST
I concur

Chemistry Review Data Sheet

**NDA 21-269**

**Cardura XL**
(doxazosin mesylate)
**Extended Release Tablets**

**Pfizer Inc.**

**Rajiv Agarwal**

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

**Chemistry Review Data Sheet**

1. NDA 21-269
2. REVIEW # 1
3. REVIEW DATE: 21-FEB-02
4. REVIEWER: Rajiv Agarwal
5. PREVIOUS DOCUMENTS: N/A
6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| ORIGINAL | 20-APR-2001 |
| AMENDMENT | 13-FEB-2002 |

7. NAME & ADDRESS OF APPLICANT:

Name: Pfizer, Inc.

Address: 235 E 42 nd Street, New York, NY 10017

Representative: Mr. Alan J Dunbar

Telephone: 212-733-4126

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Cardura XL
b) Non-Proprietary Name (USAN): Doxazosin mesylate
c) Code Name/# (ONDC only): None
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: Standard

9. LEGAL BASIS FOR SUBMISSION: Not applicable

10. PHARMACOL. CATEGORY: For the treatment of benign prostatic hyperplasia

11. DOSAGE FORM: Extended Release tablets (GITS formulation)

12. STRENGTH/POTENCY: 4 mg and 8 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note25]:

Chemistry Review Data Sheet

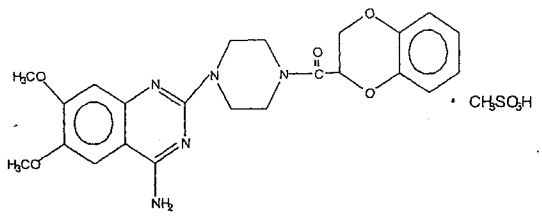
_____SPOTS product – Form Completed

____x__Not a SPOTS product

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

**Chemical Name:** 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(1,4-benzodioxan-2-ylcarbonyl) piperazine methanesulfonate

**Structural formula:**




**Molecular Formula**: $C_{23}H_{25}N_5O_5.\ CH_4O_3S$

**Molecular weight**: 547.6

17. RELATED/SUPPORTING DOCUMENTS:

- EES inspection report: Acceptable 14-DEC-2001(see the attached EER report; Appendix -1)
- [redacted]
- E-mail from Mr. Alan Dunbar dated 21-FEB-2002 (see Appendix-2)

18. STATUS:

**ONDC:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| EES | **Acceptable** | 14-DEC-2001 | Ms. S Ferguson |
| OPDRA | **Acceptable** | 17-DEC-2001 | David Diwa |

Chemistry Review Data Sheet

**The Chemistry Review for NDA 21-351**

**The Executive Summary**

*I. Recommendations*

*A. Recommendation and Conclusion on Approvability:*

This NDA may be **approved** from the CMC point of view [redacted]

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

None

*II. Summary of Chemistry Assessments*

*A. Description of the Drug Product(s) and Drug Substance(s)*

**Drug Product:**

The Cardura XL, extented release tablet, utilizes Gastrointestinal Therapeutic System (**GITS**), which is designed to provide a controlled rate of delivery of doxazosin into the gastrointestinal lumen. Tablet is consists of an osmotically active drug core surrounded by semi-permeable membrane. The core is further divided into an active layer containing the drug and a push layer containing osmotically active components. The membrane surrounding the tablet is permeable to water but not to drug or osmotic excipients. Water from the GI tract enters the tablet, pressure increases in the osmotic layer and pushes against the drug layer, resulting in the release of drug through a small, laser drilled orifice in the membrane on the drug side of the tablet.

The **active ingredient** is **doxazosin mesylate** and inactive excipients are polyethylene oxide, sodium chloride, [redacted] red ferric oxide, titanium dioxide, magnesium stearate, cellulose acetate, Macrogol, pharmaceutical glaze and black iron oxide.

The drug product is manufactured at Pfizer Inc. in Brooklyn, NY and the facility is **in compliance with cGMP**. The **EER** was forwarded to the Office of Compliance on 27-AUG-2001 for NDA 21-269. An **acceptable** recommendation was issued on 14-DEC-2001 (see Appendix 1).

Based on the available data only [redacted] **expiry date** can be granted for the product packaged in [redacted] **bottles**.

The trade name **Cardura XL** was accepted by **OPDRA**.

[redacted]

Chemistry Review Data Sheet

**Drug Substance:**

Doxazosin mesylate is a quinazoline compound and is a selective inhibitor of the alpha subtype of alpha adrenergic receptors. Drug substance is manufactured at four different sites (Pfizer Inc. in Groton, CT, USA; Pfizer Inc. in Barceloneta, Puerto Rico; Pfizer Inc. in Sandwich, Kent, UK; and Pfizer Inc. in Ringaskiddy, Cork, IRL). All four facility are **in compliance with cGMP**

[redacted]

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

Cardura XL is formulated as a once-a-day controlled release tablet for oral use and is designed to deliver 4 or 8 mg of doxazosin as the free base.

*C. Basis for Approvability or Not-Approval Recommendation:*

None

*III. Administrative*

*A. Reviewer's Signature*

*B. Endorsement Block*

Rajiv Agarwal/Moo-Jhong Rhee/Evelyn Farinas: Date 21-FEB-2002

*C. CC Block*

HFD-580/Division File/NDA 21-269

7 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

*Withheld Track Number: Chemistry-* 3

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/s/

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Rajiv Agarwal
2/21/02 04:59:16 PM
CHEMIST

Moo-Jhong Rhee
2/21/02 05:32:31 PM
CHEMIST