CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-269

PHARMACOLOGY REVIEW

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

PHARMACOLOGY/TOXICOLOGY MEMO TO FILE

NDA NUMBER:	21-269
DATE RECEIVED BY CENTER:	8/20/2004
DRUG NAME:	Cardura XL (doxazosin mesylate)
INDICATION:	treatment of [redacted] BPH
SPONSOR:	Pfizer
PHARM/TOX SUPERVISOR:	Lynnda Reid, Ph.D.

BACKGROUND: On June 17, 204, Pfizer was issued an 'approvable' letter for Cardura XL. Outstanding nonclinical issues were the quantification and qualification of [redacted] impurities in the drug product.

Deficiency: We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following deficiency: [redacted] of the drug substance as well as the drug product. [redacted], are known genotoxins and potential human carcinogens. To ensure patient safety, the Division requires a limit on the total concentration of [redacted] in the active pharmaceutical ingredient (API) and in the drug product. At this time no agreed-upon standard exists in the scientific community for limits on these specific impurities. Therefore, for this NDA, we require an interim standard of [redacted] You have not demonstrated that the total amount of [redacted] in the API and the drug product is consistently [redacted]

Information needed to resolve this deficiency:

1. Demonstrate that your analytical method for detecting [redacted]
2. Using a validated analytical method, provide data from the analysis of 12 batches each of the API, Cardura®, and Cardura XL® to confirm that the amount of [redacted]

Response: The Sponsor has submitted analytical data demonstrating the concentration of possible [redacted] The submission was reviewed by Chemistry and they concur with the findings (See Chemistry Review for details).

RECOMMENDATION: From a pharmacology and toxicology perspective, the NDA deficiencies have been adequately addressed and we recommend approval of this NDA.

Note: This information has no impact on labeling as previously proposed in the original NDA review.

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/s/

Lynnda Reid
11/30/04 02:13:25 PM
PHARMACOLOGIST

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

PHARMACOLOGY/TOXICOLOGY MEMO TO FILE

NDA NUMBER:	21-269
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	12/17/2003
DRUG NAME:	Cardura XL (doxazosin mesylate)
INDICATION:	treatment of [redacted] BPH
SPONSOR:	Pfizer
REVIEW DIVISION:	Division of Reproductive and Urologic Drug Products (HFD-580)
PHARM/TOX SUPERVISOR:	Lynnda Reid, Ph.D.
DIVISION DIRECTOR:	Daniel Shames, M.D.
PROJECT MANAGER:	Martin Kaufman
RECOMMENDATION:	Pharmacology and toxicology recommends approvable for this NDA. Outstanding issues are quantification and qualification of [redacted] impurities in the drug product.

[redacted]

Impurities and degradation products can generally be qualified through genotoxicity and carcinogenicity studies. However, in the case of Cardura XL, only the base (not the mesylated salt) was tested in the genotoxicity studies which demonstrated that doxazosin was not genotoxic. Two-year carcinogenicity studies were conducted in mice and rats with doxazosin mesylate, thus qualifying the drug substance. However, [redacted] in the manufacturing of the final drug product. The drug product has not been qualified. There is also a possibility for [redacted]

For approval of Cardura XL we would like to have the following information:

1) The drug substance and drug product should be evaluated for [redacted] impurities and degradation products.
2) To determine the sensitivity of the analytical method, we want the lower limit of detection (LOQ) defined.

3) If the assay is not robust, a sufficient number of batches available for analysis, or aged drug product is not available for analysis, it may be necessary to set a specification for the drug product until enough data has been generated to assure the Division that [redacted] impurities remain well [redacted] for the shelf life of the drug product.

Labeling: I concur with the labeling recommendations of the primary pharmacology/toxicology reviewer, Dr. Suzanne Thornton-Jones.

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/s/

Lynnda Reid
6/14/04 10:17:03 AM
PHARMACOLOGIST

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-269**
SERIAL NUMBER:	**N000 AZ**
DATE RECEIVED BY CENTER:	**12/17/2003**
DRUG NAME:	**doxazosin mesylate (Cardura XL)**
INDICATION:	**treatment of [redacted] BPH**
SPONSOR:	**Pfizer**
DOCUMENTS REVIEWED:	**electronic**
REVIEW DIVISION:	**Division of Reproductive and Urologic Drug Products (HFD-580)**
PHARM/TOX REVIEWER:	**Suzanne R. Thornton-Jones, Ph.D.**
PHARM/TOX SUPERVISOR:	**Lynnda Reid, Ph.D.**
DIVISION DIRECTOR:	**Daniel Shames, M.D.**
PROJECT MANAGER:	**Martin Kaufman**

Date of review submission to Division File System (DFS): 10 June 2004

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on acceptability.
The NDA is approvable from a pharmacology/toxicology perspective. The only issue is the potential for the production of the 'in process' impurity [redacted] in the drug substance and product. This impurity is a genotoxic agent that has been shown to cause tumors in animals. In this light the Sponsor needs to quantitate the [redacted] impurity. If measurable amounts of the impurity are detected in either the drug substance or drug product, the impurity must be qualified according to ICH-Q3A: Impurities in New Drug Substances and/or ICH-Q3B: Impurities in New Drug Products, and an appropriate manufacturing specification established.

B. Recommendation for nonclinical studies.
None.

C. Recommendations on labeling
None.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings
Not applicable.

B. Pharmacologic activity
Doxazosin mesylate is an alpha-1 adrenergic receptor antagonist.

C. Nonclinical safety issues relevant to clinical use
The drug substance is a mesylate salt which can lead to the production of [redacted] processing of the drug substance and drug product. [redacted] is a genotoxic agent that has been shown to cause tumors in animals. The Sponsor is working with CMC to develop an analytical method to determine the levels of these process impurities.

Reviewer Signature Suzanne R. Thornton-Jones, Ph.D.

Supervisor Signature Lynnda Reid, Ph.D. Concurrence Yes X No ___

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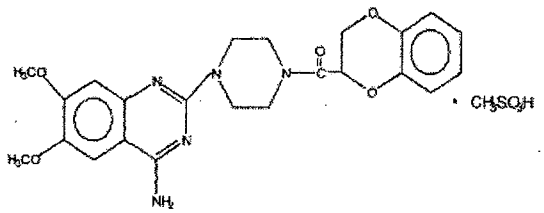
2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA NUMBER:	21-269
REVIEW NUMBER:	1
SEQUENCE NUMBER/DATE/TYPE OF SUBMISSION:	N000/17 December 2003/AZ
INFORMATION TO SPONSOR:	Yes ( ) No (X)
SPONSOR:	Pfizer Pharmaceutical Group Pfizer Inc. 235 East 42nd Street New York, NY 10017
MANUFACTURER FOR DRUG SUBSTANCE :	Pfizer
REVIEWER NAME:	Suzanne R. Thornton-Jones, Ph.D.
DIVISION NAME:	DRUDP
HFD #:	580
REVIEW COMPLETION DATE:	09 June 2004
DRUG:	
TRADE NAME:	doxazosin mesylate GITS
GENERIC NAME (LIST ALPHABETICALLY):	Cardura XL
CODE NAME:	NA
CHEMICAL NAME:	1-(4-amino-6, 7-dimethoxy-2-quinazolinyl)-4-(1,4-benzodioxan-2-ylcarbonyl) piperazine methanesulfonate.
CAS REGISTRY NUMBER:	77883-43-3
MOLE FILE NUMBER:	not specified
MOLECULAR FORMULA/MOLECULAR WEIGHT:	$C_{23}H_{25}N_5O_5$/547.6
STRUCTURE:	



RELEVANT INDS/NDAS/DMFS:	[redacted] 32,633, [redacted], NDA 19-668, 20-371
DRUG CLASS:	alpha-1 adrenergic receptor antagonist
INTENDED CLINICAL POPULATION:	urinary obstruction in BPH
CLINICAL FORMULATION:	gastrointestinal therapeutic system (GITS) extended release tablet
ROUTE OF ADMINISTRATION:	oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission: No new studies were submitted. All original studies were reviewed by the Division of Cardio-renal Drug Products under NDA 19-668.

Studies not reviewed within this submission: Not applicable.

2.6.2 PHARMACOLOGY: No new studies were submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY: No new studies were submitted.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS: No new studies were submitted.

2.6.6 TOXICOLOGY: No new studies were submitted.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: Not applicable.

Unresolved toxicology issues: A new concern within CDER is the possible production of genotoxic impurities which can be produced when free base drugs are converted to a mesylate salt. The problem arises when [redacted] are used [redacted] processing of the drug substance and/or drug product. These [redacted] These process impurities are known genotoxic agents and [redacted] is commonly used as positive genotoxic control in genotoxicity assays. Further, IARC Monographs have reported that [redacted] the one of primary interest for this submission, has been shown to cause cancer in mice followed s.c. administration (lung tumors), and in mice and rats following i.p. administration (lung and kidney tumors).

The possibility for these process impurities in the drug substance and product exists for Cardura XL because [redacted] is used during manufacturing. It should be noted that the concern for these process impurities was not identified in the original review cycle or with prior NDA submissions because the issue was only recently identified. The issue regarding these process impurities was conveyed to the NDA review team at the beginning of the review cycle and it was determined that CMC and pharmacology/toxicology would work together to resolve the issue. The first priority was to contact the Sponsor to convey to them our concern and discuss the process for resolving the issue which would likely be the development of an analytical method to determine if either of the process impurities was present.

Two approaches to establishing a limit specification for the impurities are being explored within CDER and include: 1) limiting the amount in the drug substance to [redacted] (Division of Cardio-renal Drug Products); or 2) limiting the amount based on the total daily intake (TDI) (Division of Anesthetic, Critical Care, and Addiction Drug Products). The [redacted] limit proposal uses benzene as the model compound with the caveat that benzene may not be the correct model for assessing mutagenic risks of genotoxic impurities because it and these

impurities may act by different mechanisms. The EPA limit of benzene is 5 ppb in drinking or 5 micrograms benzene/L. The limit was established assuming a 2L intake of water daily which is equivalent to 10 micrograms/day of benzene with a probability of 1 in a million risk of cancer.

The pharmacology/toxicology reviewer for this NDA agrees with the [redacted] limit approach of the Division of Cardio-renal, who originally reviewed the Cardura NDA. I feel it is more prudent to establish a limit and set the specification at the drug substance level rather than using the TDI approach. However, since the [redacted] limit is an arbitrarily established limit, it would also appear more prudent to have the Sponsor try to quantitate the impurity and to set the specification limit based on that level, which may be lower than the proposed [redacted] The Sponsor has been working on the analytical method for the impurity detection and is anticipating forwarding the results in August 2004. Unfortunately this date will be past the PDUFA goal date for this submission.

Many of the previously conducted non-clinical studies used the doxasozin base, including the genotoxicity assays, but the embryo-fetal development reproductive toxicity study in rabbits, and the 2-year mouse and rat carcinogenicity bioassays used the mesylate salt. Further the non-clinical studies used early batches of the drug substance that were extensively processed [redacted] In this light, it is possible that the impurities were present at much higher amounts than the currently marked product. A caveat to this qualification potential is that other than a Certificate of Analysis, which will not likely have information on these specific impurities, it is unlikely that there are any retention samples available for analysis of these impurities as most laboratories only maintain retention samples from non-clinical studies for 10 years. Further if these impurities are detected in any remaining retention samples, it will be difficult to determine if they were there when the studies were conducted or if they were created through breakdown during storage. The impurity results from the current drug substance and drug product batches will be the key to resolving this issue. Based on the negative carcinogenicity study results for the drug substance, it is likely that it could be qualified; however the drug product will not be qualified.

In summary, the potential for the formation of [redacted] a known genotoxic and carcinogenic agent, is possible during the manufacture of the drug substance and drug product as [redacted] is used during the process. The drug substance may be qualified for the impurity as doxazosin mesylate was used in the 2-year mouse and rat carcinogenicity bioassays and was negative. However, no genotoxicity data is available for doxazosin mesylate as doxazosin base was used in the standard genotoxicity battery. The drug product was not examined and further qualification is required.

Recommendations: The Sponsor needs to quantitate the [redacted] in-process impurity. If measurable amounts of the impurity are detected in either the drug substance or drug product, the impurity must be qualified according to ICH-Q3A: Impurities in New Drug Substances and/or ICH-Q3B: Impurities in New Drug Products, and an appropriate manufacturing specification established.

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✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Pharm/Tox- 4

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/s/

Suzanne Thornton-Jones
6/10/04 07:28:35 AM
PHARMACOLOGIST

Lynnda Reid
6/10/04 10:00:58 AM
PHARMACOLOGIST

NDA 21-269

Cardura XL

Supervisory Pharmacologist Labeling Memo

The preclinical portion of this NDA was reviewed by the Division of Cardiorenal Drug Products. I have reviewed the labeling changes they made for the GITS product and they are satisfactory for all clinical indications.

Alex Jordan, PhD

NDA 21-269
HFD-580

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/s/

Alexander W. Jordan
2/11/02 10:45:01 AM
PHARMACOLOGIST