CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-269

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 21-269

Section 14:

PATENT AND EXCLUSIVITY INFORMATION FOR CARDURA XL®

1.	Active Ingredient:	doxazosin mesylate	
2.	Strengths:	4 and 8 mg	
3.	Trade Name:	Cardura XL®	
4.	Dosage Form/Route of Administration:	Extended Release Oral Tablets	
5.	Application Firm Name:	Pfizer, Inc.	
6.	NDA Number:	21-269	
7.	Exclusivity Period:	Three years from date of approval	
8.	Applicable Patent Numbers and Expiration Dates:	4,612,008 4,765,989 4,837,111 4,946,687	September 16, 2003 September 16, 2003 March 21, 2008 October 2, 2007

EXCLUSIVITY SUMMARY FOR NDA # 21-269 SUPPL #_____

Trade Name Cardura XL Generic Name doxazosin mesylate

Applicant Name Pfizer, Inc. HFD # 580

Approval Date If Known February 23, 2005

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_X_/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b) (1)

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

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

YES /___/ NO /_X_/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES /_X_/ NO /___/

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

NDA# 20-371 Cardura

NDA# 19-688 Cardura

NDA# _____ _____

2. Combination product.

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

YES /___/ NO /___/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

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

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any

investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

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

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

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

YES /_X_/ NO /___/

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

_____

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

YES /___/ NO /_X_/

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

YES /___/ NO /___/

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:

NSDK95001; NY95001; NY95001B A0351061

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

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

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

Investigation #1 NSDK95001 YES /___/ NO /_X_/

Investigation #2 NY95001 YES /___/ NO /_X_/

Investigation #3 NY95001B YES /___/ NO /_X_/

Investigation #4 A0351061 YES /___/ NO /_X_/

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

_____ _____

_____ _____

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

Investigation #1 NSDK95001 YES /___/ NO /_X_/

Investigation #2 NY95001 YES /___/ NO /_X_/

Investigation #3 NY95001B YES /___/ NO /_X_/

Investigation #4 A0351061 YES /___/ NO /_X_/

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

_____ _____

_____ _____

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

Investigation #1 NSDK95001 YES /_X_/ NO /__/

Investigation #2 NY95001 YES /_X_/ NO /__/

Investigation #3 NY95001B YES /X__/ NO /__/

Investigation #4 A0351061 YES /X__/ NO /__/

4. To be eligible for exclusivity, a new investigation that is

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

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

Investigation #1		
IND # _____	YES /___/	NO /___/ Explain: _____
Investigation #2		
IND # _____	YES /___/	NO /___/ Explain: _____
Investigation #3		
IND # _____	YES /___/	NO /___/ Explain: _____
Investigation #4		
IND # 32,633	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 /_X_/ Explain _____
_____	Foreign study
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /_X_/ Explain _____

_____	!	Foreign study_____
_____	!	_____
Investigation #3	!	
YES /___/ Explain _____	!	NO /_X__/ Explain _____
_____	!	Foreign study_____
_____	!	_____

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

YES /___/ NO /_X_/

If yes, explain: _____

_____

Signature Date
Title:

Signature of Office/ Date
Division Director

Form OGD-011347 Revised 05/10/2004

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/s/

Daniel A. Shames
3/1/05 07:22:53 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA # : 21-269 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: August 20, 2004 **Action Date:** February 22, 2005

HFD-580 **Trade and generic names/dosage form:** Cardura XL (doxazosin mesylate)

Applicant: Pfizer, Inc. **Therapeutic Class:**

Indication(s) previously approved: None

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

Number of indications for this application(s): 1

Indication #1: Treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

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

☒ **Yes: Please proceed to Section A.**

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

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

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

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

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

Reason(s) for deferral:

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

Other:_____

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

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

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 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 21-269**
HFD-960/ Grace Carmouze

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

(revised 12-22-03)

Attachment A

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

Indication #2: _____

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

- ❑ **Yes: Please proceed to Section A.**

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

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived:

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

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred:

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

Reason(s) for deferral:

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

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

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

›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 21-269**
HFD-960/ Grace Carmouze

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

(revised 10-14-03)

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/s/

Martin Kaufman
2/22/05 04:21:01 PM

NDA 21-269

Doxazosin Mesylate Extended Release Oral Tablets

DEBARMENT CERTIFICATION
[FD&C Act 306(k)(1)]

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.

Authorized Representative:

John Picciano March 23, 2001

John Picciano — Date

Director

Worldwide Regulatory Strategy

MEMORANDUM

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

DATE: February 17, 2005

TO: NDA 21-269

FROM: Martin Kaufman, D.P.M., M.B.A.
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products (HFD-580)

SUBJECT: **Statistical Review**
NDA 21-269, Cardura XL (doxazosin mesylate)

Dr. Mike Welch, Biometrics Team Leader, had the following statistical comments, which were conveyed by email on January 26, 2005:

> I would add in tables 2 and 3 (+/- SD) to the headers for MEAN BASELINE. It confuses with MEAN CHANGE which has (+/- SE). Footnote b, [redacted] I would just leave it as mean change. All Figures should denote what the error bars are - are they +/- one SE? Are they 95% C's?

The comments were conveyed to Mark Hirsch, M.D., Medical Team Leader, who incorporated them in the draft label.

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/s/

Martin Kaufman
2/17/05 10:08:47 AM
CSO

Kaufman, Martin

'om: Kulick, Corrinne
ent: Wednesday, January 19, 2005 2:51 PM
To: Kaufman, Martin
Cc: Williams, Rebecca
Subject: Cardura-XL NDA 21-269

Martin,

Please accept my apology, I just realized I have not responded to your request for consult on the Cardura-XL container labels. I would like to offer the following comment for consistency. The sponsor includes a [redacted] If the containers have been finalized then please disregard my comment.

Thanks,

Corrinne

Corrinne Kulick, Pharm.D., BCNSP
LCDR, USPHS
Division of Drug Marketing, Advertising, and Communications
Phone 301-827-9125
Fax: 301-827-6759

MEMORANDUM OF TELECON

DATE: December 9, 2004

APPLICATION NUMBER: NDA 21-269

BETWEEN:

Name: Martin Mikelsons, Director, Analytical Support Sciences
David McCollum, Senior Research Scientist, Analytical Support
Alan Dunbar, Director, U.S. Regulatory
Joseph Volpe, U.S. Regulatory

Phone: 877-630-9422
Representing: Pfizer

AND

Name: Rajiv Agarwal, Ph.D., Chemist, Division of New Drug Chemistry (DNDC II), @ Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580
Martin Kaufman, D.P.M., M.B.A., Regulatory Health Project Manager, DRUDP, HFD-580

SUBJECT: Clarification of CMC submission

Background: On August 20, 2004, the sponsor submitted a complete response to the Division's approvable letter of June 17, 2004. In response to a teleconference held November 18, 2004, the sponsor submitted additional CMC data on December 2, 2004. This teleconference was scheduled to obtain clarification of two items presented in the December 2, 2004, submission.

Discussion:

- The Division requested clarification of the data presented under the columns entitled "Results from Validated Limit Test" and "Estimated Results from Day of Sample Analysis." The sponsor explained that the validation of methods and analysis of samples were done on different days. The Detection Limit (DL) and the Quantitation Limit (QL) reported under the "Estimated Results from Day of Sample Analysis" column are estimates of the DL and QL on the day of sample analysis.
- The Division also requested clarification on whether the tablets that were used for the assays were 8 mg or 4 mg. The sponsor confirmed that the 8 mg tablet was used for both Cardura XL and Cardura IR.

Action Items:

- Sponsor should submit these clarifications to the NDA.

Rajiv Agarwal, Ph.D.
Chemist

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/s/

Martin Kaufman
12/15/04 12:59:40 PM
CSO

Rajiv Agarwal
12/17/04 11:52:26 AM
CHEMIST

Office of Drug Safety

MEMO

To: Daniel Shames, M.D.
Director, Division of Reproductive and Urologic Drug Products, HFD-580

From: Linda Y. Kim-Jung, Pharm.D., Acting Team Leader
Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

Through: Denise P. Toyer, Pharm.D., Deputy Director
Carol A. Holquist, R.Ph, Director
Division of Medication Errors and Technical Support, Office of Drug Safety, HFD-420

CC: Martin Kaufman
Project Manager, Division of Reproductive and Urologic Drug Products, HFD-580

Date: December 8, 2004

Re: ODS Consult 01-0123-2, Cardura XL® (Doxazosin Mesylate Extended-release Tablets) 4 mg and 8 mg; NDA 21-269

This memorandum is in response to a November 18, 2004 request from your Division for a final review of the proprietary name, Cardura XL. The container label and insert labeling were provided for review and comment.

The proposed proprietary name was found acceptable by DMETS on March 3, 2004 (ODS Consult 01-0123-1). The Division of Medication Errors and Technical Support (DMETS) has not identified any additional proprietary or established names that have the potential for confusion with Cardura XL since we conducted the initial review that would render the name objectionable.

Upon the introduction of a new formulation into the marketplace, the potential for medication errors due to confusion between two products with the same root name often increases. The likelihood for confusion between Cardura and Cardura XL is high in that the "XL" modifier can be overlooked or omitted on a prescription. To compound the potential for confusion between the two drug products, both drugs have overlapping product characteristics such as strength (4 mg and 8 mg) and both products can be dosed once daily. Therefore, DMETS reiterates its concern that the potential for confusion between these two products may occur, especially when Cardura XL is launched into the marketplace. DMETS encourages the sponsor to ensure that healthcare practitioners are educated about Cardura XL, before and during its launch into the marketplace. DMETS also encourages the sponsor to differentiate the labels and labeling of Cardura and Cardura XL to decrease the potential for confusion between these two products.

In the review of the labels and labeling of Cardura XL, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user errors.

A. GENERAL COMMENTS

1. Increase the prominence of the established name so that it is at least half as large as the letters comprising the proprietary name in accordance with 21 CFR 201.10(g)(2).

2. Revise the statement "**Each tablet contains XX mg of doxazosin mesylate which includes an overage to provide XX mg of doxazosin*" to read "*Each extended-release tablet contains doxazosin mesylate equivalent to XX mg of doxazosin."

3. It is likely that Cardura and Cardura XL may be placed next to each other on the pharmacy shelf. In order to minimize the risk of product confusion between Cardura and Cardura XL, ensure that the label and labeling are different and readily distinguishable.

B. CARTON LABEL

1. Professional Sample Outer Carton (4 mg and 8 mg)
   a. Increase the prominence of "Professional Sample – Not for Sale" and "Package not child resistant. Keep out of reach of children" on the front principal display.
   b. Revise "Contains: 8 blister packs, 7 tablets each" to read "Contains: 8 blister packs. Each blister pack contains 7 tablets." Additionally, place this statement on the front principal display.

2. Professional Sample Inner Carton
   a. Increase the prominence of "Professional Sample – Not for Sale" on the front principal display.
   b. State "Package not child resistant. Keep out of reach of children" on the front principal display.

C. BLISTER LABEL (Professional Sample: 4 mg and 8 mg)

Revise the strength to read "X mg/Tablet" on the blister labels.

D. INSERT LABELING

Reorganize the content of Information for Patients in the order of:

- "Cardura XL should be taken each day with breakfast..."
- "Patients should be informed that Cardura XL extended-release tablets should be swallowed whole..."
- "Patients should be told about the possible occurrence of symptoms related to postural hypotension..."

In summary, the Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the proposed name, Cardura XL, acceptable from a promotional perspective. Additionally, DMETS has no objection to the use of the proprietary name, Cardura XL. DMETS recommends implementation of the aforementioned label and labeling revisions that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer. We consider this a final review. If the approval of the NDA is delayed beyond 90 days from the signature date of this document, the name with its associated labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document.

We would be willing to meet with the Division for further discussion if needed. If you have any questions or need clarification, please contact Sammie Beam at 301-827-2102.

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/s/

Linda Kim-Jung
12/16/04 03:46:55 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
12/17/04 10:13:10 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
12/17/04 10:34:11 AM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM OF TELECON

DATE: November 18, 2004

APPLICATION NUMBER: NDA 21-269

BETWEEN:

Name: Martin Mikelsons, Director – Analytical Support Sciences
David McCollum, Senior Research Scientist, Analytical Support
[redacted]
Alan Dunbar, Director, U.S. Regulatory

Phone: 866-459-0303
Representing: Pfizer

AND

Name: Rajiv Agarwal, Ph.D., Chemist, Division of New Drug Chemistry (DNDC II), @ Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580
Martin Kaufman, D.P.M., M.B.A., Regulatory Health Project Manager, DRUDP, HFD-580

SUBJECT: Clarification of CMC issues

Background: On August 20, 2004, the sponsor submitted a complete response to the Division's approvable letter of June 17, 2004. During review of the CMC section of the submission, several issues, requiring additional data, were discovered. This teleconference was scheduled to request additional CMC data.

Discussion:

- The NDC number on the container closure labels is different from the number in the PI. Sponsor should verify which number is correct, and submit it.
- The container closures which were submitted electronically could not be printed. Sponsor should submit mock-ups of the container closures.
- The submission did not contain the limit of detection and the limit of quantification for the assays. These should be submitted to the NDA.
- The Division requested the numerical values for the assays that were reported as [redacted] There was a discussion concerning the validity of these numbers. Since the assay was not validated [redacted], the sponsor does not have confidence in the specific values. The sponsor agreed to provide copies of the [redacted] rather than numerical values.
- The sponsor should provide a copy of the August 20, 2004, submission as well as all subsequent submissions to the Division of Cardio-Renal Drug Products.

Action Items:

- Sponsor should submit the following:
  1. Correct NDC number.
  2. Mock-ups of the container closures.
  3. The limit of detection and the limit of quantification for the assays performed.
  4. Copies of the [redacted]
- A copy of the August 20, 2004, submission, and all subsequent submissions should be submitted to the Division of Cardio-Renal Drug Products.

Rajiv Agarwal, Ph.D.
Chemist

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/s/

Martin Kaufman
12/10/04 04:51:01 PM
CSO

Rajiv Agarwal
12/14/04 09:10:16 AM
CHEMIST

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-269

Pfizer Inc.
Attention: Alan Dunbar
Director, Worldwide Regulatory Strategy
235 E. 42nd Street
New York, NY 10017

Dear Mr. Dunbar:

We acknowledge receipt on August 23, 2004, of your August 20, 2004, resubmission to your new drug application for Cardura XL® (doxazosin mesylate) extended release tablets.

We consider this a complete, class 2 response to our June 17, 2004, action letter. Therefore, the user fee goal date is February 23, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the waiver granted on February 2, 2002, for the pediatric study requirement for this application.

If you have any question, call Martin Kaufman, D.P.M., M.B.A., Regulatory Health Project Manager, at (301) 827-4234.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jennifer L. Mercier
9/3/04 11:48:11 AM

MEMORANDUM OF TELECON

DATE: June 7, 2004

APPLICATION NUMBER: NDA 21-269, Cardura XL (doxazosin mesylate)

BETWEEN:

Name: Alan Dunbar, Director, U.S. Regulatory
Representing: Pfizer Pharmaceuticals

AND

Name: Rajiv Agarwal, Ph.D., Chemistry Reviewer, Division of New Drug Chemistry (DNDC II), @ Division of Reproductive and Urologic Drug Products (DRUDP), HFD-580
Martin Kaufman, D.P.M., M.B.A., Regulatory Health Project Manager, DRUDP, HFD-580

SUBJECT: Discussion of product packaging for Cardura® XL.

BACKGROUND:

Cardura® (doxazosin mesylate) is a selective α_1- blocker, approved for the treatment of hypertension and benign prostatic hyperplasia (BPH). It was approved for BPH in an immediate release form under NDA 20-371. The Sponsor has submitted NDA 21-269 for Cardura® XL, which is an extended release version of Cardura® utilizing the GITS (Gastrointestinal Therapeutic System) process.

DISCUSSION:

- The Division expressed concern regarding the similarity of colors used for product identification in the packaging for 1 mg immediate release Cardura® and 8 mg Cardura® XL, and requested that the Sponsor use a color other than black for the XL product. The Sponsor stated that the XL product would be distributed by [redacted] and that they had developed art work which should address these concerns. The Sponsor will send mock-ups today or tomorrow.
- The Division requested that for the text of the drug name should include "extended release tablets" within the parenthesis with the words "doxazosin mesylate", i.e. move the closing parenthesis from after the word "mesylate" to after the word "tablets". The Sponsor agreed to this change.
- The Sponsor confirmed that they would be using [redacted]
- The Sponsor confirmed the batch records for the 8 mg tablets were being sent today for delivery tomorrow, and that the container labels, blister packaging, and secondary packaging for the blisters and bottles would be sent within the next two to three days.

ACTION ITEMS:

- The Sponsor will send mock-ups with color changes, and change to placement of the closing parenthesis today or tomorrow.

Rajiv Agarwal, Ph.D.
Chemistry Reviewer

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/s/

Martin Kaufman
6/10/04 03:30:37 PM
CSO

Rajiv Agarwal
6/14/04 08:38:30 AM
CHEMIST

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-269

INFORMATION REQUEST LETTER

Pfizer
Attention: Alan Dunbar
235 East 42nd Street
New York, NY 10017

Dear Mr. Dunbar:

Please refer to your February 22, 2002 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cardura® XL (doxazosin mesylate) extended release tablets.

We also refer you to your submission of December 17, 2003 which constituted a complete response to our approvable letter of February 22, 2002.

We have initiated our review of your submission, and have the following requests for information:

1. Provide postmarketing safety information specifically for Cardura XL in the countries where the product is marketed.

2. Provide all information available on the effect of doxazosin on QT prolongation. If no information is available, provide justification why a comprehensive evaluation of QT is not required for this alpha-blocker.

3. Since the first dose blood pressure study had only one subject aged 70 or greater, justify use of Cardura XL in men over age 70 years

4. Provide full information on subject number 10010009. Were the blood pressure changes for this patient (for the GITS 4mg treatment) included in the statistical analysis? If not, please justify why baseline orthostatic changes in the second crossover arm treatment should exclude results from the first crossover treatment.

5. Provide additional clinical information and Case Report Form (CRF) on subject 10010024 with regard to blood pressure and pulse results and how his results impacted the statistical analysis of the entire study.

6. Provide additional clinical information and CRF for subject 10010012 who was withdrawn due to unstable cardiac condition.

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/s/

Margaret Kober
2/17/04 02:28:00 PM
Chief, Project Management Staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-269

Pfizer Pharmaceuticals
Attention: Alan Dunbar
Director, Worldwide Regulatory Strategy
235 E 42nd Street
New York, NY

Dear Mr. Dunbar:

We acknowledge receipt on December 18, 2003 of your December 17, 2003 resubmission to your new drug application for Cardura XL (doxazosin mesylate) Extended Release Tablets.

We consider this a complete, class 2 response to our February 22, 2002 action letter. Therefore, the user fee goal date is June 18, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the waiver granted on February 2, 2002 for the pediatric study requirement for this application.

If you have any question, call me at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products; HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jennifer L. Mercier
1/2/04 10:13:06 AM

Teleconference Minutes

Date: June 3, 2002 **Time:** 1:00-1:30 PM, EST **Location:** PKLN; 17B43

NDA 21-269 **Drug:** Cardura XL **Indication:** Benign prostatic hyperplasia (BPH)

Sponsor: Pfizer, Inc.

Type of Meeting: Post-Action Guidance

Meeting Chair: Mark Hirsch, M.D. – Clinical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Lead: Alan Dunbar, Director, Regulatory Affairs

Meeting Recorder: Jennifer Mercier - Regulatory Health Project Manager, DRUDP (HFD-580)

FDA Attendees:
Mark Hirsch, M.D. - Medical Team Leader, DRUDP (HFD-580)
Gerald Willett, M.D. - Medical Officer, DRUDP (HFD-580)
Jennifer Mercier – Regulatory Health Project Manager, DRUDP (HFD-580)

External Attendees:

Alan Dunbar

Meeting Objective: To guide the sponsor in their resubmission of this NDA for review.

Discussion/Decisions Made:

1. Are the data from the 12 patient Japanese study (DAZ-JP-97-501) sufficient to answer the first deficiency?

   Answer:
   - The Division does not agree that this study represents the patient population that the drug under review is intended for and would not provide the Agency with adequate information to determine the safety and efficacy of this drug product.
   - The Division would recommend the sponsor conduct another study in the population that this drug is intended for use.
   - The sponsor contends that young men are prone to sudden lowering of the blood pressure; the Division reiterated that the age difference between the young Japanese men and the older BPH population would be a major review issue.

2. Does the combined safety analysis for the pivotal BPH and HTN trials for Cardura XL provide sufficient safety data to answer the second deficiency?

   Answer:
   - The proposed safety analysis appears acceptable to answer the second deficiency but, the Division would like the sponsor to pool any and all additional information relevant for this analysis.
   - The sponsor should provide their opinion of the results of this analysis comparing vasodilatory adverse events between the old formulation and the new formulation.

Action Items:
- Fax meeting minutes to the sponsor within 30 days.
- The sponsor should submit their resubmission with the recommendations provided in this teleconference and the requirements in the approvable letter.

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

Drafted: Farinas/2.26.02
Concurrence: Shames/Hirsch 2.26.02/Willett 3.08.02/Stephens/Kober
Finalized: Farinas

MEETING MINUTES

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/s/

Jennifer L. Mercier
6/18/02 11:47:47 AM
CSO

Mark S. Hirsch
6/20/02 07:15:18 PM
MEDICAL OFFICER
I concur.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-269

Pfizer Pharmaceuticals Group
Attention: Alan Dunbar
235 E 42nd Street
New York, NY 10017

Dear Mr. Dunbar:

We received your May 10, 2002 correspondence on May 13, 2002 requesting a meeting to discuss the resubmission to the Approvable letter dated February 22, 2002. The guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000), describes three types of meetings:

> Type A: Meetings that are necessary before a company can proceed with a stalled drug development program.
>
> Type B: Meetings described under drug regulations [e.g., Pre-IND, End of Phase 1 (for Subpart E or Subpart H or similar products), End of Phase 2, Pre-NDA].
>
> Type C: Meetings that do not qualify for Type A or B.

The guidance can be found at http://www.fda.gov/cder/guidance/2125fnl.htm.

You requested a type A meeting, but the Division is granting this meeting as a Type B meeting. The meeting is scheduled for:

Date: June 3, 2002
Time: 1:00 PM
Location: Teleconference

Provide the background information for this meeting at least two weeks prior to the meeting.
We have received the meeting materials were presented in the meeting request.

If you have any questions contact me at (301) 827-4260.

Sincerely,

Jennifer Mercier
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jennifer L. Mercier
5/24/02 10:42:51 AM

Status Meeting Minutes

Date: February 11, 2002 **Time**: 10:30-11:00 PM, EST **Location**: PKLN; 17B43

NDA 21-269 **Drug:** Cardura XL **Indication:** Benign Prostatic hyperplasia (BPH)

Sponsor: Pfizer, Inc.

Type of Meeting: Status

Meeting Chair: Mark Hirsch, MD, Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Project Manager, DRUDP (HFD-580)

FDA Attendees:
Mark Hirsch, M.D. – Urology Team Leader, DRUDP (HFD-580)
Gerald Willett, M.D. – Medical Officer, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Rajiv Agarwal, Ph.D.- Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Team Leader, Clinical Pharmacology and Biopharmaceutics, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss the status of the review for this application.

Background: In a submission dated April 20, 2001, Pfizer submitted NDA 21-269 for Cardura XL® (doxazosin mesylate) Extended Release tablets for the treatment of BPH. This NDA is for a modified release tablet formulation which uses a controlled rate of delivery of doxazosin into the gastrointestinal lumen (Gastrointestinal Therapeutic System or GITS). Cardura XL is formulated as a once-a-day controlled release tablet for oral use, to deliver 4 or 8 mg of doxazosin. The 10-month goal date is February 21. [redacted]

[redacted]

Discussion:
Clinical:

- there are outstanding safety issues; adverse events were observed in the first seven days of Cardura GITS administration in the BPH trials, and it appears that a 2 mg dose of the Cardura immediate release formulation was administered instead of the 1mg dose; this is a protocol violation and affects the interpretation of the safety profile for the Cardura GITS formulation
  - these safety concerns may lead to an approvable action
  - to obtain an approval, the sponsor may be required to submit data on blood pressure measurements during the first week of Cardura GITS dosing; the sponsor should also submit an

explanation for the protocol violation, and may be required to submit additional information relevant to a comparison of 1 mg standard to 4 mg GITS in terms of clinical adverse events during the first week of treatment

- the Medical Team leader apprised the team of Office level recommendations:
  - blood pressure-lowering effects could be described in the BPH Cardura GITS labeling
  - DRUDP should proceed with the review of the new BPH label and this application
- [redacted]
  - the sponsor was informed that the Cardura GITS formulation is not equivalent for efficacy to the standard in either of the two pivotal trials; further exploration of dose range is required

Clinical Pharmacology and Biopharmaceutics:

- at the OCPB briefing on Friday, February 8, 2002, it was agreed that the Cardio-Renal Clinical Pharmacology review team will re-review the PK studies having active controls, to identify if there are blood pressure monitoring points in the raw data
- the data is "acceptable" to OCPB but the final dissolution release specification has not been formally accepted by the sponsor
- labeling must be updated to reflect current labeling standards for the Clinical Pharmacology section prior to an approval action

Chemistry:

- if the dissolution specifications and the [redacted] expiry dating recommended by the Cardio Renal Division are not accepted formally by the sponsor, these should be included as items in an Approvable Action letter
- it was recommended that the Cardio Renal Division request a written agreement (via facsimile) from the sponsor regarding the dissolution specifications and expiry date

Decisions made:

- an approval action is unlikely during this review cycle; therefore, label negotiations will be deferred until the next review cycle

Action Items:

- the second draft Medical Officer review will be forwarded to the Medical Team Leader on Tuesday, February 12, 2002
- draft or final reviews will be forwarded to the Medical Team Leader on Tuesday, February 12, 2002
- the Action Package will be forwarded to the Division Director on Friday, February 15, 2002
- draft or final reviews from all disciplines must be included in the Action Package by Friday, February 15, 2002

Drafted: Farinas/2.13.02
Reviewed: Best 2.13.02/Hirsch 2.14.02/Willett/Agarwal/Rhee/Parekh 2.28.02
Finalized: Farinas/3.1.02

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/s/

Mark S. Hirsch
3/1/02 03:00:27 PM

Status Meeting Minutes

Date: December 21, 2001 **Time**: 11:00-11:20 AM, EST **Location**: PKLN; 17B43

NDA 21-269 **Drug:** Cardura XL

Indication: Benign Prostatic Hyperplasia (BPH) [redacted]

Sponsor: Pfizer

Type of Meeting: Status

Meeting Chair: Mark Hirsch, MD, Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Project Manager, DRUDP (HFD-580)

FDA Attendees:
Mark Hirsch, M.D. – Urology Team Leader, DRUDP (HFD-580)
James Gebert, Ph.D. – Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Rajiv Agarwal, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss review status for NDA 21-269.

Background: In a submission dated April 20, 2001, Pfizer submitted NDA 21-269 for Cardura XL® (doxazosin mesylate) Extended Release tablets for the treatment of BPH. This NDA is for a modified release tablet formulation which uses a controlled rate of delivery of doxazosin into the gastrointestinal lumen (Gastrointestinal Therapeutic System or GITS). Cardura XL is formulated as a once-a-day controlled release tablet for oral use, to deliver 4 or 8 mg of doxazosin. The 10-month goal date is February 21. [redacted]

Discussion:
Statistics:
- review is complete and has been entered into DFS; review has been signed by the Statistics Team Leader
- Table 2 should be amended in the label; edits on the N drive will follow

Clinical:
- Medical Officer requested that the statistical review be sent to him electronically
- Medical Officer will most likely include the tables from the statistical review in the MO review

Chemistry:

- additional information was requested by the Cardio Renal Chemistry reviewer; upon receipt, a determination will be made as to whether the data constitutes a major or minor amendment to the NDA

Decisions made:

- the Statistics reviewer will edit Table 2 in the proposed Cardura XL label, and will send a copy of the final Statistics review to the Medical Officer
- the Medical Team Leader will assist the primary Medical Officer with the labeling
- Chemistry reviewer to assess new submission of data when it arrives

Action Items:

- Project Manager to schedule a status meeting in approximately three weeks

Drafted: Farinas/1.15.02
Concurrence: Agarwal 1. 15. 2002/Best 1.16.02; Hirsch 2.4.02
Finalized: Farinas/2.4.02

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/s/

Mark S. Hirsch
2/4/02 03:01:06 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-269

Pfizer, Inc.
Attention: Mr. Robert Clark
235 East 42nd Street
New York, NY 10017

Dear Mr. Clark:

Please refer to your correspondence dated April 20, 2001, that requested a waiver for pediatric studies under 21 CFR 314.55(c).

We have reviewed the information you have submitted and agree that a waiver is justified for Cardura XL for the indication [redacted] benign prostatic hyperplasia for the pediatric population because:

1. Benign prostatic hyperplasia is a condition only of adult males (NDA 21-269).

2. [redacted]

Accordingly, a waiver for pediatric studies for these applications is granted under 21 CFR 314.55 at this time.

If you have questions, please contact:

Mr. Daryl Allis
Regulatory Project Manager
301-594-5309.

Sincerely,

{See appended electronic signature page}

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Daniel Shames, M.D.
Acting Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Daniel A. Shames
2/12/02 02:36:54 PM

Raymond Lipicky
2/12/02 04:28:30 PM

Status Meeting Minutes

Date: December 04, 2001 **Time**: 3:00-4:00 PM, EST **Location**: PKLN; 17B43

NDA 21-269 **Drug:** Cardura XL

Indication: Benign Prostatic Hyperplasia (BPH) [redacted]

Sponsor: Pfizer

Type of Meeting: Status

Meeting Chair: Mark Hirsch, MD, Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Project Manager, DRUDP (HFD-580)

FDA Attendees:
Mark Hirsch, M.D. – Urology Team Leader, DRUDP (HFD-580)
Gerald Willett, M.D. – Medical Officer, DRUDP (HFD-580)
James Gebert, Ph.D. – Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Rajiv Agarwal, Ph.D. - Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss review status for NDA 21-269.

Background: In a submission dated April 20, 2001, Pfizer submitted NDA 21-269 for Cardura XL® (doxazosin mesylate) Extended Release tablets for the treatment of BPH. This NDA is for a modified release tablet formulation which uses a controlled rate of delivery of doxazosin into the gastrointestinal lumen (Gastrointestinal Therapeutic System or GITS). Cardura XL is formulated as a once-a-day controlled release tablet for oral use, to deliver 4 or 8 mg of doxazosin. The 10-month goal date is February 21. [redacted]

Discussion:
Clinical:
- Review: is ongoing
- Issues: the two pivotal trials are being reviewed to document that Cardura XL is more efficacious than placebo
- Label: will consider adding the advice "not to chew' in the label; Table 2 needs to be reviewed by the Statistics reviewer
- Assessment: approval likely

Statistics:
- Review: Completed and entered in DFS

- Label: review is ongoing
- Assessment: data supports the sponsor's claim

Chemistry:

- Review: CardioRenal Chemistry reviewer is conducting the review of this application
- Issues:
  - dissolution [redacted] CardioRenal Chemistry reviewer will call the sponsor to request more real time stability data
  - some site inspections are pending
- Label: review ongoing

Decisions:

- Statistics reviewer will review Table 2 in the proposed label
- CardioRenal division reviewers will be contacted for updates regarding the status of the Chemistry and Clinical Pharmacology and Biopharmaceutics reviews

Drafted: Farinas/1.15.02
Concurrence: Best 1.15.02/Gebert 1.16.01/Agarwal 1.28.02/Willett 1.30.02/Hirsch 1.30.03
Finalized: Farinas 1.31.02

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/s/

Mark S. Hirsch
2/3/02 09:55:20 AM

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: January 15, 2002

TO: Evelyn Farinas, R.Ph., M.G.A., Regulatory Project Manager
Gerald D. Willett, M.D., Clinical Reviewer
Division of Reproductive and Drug Products, HFD-580

THROUGH: John R. Martin, M.D., Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Constance Lewin, M.D.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-269

APPLICANT: Pfizer, Inc.

DRUG: Cardura XL (doxazosin mesylate) Extended-Release Tablets

REVIEW CLASSIFICATION: Standard

INDICATION: Treatment of benign prostatic hyperplasia

CONSULTATION REQUEST DATE: July 18, 2001

ACTION GOAL DATE: February 23, 2002

I. BACKGROUND:

Routine clinical inspections were conducted in support of the above-noted application and focused on the conduct of protocol DAZ-NY-95-001. The inspected protocol was not conducted under a U.S. IND. Doctors Louis Duval, Ives Fradet, and Alvaro Morales were chosen for inspection. Goals of the inspection included validation of the primary efficacy endpoint data and safety data, as well as an evaluation of the adequacy of informed consent.

II. RESULTS (by protocol/site):

NAME	LOCATION	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Duval	Laval, Quebec, Canada	September 24, 2001	January 3, 2002	VAI
Fradet	Quebec City, Quebec, Canada	September 24, 2001	January 8, 2002	VAI
Morales	Kingston, Ontario, Canada	September 24, 2001	January 3, 2002	VAI

Protocol DAZ-NY-95-001

1. Site #1 (Louis Duval, M.D. – Laval, Quebec, Canada):

Twenty-four subjects were randomized at this site, 20 of whom completed the double-blind study. Four subjects discontinued (three due to non-serious adverse events, and one due to insufficient clinical response). Nine subjects entered, and eight subjects completed, the open-label extension of the study.

Records were reviewed for eleven subjects. A Form FDA 483 was issued, noting several protocol violations and recordkeeping inadequacies/inaccuracies and one unreported adverse event. None of the inspectional findings are considered to adversely impact the acceptability of the study data generated at this site. Significant inspectional findings are as follows:

a. Subjects 0619 and 0631 did not meet all study entry criteria. These subjects were treated for angina, an exclusionary condition, prior to enrollment and during participation in the study.

b. For Subjects 0624, 0632, 0861, and 0862, Visit 1 blood samples were lost in transit and were not re-drawn prior to treatment with study drug. Of note, these samples were to be used to determine eligibility regarding PSA, creatinine, and hepatic enzyme levels.

c. For Subjects 0615, 0617, and 0624, Visit 1 physical examinations were signed by Dr. Duval approximately three months after the examinations were conducted.

d. Subject 0615 experienced an adverse event (urinary tract infection from January 26 to February 2, 1997) which was not recorded in the case report form.

Data appear acceptable.

2. Site #2 (Ives Fradet, M.D. – Quebec City, Quebec, Canada):

Fourteen subjects were randomized at this site. All subjects completed the double-blind study. Eleven subjects entered, and eight subjects completed, the open-label extension. The three subjects who discontinued from the open-label study did so because of insufficient clinical response.

Records were reviewed for all subjects. A Form FDA 483 was issued, noting several protocol violations and failure to report a few non-serious adverse events for one subject. None of the inspectional findings are considered to adversely impact the acceptability of the data generated at this site. Significant inspectional findings are as follows:

a. Subject 0383 did not meet all inclusion criteria. Study records indicate that the subject began phytotherapy (Artechol, an artichoke derivative, for digestive problems) approximately one month prior to enrollment and continued its use through the end of the open-label study.

b. Subject 0376 experienced adverse events (AEs) of fatigue, palpitations and dizziness, which were reported by the subject on May 20, 1997 (final visit for open-label phase); however, these AEs were not captured in the case report form.

Data appear acceptable.

3. Site #3 (Alvaro Morales, M.D. – Kingston, Ontario, Canada):

Nineteen subjects were randomized at this site, 18 of whom completed the double-blind study. One subject was discontinued due to a protocol violation (discontinuation of diuretic during the study). Four subjects entered, and two subjects completed, the open-label extension.

Records were reviewed for 13 subjects. A Form FDA 483 was not issued, but several observations were verbally discussed at the close of the inspection. None of the inspectional findings are considered to adversely impact the acceptability of the data generated at this site. Significant inspectional findings are as follows:

a. Subject 0398 was enrolled in the study despite ongoing use of the tricyclic antidepressant imipramine, an exclusion criterion. It is also noted that the exclusion criteria checklist that was completed for this subject at screening indicates that the subject was not receiving a tricyclic antidepressant.

b. Study records for Subject 0859 did not include results of a 12-lead electrocardiogram (ECG) obtained either at Visit 1 or within six months prior to study enrollment, as required by the protocol. The only ECG results available for this subject were those related to a stress test conducted more than one year before the subject was enrolled.

Data appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Routine clinical inspections were conducted in support of pending NDA #21-269 and focused on protocol DAZ-NY-95-001 as conducted by Drs. Louis Duval, Ives Fradet, and Alvaro Morales. Inspection of these clinical investigators revealed several protocol violations and recordkeeping inadequacies/inaccuracies. Additionally, inspection of Drs. Duval and Fradet revealed that these investigators each failed to report one non-serious adverse event. Significant inspectional observations are detailed in Section II above. None of the inspectional findings are considered to adversely impact the acceptability of the study data generated at these sites.

Accordingly, it appears that the data generated by Drs. Duval, Fradet, and Morales may be used in support of the pending application.

Constance Lewin, M.D.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

John R. Martin, M.D., Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

DISTRIBUTION:
NDA #21-269
Division File
HFD-45/Program Management Staff (electronic copy)
HFD-46/Lewin
HFD-47/Ibarra-Pratt
HFD-46/GCP 1 Branch Chief/Martin
HFD-46/Reading File

Telecon/ Internal Team Meeting Minutes

Meeting Date:	December 5, 2001
Type of Meeting:	Telecon Team Meeting

[redacted]

HFD-580 NDA:	21-269 Cardura XL (doxazosin mesylate) 4 and 8 mg Tablets Treatment for benign prostatic hyperplasia
Sponsor:	Pfizer, Inc.
Type:	3S, Anti-hypertensive Agent
Application Date:	April 20, 2001
Receipt Date:	April 23, 2001
User Fee Goal Date:	February 23, 2002 (10 month) April 23, 2002 (12 month)
Meeting Chair:	Douglas Throckmorton, M.D.
Meeting Recorder:	Daryl Allis

Attendees:

Division of Cardio-Renal Drug Products

Douglas Throckmorton, M.D.	Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical, HFD-110
A. O. Williams, M.D.	Medical Officer, HFD-110
Kathleen Jongedyk, M.S.	Chemist, HFD-810
Sharon Yan, Ph.D.	Statistician, HFD-110
Lydia Kieffer, Pharm.D.	Bio-pharmacologist, HFD-860
Daryl Allis, M.S., F.N.P.	Regulatory Health Project Manager, HFD-110

Division of Reproductive and Urologic Drug Products

Mark Hirsch, M.D.	Team Leader, Medical, HFD-580
Gerald Willett, M.D.	Medical Officer, HFD-580
Ameeta Parekh, Ph.D.	Team Leader, Biopharmaceutics, HFD-870
Sayed Al-Habet, Ph.D.	Bio-pharmaceutist, HFD-870
Moo-Jong Rhee, Ph.D.	Team Leader, Chemistry, HFD-580
Rajiv Agarwal, Ph.D.	Chemist, HFD-580
James Gebert, Ph.D.	Statistician, HFD-715
Evelyn Farinas, R.Ph.	Regulatory Health Project Manager, HFD-580

Background

Doxazosin mesylate is an alpha-antagonist that was previously approved under Pfizer's registered trade name Cardura®, as an immediate release formulation for the treatment of hypertension (NDA 19-668) and

benign prostatic hyperplasia (BPH) (NDA 20-371). The current NDA applications are for a modified release tablet formulation for doxazosin mesylate, Cardura XL ®, that uses a controlled rate of delivery of doxazosin into the gastrointestinal lumen, that is independent of pH or gastrointestinal motility. Cardura XL® utilizes the patented GITS (Gastrointestinal Therapeutic System) process.

[redacted] the Division of Reproductive and Urologic Drug Products will review the clinical BPH information, BPH biopharmaceutical data and BPH labeling contained in the NDA 21-269. [redacted]

The purpose of this telecon is to discuss the progress of the reviews and identify issues requiring action or follow-up. The 10-month goal date is February 23, 2002.

Discussion

Dr. Hirsch requested that the internal goal dates be moved ahead by two weeks as follows:

Primary Review	January 18, 2002
Secondary Review	February 1, 2002
Action Package complete	February 1, 2002.

[redacted]

HFD-580 (Division of Reproductive-Urological Drug Products)

Medical — The clinical review is ongoing. This sustained release formulation shows efficacy by demonstrating improvement in the International Prostate Symptom Score (I-PSS) and urine flow. Episodes of syncope were reported for Cardura XL (4), Cardura (2) and placebo (1) in the BPH trials. One case of syncope was reported by a subject receiving Cardura standard in the primary HTN trials. It is not clear if syncope in the BPH studies occurred during micturition; however, the syncope associated with Cardura XL appears to occur later after dosing. There was a discussion related to syncope associated with other alpha-blockers, syncope associated with recent drug titration, and sensitivity of syncope in the elderly taking alpha-blockers. A decision was made to contact the Office of Post-marketing Drug Risk Assessment (OPDRA) to see if there are post-marketing case reports of syncope associated with time of dosing/ titration of alpha-blockers, specifically doxazosin.

Dr. Willett noted that the protocols had an exclusion criterion for patients with anginal signs/ symptoms in the past 6 months. The rationale for this exclusion criterion is not clear. Dr. Throckmorton believes there is nothing in the current labeling to support this exclusion criterion.

Bio-statistics — The BPH statistical review is complete and filed in DFS. Efficacy is shown with both BPH trials.

[redacted]

Conclusion/ Recommendations

The chemists will follow-up with the sponsor regarding the CMC issues and pending site investigation.

[redacted]

Drs. Throckmorton and Hirsch will discuss the [redacted] BPH labeling issues for Cardura XL compared to the approved labeling for the original Cardura formulation.

The initial/ primary reviews are to be completed and submitted to the Division secondary medical reviewers by January 18, 2002. The final action package will be complete by February 1, 2002.

Signature recorder: _____

Concurrence, Chair: _____

Draft:	12/11/01	**Final:**	01/08/02
HFD-110		**HFD-580**	
Throckmorton	01/03/02	Hirsch*	12/20/01
Karkowsky	01/07/02	Willett*	12/14/01
Williams	12/28/01	Agarwal*	
Kieffer*	12/13/01	Rhee*	
Jongedyk	12/14/01		
Srinivasachar	12/28/01	Al-Habet*	
Yan	12/13/01	Parekh*	
Morgenstern	01/07/02	Gebert*	
		Farinas*	

* Draft sent electronically

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/s/

Daryl L. Allis
1/8/02 02:05:19 PM
Dr. Throckmorton signed the final copy of minutes on 1-8-02.

Status Meeting Minutes

Date: August 28, 2001 **Time**: 1:00- 1:30 PM, EST **Location**: PKLN; 17B43

NDA 21-269 **Drug:** Cardura XL (doxazosin)

Indication: benign prostatic hyperplasia (BPH) [redacted]

Sponsor: Pfizer

Type of Meeting: Status

Meeting Chair: Mark Hirsch, MD, Medical Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Project Manager, DRUDP (HFD-580)

FDA Attendees:
Mark Hirsch, M.D. – Urology Team Leader, DRUDP (HFD-580)
Ashok Batra, M.D. – Medical Officer, DRUDP (HFD-580)
Rajiv Agarwal, Ph.D.- Chemist, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Sayed Al-Habet, Ph.D. – Pharmacokinetics Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
James Gebert, Ph.D. – Statistician, Division of Biometrics II (HFD-715)
Evelyn R. Farinas, R.Ph., M.G.A. – Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss the status of this NDA review.

Background:
In a submission dated April 20, 2001, Pfizer submitted NDA 21-269 for Cardura XL® (doxazosin mesylate) Extended Release tablets for the treatment of BPH. This NDA is for a modified release tablet formulation which uses a controlled rate of delivery of doxazosin into the gastrointestinal lumen (Gastrointestinal Therapeutic System or GITS). Cardura XL is formulated as a once-a-day controlled release tablet for oral use, to deliver 4 or 8 mg of doxazosin. The 10-month goal date is February 21, 2002.

[redacted]

Discussion:
Clinical:
- Review: review will begin in the near future
- Issues: can't comment at this time
- Label: can't comment at this time
- Assessment: premature to venture an opinion at this time

Statistics:
- Review: draft review completed, and is with the secondary reviewer
- Issues: none
- Label: started review

- Assessment: approval, most likely

Chemistry:

- Review: if needed, assistance will be provided to the CardioRenal Division; the primary CMC review is being conducted by the CardioRenal Division
- Issues: if any, these will be identified by the CardioRenal Division
- Label: DRUDP reviewer will review the BPH section of the label
- Assessment: it is premature to venture an opinion at this time

Biopharmaceutics:

- Review: if needed, assistance will be provided to the CardioRenal Division; the primary Biopharmaceutics review is being conducted by the CardioRenal Division
- Issues: if any, these will be identified by the CardioRenal Division
- Label: DRUDP reviewer will review the BPH section of the label
- Assessment: it is premature to venture an opinion at this time

Clinical Pharmacology/Toxicology:

- the reviewer was not present at the meeting
- the CardioRenal Division will take the lead for the Clinical/Pharmacology review

Project Management:

- the label proposed by the sponsor can be found in the "N" drive for review; the sponsor verified that only one label has been proposed so far to both Divisions
- Financial Disclosure: the review has been completed; adequate documentation was submitted
- Tradename review:
  - OPDRA completed their review, and found no objections to the "Cardura XL" tradename
  - OPDRA indicated some concerns about a potential confusion between the names "Cardura" and "Cardura XL"; OPDRA has recommended that the label be strengthened to avoid confusion between these two tradenames
- DSI inspections: it is premature; feedback from DSI has not been received
- the goal date agreed to during the filing meeting is for all reviews to be completed by the first week in January 2002

Decisions made:

- Biopharmaceutics, Chemistry and Toxicology reviewers will assist the lead reviewers in the CardioRenal Division, as needed
- Clinical review will start in the near future

Action Items:

- none

Drafted: Farinas/9.18.01
Concurrence: Rumble 9.20.01/Batra/Hirsch 9.20.01/Gebert 9.18.01/Agarwal 9.18.01/AlHabet
Finalized: Farinas/11.28.01

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/s/

Mark S. Hirsch
12/3/01 05:14:55 PM

Telecon/ Internal Team Meeting Minutes

Meeting Date:	October 3, 2001
Type of Meeting:	Telecon Team Meeting
[redacted]	[redacted]
HFD-580 NDA:	21-269 Cardura XL (doxazosin mesylate) 4 and 8 mg Tablets Treatment for benign prostatic hyperplasia
Sponsor:	Pfizer, Inc.
Type:	3S, Anti-hypertensive Agent
Application Date:	April 20, 2001
Receipt Date:	April 23, 2001
User Fee Goal Date:	February 23, 2002 (10 month) April 23, 2002 (12 month)
Meeting Chair:	Douglas Throckmorton, M.D.
Meeting Recorder:	Daryl Allis

Attendees:

Division of Cardio-Renal Drug Products

Douglas Throckmorton, M.D.	Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Team Leader, Medical, HFD-110
A. O. Williams, M.D.	Medical Officer, HFD-110
Kathleen Jongedyk, M.S.	Chemist, HFD-810
Sharon Yan, Ph.D.	Statistician, HFD-110
Lydia Kieffer, Pharm.D.	Bio-pharmacologist, HFD-120
Natalia A. Morgenstern	Chief, Project Management Staff, HFD-110
Daryl Allis, M.S., F.N.P.	Regulatory Health Project Manager, HFD-110

Division of Reproductive and Urologic Drug Products

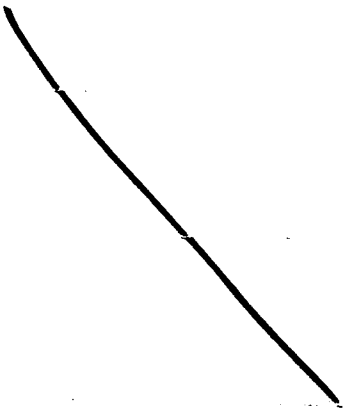
Mark Hirsch, M.D.	Team Leader, Medical, HFD-580
Ashok Batra, M.D.	Medical Officer, HFD-580
Ameeta Parekh, Ph.D.	Team Leader, Biopharmaceutics, HFD-870
Sayed Al-Habet, Ph.D.	Bio-pharmaceutist, HFD-870
Moo-Jong Rhee, Ph.D.	Team Leader, Chemistry, HFD-580
Rajiv Agarwal, Ph.D.	Chemist, HFD-580
James Gebert, Ph.D.	Statistician, HFD-715
Evelyn Farinas, R.Ph.	Regulatory Health Project Manager, HFD-580

Background

Doxazosin mesylate is an alpha-antagonist that was previously approved under Pfizer's registered trade name Cardura®, as an immediate release formulation for the treatment of hypertension (NDA 19-668) and benign prostatic hyperplasia (BPH) (NDA 20-371). The current NDA applications are for a modified release tablet formulation for doxazosin mesylate, Cardura XL ®, that uses a controlled rate of delivery of doxazosin into the gastrointestinal lumen, that is independent of pH or gastrointestinal motility. Cardura XL® utilizes the patented GITS (Gastrointestinal Therapeutic System) process.

[redacted] the Division of Reproductive and Urologic Drug Products will review the clinical BPH information, BPH biopharmaceutical data and BPH labeling contained in the NDA 21-269. [redacted]

The purpose of this telecon is to discuss the progress of the reviews and identify issues requiring action or follow-up. Primary reviews are to be completed and submitted to the secondary medical reviewers by January 4, 2002. The 10-month goal date is February 23, 2002.



[redacted]

HFD-580 (Division of Reproductive-Urological Drug Products)

Medical	The clinical review is ongoing. The sponsor has submitted 1 placebo controlled study and 1 active control study. The primary endpoint is the International Prostate Symptom Score (I-PSS).
Bio-statistics	The statistical review is ongoing. There are no review issues at the current time.
Bio-pharm	Based on a preliminary review of this submission, it appears that there are no review issues at this time. Dr. Parekh asked if there is a QT study. Dr. Throckmorton is not aware that the Agency has this data. He stated that he doesn't know of a post-marketing QT problem with doxazosin.

Conclusion/ Recommendations

The chemists will follow-up with the CMC issues and pending site investigations.

Dr. Williams will analyze the hypertension data and discuss the findings with Drs. Karkowsky and Throckmorton.

A joint telecon with HFD-110 and HFD-580 will be scheduled during the first week in December 2001. The initial/ primary reviews are to be completed and submitted to the Division secondary medical reviewers by January 4, 2002. The complete action package is to be submitted to Dr. Temple by January 23, 2002.

Signature recorder: _____

Concurrence, Chair: _____

Draft:	10/30/01	**Final:**	11/26/01
HFD-110		**HFD-580**	
Throckmorton	11/06/01	Hirsch*	11/16/01
Stockbridge	11/06/01	Batra*	
Williams	11/02/01	Agarwal*	
Kieffer*		Rhee*	
Jongedyk	11/05/01		
Srinivasachar	11/06/01	Al-Habet*	
Yan		Parekh*	11/16/01
Morgenstern	11/16/01	Gebert*	
		Farinas*	11/16/01

* Draft sent electronically

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/s/

Daryl L. Allis
11/27/01 01:49:14 PM

Filing Summary/ Meeting Minutes

Meeting Date:	June 13, 2001
Type of Meeting:	45-Day Filing Meeting

[redacted]

HFD-580 NDA:	21-269 Cardura XL (doxazosin mesylate) 4 and 8 mg Tablets Treatment for benign prostatic hyperplasia
Sponsor:	Pfizer, Inc.
Type:	3S, Anti-hypertensive Agent
Application Date:	April 20, 2001
Receipt Date:	April 23, 2001
User Fee Goal Date:	February 23, 2002 (10 month) April 23, 2002 (12 month)
User Fee Status:	Paid
Meeting Chair:	Douglas Throckmorton, M.D.
Meeting Recorder:	Daryl Allis

Attendees:

Division of Cardio-Renal Drug Products

Douglas Throckmorton, M.D.	Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Team Leader, Medical, HFD-110
Abraham Karkowsky, M.D., Ph.D.	Team Leader, Medical, HFD-110
A. O. Williams, M.D.	Medical Officer, HFD-110
Howard Lee, M.D.	Guest Worker, HFD-110
Angelica Dorantes, Ph.D.	Pharmacokineticist, HFD-860
Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry, HFD-810
Kathleen Jongedyk, M.S.	Chemist, HFD-810
James Hung, Ph.D.	Team Leader, Statistics, HFD-710
Sharon Yan, Ph.D.	Statistician, HFD-110
Natalia A. Morgenstern	Chief, Project Management Staff, HFD-110
Zelda McDonald	Regulatory Health Project Manager, HFD-110
Daryl Allis	Regulatory Health Project Manager, HFD-110

Division of Reproductive and Urologic Drug Products

Mark Hirsch, M.D.	Team Leader, Medical, HFD-580
Ashok Batra, M.D.	Medical Officer, HFD-580
Ameeta Parekh, Ph.D.	Team Leader, Biopharmaceutics, HFD-870
Rajiv Agarwal, Ph.D.	Chemist, HFD-580
Mike Welch, Ph.D.	Team Leader, Statistics HFD-715
James Gebert, Ph.D.	Statistician, HFD-715
Evelyn Farinas	Regulatory Health Project Manager, HFD-580

Division of Scientific Investigations

J. C. Rios, M.D. DSI Liaison, HFD-110
Susan Molchan, M.D. DSI Liaison, HFD-580

Submission Complete as Required Under 21 CFR 314.50?	YES
Patent Information Included?	YES
Exclusivity Requested?	YES: 3 years
Debarment Statement Included?	YES
Pediatric Rule Addressed?	Request for Full Pediatric Waiver
Financial Disclosure Information Included?	YES

Background

Doxazosin mesylate is an alpha-antagonist that was previously approved under Pfizer's registered trade name Cardura®, as an immediate release formulation for the treatment of hypertension (NDA 19-668) and benign prostatic hyperplasia (BPH) (NDA 20-371). The current NDA applications are for a modified release tablet formulation for doxazosin mesylate, Cardura XL ®, that uses a controlled rate of delivery of doxazosin into the gastrointestinal lumen, that is independent of pH or gastrointestinal motility. Cardura XL® utilizes the patented GITS (Gastrointestinal Therapeutic System) process.

Cardura XL® (doxazosin mesylate) NDA [redacted] 21-269, for the treatment of BPH). [redacted] the Division of Reproductive and Urologic Drug Products will review the clinical BPH information, BPH biopharmaceutical data and BPH labeling contained in the NDA 21-269. [redacted]

Since NDA 21-269 is a type 6 NDA, if the NDAs are approved, all supplements and other submissions (except those noted below) will be addressed [redacted] for this drug product. Pfizer, however, will submit the following documents to NDA 21-269: (20) copies of the final printed labeling; 7-day and 15-day alert reports; periodic adverse drug experience reports; quarterly periodic adverse drug experience reports; field alerts; and annual reports.

Foreign Marketing History

Since March 1998, Doxazosin GITS 4 and 8 mg tablets have been approved in 25 foreign countries and marketed in: Denmark, Germany, Norway, Sweden, Switzerland, and Spain for the treatment of hypertension and /or benign prostatic hyperplasia.

Estimated Review Completion

Discipline	**Reviewer**	**Date**
HFD-110		
Medical:	A.O. Williams, M.D.	January 4, 2002
Secondary Medical:	Douglas Throckmorton, M.D.	January 23, 2002
Biopharmaceutical:	Angelica Dorantes, Ph.D.	December 21, 2001
Pharmacology:	Albert DeFelice, Ph.D.	January 4, 2002
Chemistry:	Kathleen Jongedyk, M.S.	September 3, 2001
Statistics:	Sharon Yan, Ph.D. The sponsor has been requested to submit the treatment codes for two HTN studies.	January 4, 2002

HFD-580

Medical:	Ashok Batra, M.D.	January 4, 2002
Secondary Medical:	Mark Hirsch, M.D.	January 23, 2002
Biopharmaceutical:	Ameeta Parekh, Ph.D.	January 4, 2002
Statistics:	James Gebert, M.D.	January 4, 2002
	The sponsor has been asked to submit the treatment codes for the BPH studies.	

DSI: The Division of Reproductive and Urologic Drug Products will identify two clinical site inspections for the BPH studies.

[redacted]

Filing Status

There were no filing issues discussed. Everyone agreed the application can be filed.

Signature recorder: _____

Concurrence, Chair: _____

Draft:	06/19/01	**Final:**	07/16/01
HFD-110		**HFD-580**	
Throckmorton	06/25/01	Hirsch	07/03/01
Stockbridge	06/25/01	Batra	
Karkowsky	06/25/01	Parekh	
Williams	06/25/01	Agarwal	
Dorantes	06/26/01	Welch	
Srinivasachar	06/26/01	Gebert	06/27/01
Jongedyk	06/28/01	Molchan	
Hung	07/05/01	Farinas	
Yan	07/05/01		
Rios			
Morgenstern	07/06/01		
McDonald	06/20/01		

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/s/

Daryl L. Allis
7/23/01 10:22:44 AM

MEMORANDUM OF TELECON

DATE:	July 12 and 13, 2001
APPLICATION NUMBER:	NDA 21-269, doxasozin mesylate extended release tablets
BETWEEN:	
Name:	John Picciano, Director, Regulatory Affairs
Phone:	212-573-1975
Representing:	Pfizer
AND	
Name:	Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager Division of Reproductive and Urologic Drug Products, HFD-580
SUBJECT:	Provide clarification and additional comments to previously requested statistical information

To further clarify statistical questions previously submitted to the sponsor, Dr. James Gebert, Ph.D., statistical reviewer for this application, asked that the following comments be conveyed to the sponsor:

1. The sponsor can create the variable names. The FDA has no standardized names for these variables. There might have to be a valid visit ID variable for ITT and valid visit ID variable for per-protocol. This reviewer can not determine that from his inspection of the submission.

2. The sponsor can put the new variables into a separate datafile that does not contain efficacy variable data. The sponsor must include pat, visid, and invnum (or other investigator identifier) also in the file. There should be a define.pdf file.

Evelyn R. Farinas
Regulatory Project Manager

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/s/

Evelyn Farinas
7/13/01 08:52:52 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE #

FACSIMILE TRANSMITTAL SHEET

DATE: Today's Date

To: John Picciano	**From: Evelyn R. Farinas**
Company: Pfizer, Inc.	DRUDP
Fax number: 212-857-3558	**Fax number:** 301-827-4267
Phone number: 212-573-3412	**Phone number:** 301-827-4260

Subject: NDA 21-269, Cardura XL
Request for additional statistical information

Total no. of pages including cover: 2

Comments:

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

Document to be mailed: ☐ YES ☐☑ NO

NDA 21-269

Attachment:

Dear John:

The Statistics Reviewer asked that I request the following information:

1. Please provide files containing Indicator random variables for the two Cardura XL studies for BPH. One indicator random variable should be 1 if patient is in ITT population, 0 otherwise. Another random variable should be 1 if patient is in Per-protocol population, 0 otherwise. The last indicator random variable would be 1 if visit is a valid visit for per-protocol population, 0 otherwise. These files should contain protocol (PROTO), Investigator ID (INV), subject ID (PAT), Visit no (VISID), ITT ID, per-protocol ID, valid visit ID. It would be helpful if new variables were put in new IPSS and Urine Files.

2. Also, please include a Country ID in the files, since country was used as a factor.

3. The ITT ID is needed, as well as the per-protocol ID for both the IPSS and maximal urinary flow rate analyses.

4. Please provide information why a patient's data was not included in the ITT analyses. Please identify if there was a table containing patients excluded from ITT analysis and per-protocol analysis in their submission.

As always, thanks for your help.

Evelyn

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/s/

Evelyn Farinas
7/13/01 08:07:20 AM
CSO

Filing Meeting Minutes

Date: June 13, 2001 **Time**: 2:45:3:15 PM, EST **Location**: WOC II; HFD-110

Drug: Cardura XL

NDA 21-269 **Indication:** Benign Prostatic Hyperplasia

Sponsor: Pfizer, Inc.

Type of Meeting: Joint Filing Meeting, Division of CardioRenal Drug Products (DCRDP; HFD-110) and Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Meeting Chair: Daryl Allis, Project Manager, DCRDP (HFD-110)

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Project Manager, DRUDP (HFD-580)

FDA Attendees:

HFD 110: Blount, Allis, Williams, Throckmorton, Morgenstern, Defelice, Jonged, Srinivasach, Dorantes, McDonald, Yans, Butler, Gebert, Stockbridege, Karowsky

HFD 580: Farinas, Batra, Agarwal, Parekh, Welch, Hirsch

HFD-46: Molchan, Rios

Meeting Objective: To determine fileability of Cardura XL

Background:

with an indication for benign prostatic hyperplasia.

Discussion:

- Reviewers in each of the following disciplines from the two Divisions stated:
  - Clinical: Fileable; HFD-110 expressed concerns about the sponsor not studying the higher doses; HFD-580 recognized limitations regarding dosing, but indicated that there is a large amount of experience with this drug and that the use of 16 mg in clinical urology practice is negligible
  - Biopharmaceutics: Fileable
  - Chemistry: Fileable
  - Pharmacology: Fileable
  - Statistical: Fileable
  - Microbiology: Fileable; no issues
- Environmental assessment: categorical exclusion will be granted
- Division of Scientific Investigations: HFD-580 will submit two sites to DSI for inspection

Decisions reached:

- Decision letter will be a joined HFD-110 and HFD-580 effort, signed by Directors of both Divisions
- Completion of reviews by all disciplines is targeted for January 4, 2001

Action Items:

- Joint Division status meetings to be set up by Project Managers as needed

Minutes Preparer **Concurrence, Chair**

cc:
IND Arch:
HFD-580/DivFile

HFD-580/ Allen/Shames/
drafted: Farinas, 6.15.01
concurrence: Rumble 6.15.01/Hirsch 6.21.01/Batra 6.21.01/Agarwal 6.15.01/Parekh 7.06.01/Welch 6.15.01
final: Farinas, 7.06.01

MEETING MINUTES

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/s/

Evelyn Farinas
7/6/01 12:55:03 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-269

Pfizer, Inc.
Attention: John Picciano
Director, Worlwide Regulatory Strategy
235 East 42nd Street 150/7/5
New York, NY 10017

Dear Mr. Picciano:

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:	doxazosin mesylate extended release tablets
Review Priority Classification:	Standard (S)
Date of Application:	April 20, 2001
Date of Receipt:	April 23, 2001
Our Reference Number:	NDA 21-269

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 22, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be February 23, 2002 and the secondary user fee goal date will be April 23, 2001.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Terri F. Rumble
4/25/01 10:27:38 AM

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

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

USER FEE COVER SHEET

See Instructions on Reverse Side Before Competing This Form

1. APPLICANT'S NAME AND ADDRESS

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

2. TELEPHONE NUMBER (*Include Area Code*)
(212) 573-3412

3. PRODUCT NAME
CARDURA XL® (doxazosin mesylate)

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

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

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

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

5. USER FEE I.D. NUMBER.
3945

6. LICENSE NUMBER / NDA NUMBER
[redacted]

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

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

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

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

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

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

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

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

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

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

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO
(*See reverse side if answered YES*)

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

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

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

A agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Mr. Robert Clark *J Pracard for R. Clark*	Senior Director/Group Leader Worldwide Regulatory Strategy	April 20, 2001

FORM FDA 3397 (5/98) Created by Electronic Document Services/USDHHS: (301) 443-2454 EF

Minutes of a Meeting

Meeting Date:	March 23, 2000
Date Requested:	January 24, 2000
Date Confirmation Faxed:	February 15, 2000
Date Background Received:	March 10, 2000
Type:	Pre-NDA Chemistry
Meeting Classification:	B
INDs:	[redacted]
	32,633 (benign prostate hyperplasia)
Sponsor:	Pfizer Pharmaceuticals
Meeting Chair:	Kasturi Srinivasachar, Ph.D.
Meeting Recorder:	Zelda McDonald
External Participant Lead:	Suzanne LoGalbo

FDA Participants:

Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry, HFD-810
Moo Jhong Rhee, Ph.D.	Team Leader, Chemistry, HFD-580
J.V. Advani, Ph.D.	Chemist, HFD-580
Angelica Dorantes, Ph.D.	Pharmacokineticist, HFD-860
Zelda McDonald	Regulatory Health Project Manager, HFD-110

Pfizer Participants:

Alton Johnson	Director, Product and Process Development
Suzanne LoGalbo	Director, Team Leader, Drug Regulatory Affairs
Gerald Migliaccio	Vice President, Global Manufacturing Operations
John Picciano	Director, Drug Regulatory Affairs

Background:

Doxazosin is currently approved for the treatment of hypertension and benign prostate hyperplasia. It is supplied as 1, 2, 4 and 8 mg tablets given once daily. Doxazosin is presently formulated as a conventional immediate release tablet and patients are usually controlled at a daily dose of 4 mg to 8 mg. According to Pfizer, at these doses the high peak plasma concentrations achieved with the standard formulation can cause first-dose effects, meaning that patients need to be gradually titrated to the therapeutic dose. The recommended starting dose has been 1 mg. First-dose effects are also possible in patients already controlled on doxazosin, but who need to restart the medication after not having taken it for several days. Additionally, as a consequence of the need for gradual titration of the standard formulation, therapeutic control is not achieved at the start of treatment and frequently physicians do not titrate the drug to an adequate dose level. A meeting was held on October 22, 1999 to discuss the clinical aspects regarding the submission of an NDA for a modified-release tablet formulation (Doxazosin GITS). This formulation slows the rate of release of doxazosin and hence decreases the rate of absorption so that the maximum plasma concentration achieved is reduced while the minimum plasma concentration is maintained. Pfizer believes that this formulation could potentially reduce the number of titration steps that patients require to just one, as it is anticipated that a significant proportion of patients will be adequately controlled at the initial 4 mg dose.

Doxazosin GITS was recently approved for marketing in Europe. The application for this approval included clinical pharmacology studies that adequately described the pharmacokinetic profile of doxazosin GITS and large, controlled clinical studies that demonstrated the efficacy and safety of doxazosin GITS [redacted] in the BPH patient population. Pfizer requested this meeting to discuss the Chemistry Manufacturing and Controls (CMC) issues associated with a proposed submission of an NDA for Doxazosin GITS.

Discussion Points/Agreements Reached:

Pfizer stated that they plan to submit the NDA in May 2000. They asked if the proposed data package is acceptable for filing. If not, what are the key parameters needed to do so.

- [redacted]

- There will be two strengths of the GITS tablets, 4 mg and 8 mg. Both contain a 5% overage. The Division asked Pfizer to justify this overage based on the residual amount of drug after release. If justified, the label should state the actual amount of drug per tablet (4.2 mg and 8.4 mg) not just the deliverable amount.

- Pfizer planned to identify doxazosin by high performance liquid chromatography (HPLC). The Division asked for a more specific test, e.g., HPLC combined with diode array detection. Pfizer agreed to include an additional specific test at the time of filing.

- The tablet consists of a coated two layer core: an 'active' layer and an 'osmotic layer' contained in a semi-permeable membrane coating with a laser drilled hole to permit release of the drug substance suspension by osmotic pressure. Pfizer agreed to provide data as to whether the laser drilling has any effect on the drug substance i.e., any possibility of photo or thermal degradation.

- The dissolution test provides data for only one medium. Pfizer agreed to provide dissolution validation data on how they decided on the conditions of the proposed dissolution test.

- Pfizer was advised to utilize the In vivo/In vitro Correlation Guidance to Industry to determine the dissolution specifications.

- The Division suggested that the sponsor does not need two sets of dissolution specifications [redacted] Pfizer stated they will either address this or provide a counter proposal.

- Pfizer plans to use the Brooklyn stability data as the primary data and the Amboise, France data as supportive. The stability data from the Groton plant will not be available at the time of filing, but would be available at the time of the submission of the safety update, i.e., four months after the initial submission. The Division agreed.

- The Division said the label should state, "store at 25°C, excursions permitted between 15°C and 30°C" instead of, [redacted]

- The Division asked Pfizer to check for [redacted] content in the tablet, or justify why it has not been addressed.

- The Division agreed that the CMC section is acceptable for filing based on what has been proposed and the agreements made at this meeting.

Signature minutes preparer: _____

Concurrence, Chair: _____

Orig. IND
HFD-110
HFD-110/McDonald
HFD-110/Blount
HFD-110/Mathews
HFD-580/Rhee
Drafted 3/27/00 Finaled 4/3/00
RD:
Srinivasachar 3/31/00
Rhee 4/3/00
Advani 4/3/00
Dorantes 3/23/00

Teleconference Minutes

Date: February 24, 2000 **Time:** 4:00-4:45 PM, EDT **Location:** Parklawn; 17B-43

IND 32,633 **Drug:** Doxazosin/GITS **Indication:** Benign prostatic hyperplasia

Sponsor: Pfizer Pharmaceuticals

Type of Meeting: Guidance

Meeting Chair: Susan Allen, MD, Acting Director, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)

External Lead: John Picciano, Director, Regulatory Affairs

Meeting Recorder: Evelyn R. Farinas, RPh, Regulatory Project Manager

FDA Attendees:
Susan Allen, MD – Acting Director, DRUDP (HFD-580)
David Hoberman, Ph.D. – Statistician @ DRUDP (HFD-580)
Daniel Shames, MD – Team Leader, DRUDP (HFD-580)
George Benson, MD – Medical Officer, DRUDP (HFD-580)
Terri Rumble, BSN – Chief, Project Staff Management, DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph. – Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
John Picciano - Director, Regulatory Affairs
Robert Clark – Group Leader/Director, Regulatory Affairs
Sharon Mallen, MD – Medical Director
Elizabeth Putnam – Clinical Research
Sheila Quinn Assistant Director, Biometrics
Sarah Young – Director, Biometrics
Suzanne LoGalbo – Director, Team Leader, Drug Regulatory Affairs
V.J. Vashi, Ph.D. – Clinical Pharmacology

Meeting Objective: To discuss the adequacy of Pfizer's plans to use the Cardura GITS MAA as the basis for the NDA filing.

Background: In the meeting package of October 11, 1999, which was submitted to the Division of CardioRenal Drug Products, the sponsor asked to discuss clinical aspects regarding the submission of an NDA to that division for a modified-release tablet formulation (Doxazosin GITS) based on results of trials which supported a European Marketing Authorization Application (MAA). The sponsor indicated that this formulation would decrease the number of titration steps to one, instead of the incremental approach required by patients who are using the immediate release formulation for either hypertension or benign prostatic hypertrophy. DRUDP did not receive the meeting package from October, 1999, and was not a participant in the pre-NDA meeting which occurred with the sponsor on October 22, 1999. Following the pre-NDA meeting, the sponsor submitted to DRUDP

on December 17, 1999, the following studies and clinical analyses: Study DAZ-NY-95-001, "A 15-Week, Prospective, Randomized, Double-Blind, Trial of the Efficacy and Safety of Doxazosin vs. Doxazosin GIT in Patients with Benign Prostatic Hyperplasia," and Study DAZ-N/S/DK/95-001, "A 15-Week, Double-Blind, Placebo Controlled Trial of the Efficacy and Safety of Doxazosin vs. Doxazosin GIT in Patients with Benign Prostatic Hyperplasia."

Discussion:

- general comments:
  - DRUDP indicated that the purpose of this teleconference was to clarify information previously conveyed to the sponsor by the Cardiorenal Division in October 1999
  - a second purpose of this teleconference is to provide guidance to the sponsor regarding submission of an NDA to DRUDP for the treatment of BPH
- clinical comments:
  - data submitted from European clinical trials appears adequate to support BPH indication; number of trials and trial design is appropriate; SAS data sets are sufficient;
  - superiority claim for the doxazosin/GITS tablets is a review issue
  - sponsor clarified that the format by which safety information will be conveyed in the label has not yet been decided (i.e., how to display the adverse events reported from the 2 dosage forms); DRUDP recommends that safety data from the immediate release product and that from the modified-release tablet be kept separate in the label
- statistics comments:
  - the protocol received by DRUDP did not specify the analysis of flow rate in Protocol DAZ-NY-95-001, nor plan for analysis of flow rate or multiple comparisons in Protocol DAZ-N/S/DK- 95-001
  - of concern is the lack of a plan for analyzing primary endpoints and lack of a plan to control Type I error
  - sponsor stated that there was a more recent submission that addressed the Division's statistical concerns; this submission will be faxed to the Division; DRUDP indicated that analysis of flow rate and multiple comparisons should be included in this submission
  - DRUDP recommended that sponsor analyze data in standard fashion, state explicitly which test was used for multiple comparisons, and use covariance model to analyze maximum flow rate
- Biopharmaceutics comments:
  - it is not clear if the clinical trial formulation is identical to the to-be-marketed formulation
  - regarding food-effect study with 8 mg GITS (Study DAZ-NY-96-008), clarify if there were safety parameters recorded at early time points coinciding with the Cmax values
  - reports of postural hypotension with the 8 mg GITS formulation is a concern
  - sponsor should provide an analysis addressing the frequency of adverse events reported in young females and elderly subjects in Study DAZ-NY-96009 (Effect of age and gender on pharmacokinetics of doxazosin GITS);
  - there is a safety concern in young females and elderly subjects (who showed a greater frequency of adverse events) if doxazosin GITS were administered with meals, since coadministration with meals increases the Cmax by 30%
  - an explanation of how titration will take place in clinical practice if adverse events are seen with the lowest planned dose of 4 mg is needed
  - if a study is planned to assess pharmacokinetics and pharmacodynamics in renally impaired subjects, it should be included in the NDA submission; sponsor indicated that such study was planned [redacted]

- sponsor should submit *in-vitro* dissolution profiles over the entire physiological pH range
- electronic submission of the Clinical Pharmacology and Biopharmaceutics section is preferred to facilitate the review; sponsor indicated that the NDA submission will not be in electronic format, and that it plans to submit the MAA summary document

- NDA submission comments:
  - [redacted]
  - sponsor must follow the NDA submission format as stated in the regulations, not the MAA format; sponsor indicated that the submission will be reformatted according to the regulations
  - sponsor indicated that CMC data for the BPH indication submission would be referenced to the [redacted]
  - labeling information will be submitted in electronic format
  - sponsor indicated proposed submission for the NDA is second quarter of 2000

Decisions made:

- the design and number of trials in the submission of December 17, 1999 appears to be adequate for filing, but a definite determination of fileability will be made after the BPH NDA is submitted
- sponsor to submit statistics data indicating endpoint, flow rate and multiple comparison analysis
- sponsor will resubmit data or reference the immediate release doxazosin NDA to clarify the clinical pharmacology and biopharmaceutics issues
- sponsor will address the *in-vitro* dissolution issues
- [redacted]
- NDA submission will follow format established in the CFR, not those of the MAA

Action Items:

- minutes to be sent to sponsor within 30 days
- minutes to be sent to the DCRDP
- sponsor to FAX to DRUDP additional statistical data indicating endpoints,

Carolyn Reaves Farinas
Minutes Preparer

Susan Alter, MD
Concurrence, Chair 3/24/00

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

ADDENDUM

Date: February 25, 2000

- Ms. Terri Rumble, Chief Project Management Staff, called sponsor to clarify the process of NDA submission for the BPH indication
- [redacted]

- the sponsor would pay one full User Fee
- when the submission in DRUDP is approved, all the BPH records will revert to the Division of CardioRenal Drug Products under the "parent" NDA as with the original Cardura NDA

cc:
Original IND
HFD-580/DivFile
HFD-580/Allen/Mann/Shames/Benson/Hoberman/Parekh/Rumble/Farinas

drafted: erf/03.06.00
concurrence: Allen 03.15.00/Shames 03.06.00/Benson 03.07.00/Hoberman 03.07.00/Rumble 03.06.00
final: erf/03.16.00

MEETING MINUTES

Minutes of a Meeting

Meeting Date:	October 22, 1999
Date Requested:	September 29, 1999
Date Confirmation Faxed:	September 30, 1999
Type:	Guidance – Discuss NDA for GITS formulation
Classification:	C
INDs:	[redacted]
	32,633 doxazosin (benign prostate hyperplasia)
Sponsor:	Pfizer Inc.
Meeting Chair:	Raymond Lipicky, M.D.
Meeting Recorder:	Zelda McDonald
External Participant Lead:	Suzanne LoGalbo, Rph, JD

FDA Participants:

Raymond Lipicky, M.D.	Director, Div. Cardio-Renal Drug Products, HFD-110
Robert Fenichel, M.D., Ph.D.	Deputy Director, HFD-110
Shaw Chen, M.D., Ph.D.	Team Leader, Medical, HFD-110
Maryann Gordon, M.D.	Medical Officer, HFD-110
Albert DeFelice, Ph.D.	Team Leader, HFD-110
Elizabeth Hausner, DVM.	Pharmacologist, HFD-110
J.V. Advani, Ph.D.	Chemist, HFD-810
Angelica Dorantes, Ph.D.	Acting Team Leader, Biopharmaceutics, HFD-860
Zelda McDonald	RHPM, HFD-110

Pfizer

Margaret Cary	Senior Associate director, Biometrics
Susan DeCorte	Director, Regulatory Affairs, Central Research
David Helgans	Director, Team Leader, Cardura Worldwide Team
Suzanne LoGalbo	Director, Team leader, Drug Regulatory Affairs
John Picciano	Director, Drug Regulatory Affairs
Michael Sweeney, M.D.	Medical Director

[redacted]

Background:

Doxazosin is currently approved for the treatment of hypertension and benign prostate hyperplasia. It is supplied as 1, 2, 4 and 8 mg tablets given once daily. Doxazosin is presently formulated as a conventional tablet and patients are usually controlled at a daily dose of 4 mg to 8 mg. According to Pfizer, at these doses the high peak plasma concentrations achieved with the standard formulation can cause first-dose effects, meaning that patients need to be gradually titrated to the therapeutic dose. The recommended starting dose has been 1 mg. First-dose effects are also possible in patients already controlled on doxazosin, but who need to restart the medication after not having taken it for several days.

Additionally, as a consequence of the need for gradual titration of the standard formulation, therapeutic control is not achieved at the start of treatment and frequently physicians do not titrate the drug to an adequate dose level.
Pfizer requested this exploratory meeting to discuss the clinical aspects regarding the submission of an NDA for a modified-release tablet formulation (Doxazosin GITS). This formulation slows the rate of release of doxazosin and hence decreases the rate of absorption so that the maximum plasma concentration achieved is reduced while the minimum plasma concentration is maintained. Pfizer believes that this formulation could potentially reduce the number of titration steps that patients require to just one, as it is anticipated that a significant proportion of patients will be adequately controlled at the initial 4 mg dose.

Doxazosin GITS was recently approved for marketing in Europe. The application for this approval included clinical pharmacology studies that adequately described the pharmacokinetic profile of doxazosin GITS and large, controlled clinical studies that demonstrated the efficacy and safety of doxazosin GITS [redacted] in the BPH patient population.

Discussion Points/Agreements Reached:

1. Pfizer stated that they expected to file the application as a supplement to the NDA and that the Division (Cardio-Renal) would review [redacted]

   - The Division stated that the application would have to be filed as a new NDA because the GITS is a new formulation. Division believed that the BPH section would be consulted to the Division of Reproductive and Urologic Drug Products (DRUDP). The Division will check to make sure this is so and that another NDA to DRUDP is not required. The GITS NDA can cross-reference the standard product (doxazosin) hypertension and BPH NDAs for drug substance, preclinical and patient sub-population information.

2. Pfizer asked if the Division considered the clinical program for Doxazosin GITS acceptable for filing since the application will contain the following:

   - one placebo controlled trial and one comparator trial for each indication
   - placebo controlled trials conducted in a Caucasian patient population
   - clinical program encompasses non-US data

   - The Division agreed that the above was acceptable for filing.

3. Pfizer asked if the Marketing Authorization Application (MAA) summary documents can be used for filing.

   - The Division agreed that the MAA clinical program is acceptable. The Division will need to get concurrence from the DRUDP regarding the BPH indication.

4. Pfizer asked if the efficacy and safety derived from the GITS studies could be described in the labeling, i.e., discussion of what the physician can expect in clinical practice.

   - The Division did not believe that would be possible because some critical information is missing, e.g., there is no data about patients on diuretics. The labeling will be complicated; the Division was not sure what the labeling would say, but it would not be a refusal to file issue.

The Division stated that the labeling should be similar to that of the immediate release formulation. [redacted] The GITS adverse event database will be small compared to the immediate release, so there is always a question as to whether to have both or only those known for the immediate release. If both, what format? The Division agreed that if a "therapy related effects analysis" is the same for both indications, those effects could be collapsed into one set for labeling.

- Pfizer agreed to submit the labeling in electronic format.

5. Pfizer stated that the electronic submission will not have an interactive format.

   - The Division stated that the submission can be SAS data sets for Cardio-Renal, however, the DRUDP may find that format unacceptable.

Action Items:

1. The Division will discuss the proposed application with the DRUDP and get back to Pfizer as to whether the DRUDP will accept:
   - the application as a consult
   - the application in MAA format
   - SAS data sets

Signature minutes preparer: _____

Concurrence, Chair: _____

Orig. IND
HFD-110
HFD-110/McDonald
HFD-110/Blount
HFD-110/Mathews
Drafted 10/26/99 Finaled 11/3/99
RD:

Fenichel	10/27/99
Chen	10/27/99
Gordon	10/27/99
DeFelice	10/28/99
Hausner	10/28/99 by DeFelice
Advani	11/1/99
Dorantes	10/26/99