CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-269

MEDICAL REVIEW

Medical Team Leader's Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
ODE 3
Division of Reproductive and Urologic Drug Products

Date: February 22, 2005

From: Mark S. Hirsch, M.D., Medical Team Leader, HFD-580

To: Dan A. Shames, M.D., Division Director, HFD-580

Subject: NDA 21-269
Cardura® XL (doxazosin mesylate extended release tablets for the treatment of the [redacted] symptoms associated with benign prostatic [redacted] (BPH)

1. Executive Summary

The purpose of this memo is to provide the Division Director with my recommendation regarding regulatory action on this NDA. I recommend that this application should be **approved**. The sponsor has satisfactorily responded to the most recent approvable deficiency, demonstrating that the amount of [redacted] in both the drug substance and drug product are well [redacted] The sponsor submitted a clinical safety update which reveals no new safety concerns. Finally, labeling discussions have been successful in resolving all other outstanding issues. Therefore, in my opinion, this application may now be approved.

2. Brief Regulatory Background

This is the third review cycle for this application.

2.1. Original NDA review

On April 23, 2001, Pfizer Pharmaceuticals Group submitted [redacted] new drug applications for Cardura XL. [redacted] NDA 21-269 was for the treatment of the symptoms of BPH. During the course of the original NDA reviews, the Division of Cardio-Renal Drug Products (hereafter referred to as "CR Division") provided comments to the sponsor that led to the eventual withdrawal of NDA 21-269 from the CR Division. In the last few weeks of this review cycle, the sponsor elected to proceed with the application for BPH Only two other agents in this class, Flomax (tamsulosin) and Uroxatral (alfuzosin) are currently approved for BPH [redacted]

On February 22, 2002, our Division issued an approvable action for the BPH NDA (21-269). While the evidence for efficacy for BPH was convincing and the overall safety appeared adequate, there was a persistent safety concern in regard to safety of the very first day and first week of dosing. Since Cardura XL 4mg extended release tablets produce a pharmacokinetic profile similar to the Cardura immediate release 2mg tablet (not the 1mg tablet), the Division requested additional clinical data to support the safety of the first dose and first week of therapy. The exact items that were requested in order to resolve this concern were:

1. Results from a dedicated pharmacodynamic study comparing blood pressure for 24 hours following dosing with Cardura XL 4mg and doxazosin IR 1mg, and
2. A critical analysis from the available controlled safety databases of all vasodilatory AEs occurring within 24 hours and 7 days for Cardura XL and doxazosin IR.

Finally, although not approvable issues, the sponsor was asked to provide information regarding: safety in black men, safety in men older than 75 years of age, clarifications of some safety data line listings, additional pharmakinetic data relevant to intra-subject variability, and revised package insert and container/carton labeling.

3.1. Second cycle review

On December 17, 2003, Pfizer submitted a Complete Response to this first Approvable action. The original Response contained the two required Clinical items (as above); the remaining "minor" Clinical and Clinical Pharmacology items were submitted as amendments during the second review cycle.

Selected results from the dedicated "first-dose" blood pressure study comparing Cardura XL 4mg to doxazosin standard 1 mg (Study A035-1061) may be found in the primary medical officer's second cycle review. In summary, while the study was admittedly small (n=26) and not powered to show statistical non-inferiority; the Division believed that the study still provided useful information to support the contention that orthostasis seen after first-dosing with Cardura XL was not substantially worse than that seen after doxazosin standard in terms of blood pressure changes and clinical orthostatic adverse events.

The sponsor also provided the requested comparative safety analysis of the four pivotal trials (BPH and HTN) from the original NDA. These included a total of 2180 patients; 984 who received Cardura XL, 964 who received doxazosin standard, and 232 who received placebo. The results of this analysis may be found in the primary medical officer's and medical team leader's reviews of the second cycle. In summary, the results appeared to show that the incidence rates of expected vasodilatory and cardiovascular events on Days 1, Days 2-7, and thereafter were similar between active treatment groups, and overall were fairly low in incidence in a very large controlled cohort.

Additional information to address the primary clinical deficiency was also submitted, including: safety results from four small clinical trials, post-marketing experience with Cardura XL, and a 2-year Safety Update. These were all supportive of product safety for the intended use, especially in regard to vasodilatory adverse reactions. Finally, sponsor submitted sufficient information to resolve the minor clinical deficiencies, including: safety in African-Americans, safety in men older than 75 years of age, potential effect on the QT interval, and an issue related to intra-subject variability in systemic drug exposure. The reader is referred to my team leader's memo dated June 17, 2004 for details of these items.

However, during the second cycle review, another safety issue arose: *the potential for unqualified* [redacted] *to be present in the final drug product.* The primary pharmacology/toxicology reviewer, Dr. Thornton-Jones, summarized the concern as follows (only selected passages presented):

> "A new concern within CDER is the possible production of genotoxic impurities which can be produced when free base drugs are converted to a mesylate salt. The problem arises when [redacted] processing of drug

substance and/or drug product. These [redacted] can interact with [redacted]

These process impurities are known genotoxic agents and [redacted] is commonly used as (a) positive genotoxic control in genotoxicity assays. Furthur, IARC Monographs have reported the [redacted] the one of primary interest for this submission, has been shown to cause cancer in mice following s.c. administration (lung tumors), and mice and rats following i.p. administration (lung and kidney tumors).

The possibility for these process impurities in the drug substance and product exists for Cardura XL because [redacted] is used during manufacturing."

In her summation memo, the supervisory toxicologist, Dr. Reid, stated (selected passage only):

[redacted] impurities have been detected at greater than one part per million (ppm) in some mesylated drug substances and/or products. Consistent with other CDER divisions, DRUDP is adopting an interim standard of [redacted] for [redacted] in drug substances and drug products."

In conjunction with Drs Agarwal and Rhee, who conducted the chemistry review of the application, the NDA review team discussed the potential for [redacted] impurities in both the Cardura XL drug product and in the doxazosin mesylate drug substance. We were informed that these impurities could be present in the drug product, either due to reaction between [redacted] and trace amounts of [redacted] in doxazosin mesylate, or due to potential carryover of the impurities from the drug substance. Further, these impurities could also be present in the drug substance, either through formation during drug substance synthesis [redacted] in doxazosin reacting with [redacted] l) or as process impurities in [redacted] itself.

Following extensive internal discussion between the pharm/tox, chemistry, and clinical review teams, the following NDA Approvable Deficiency and Required Items for Resolution were agreed-upon:

Approvable Deficiency

[redacted] impurities may form when [redacted] during the manufacturing process of the drug substance as well as the drug product. [redacted] known genotoxins and potential human carcinogens.

To ensure patient safety, the Division requires a limit on the total concentration of [redacted] in the active pharmaceutical ingredient (API) and in the drug product. At this time, no agreed-upon standard exists in the scientific community for limits on these specific impurities. Therefore, for this NDA, we require an interim standard of not [redacted] for [redacted]

You have not demonstrated that the total amount of [redacted] in the API and the drug product is consistently [redacted]

Items Required to Address the Deficiency

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

Therefore, on June 17, 2004, the Division issued a second Approvable letter for NDA 21-269, requesting the above information about [redacted], a Safety Update, and revised package insert and container/carton labeling.

3.1. Third cycle review
On August 20, 2004, the sponsor submitted a Response to the second Approvable action. According to the sponsor:

> "The response includes assay data that confirms that the presence of [redacted] for doxazaosin mesylate API, Cardura and Cardura XL is indeed [redacted]

In addition, sponsor provided the requested Safety Update (covering the period January 1, 2003 through December 31, 2003), and the revised package insert and container/carton labeling.

In conducting my team leader's review for this third cycle, I reviewed the following items:

1. Primary reviews by the chemist, the supervisory pharmacologist, the primary medical officer, and the primary clinical pharmacologist.
2. My team leader's memo from the previous cycle.
3. Summary report of a 1998 in vitro metabolism study using doxazosin, as faxed by sponsor on February 3, 2005.
4. Revised package insert labeling, and the May 2004 review by the Division of Drug Marketing, Advertising and Communications (DDMAC).
5. Revised container/carton labeling, and the December 2004 review by the Division of Medication Errors and Technical Support (DMETS).

For details in regard to the clinical efficacy and safety of Cardura XL, as demonstrated in the BPH pivotal trials, the reviewer is referred to the original review of the primary MO and my original and second cycle team leader's memos. The results of these studies are not reiterated in this memo.

3. Materials Submitted in Response to the Approvable Action (3rd cycle).

3.1. [redacted] Issue
According to the February 16, 2005, draft Chemistry review provided to me by Dr. Agarwal, the applicant has "responded satisfactorily to the issues raised in the June 17, 2004, (Approvable) letter". Dr. Agarwal states that the provided data indicates that the drug substance and the drug product contain [redacted]

Dr. Agarwal provided more extensive information about the [redacted] analysis on pages 8-13 of his draft review, under the heading "Chemistry Assessment". Herein, I provide relevant excerpts from this section.

1. The sponsor analyzed twelve lots each of drug substance, Cardura IR and Cardura XL.
2. The sponsor used a validated [redacted]
3. [redacted]
4. The sponsor did a one-time test only.
5. The method of analysis was capable of detecting [redacted] impurities at [redacted]

6. For Cardura XL, [redacted] was added as an internal standard because the primary analyte of interest was [redacted]
7. For doxazosin mesylate (drug substance), [redacted] was used as an internal standard because the primary analytes of interest were [redacted]
8. For Cardura XL, the sample was spiked with [redacted] (which was easily detected). [redacted] was not detected in any sample.
9. For doxazosin mesylate (drug substance), the sample was spiked with [redacted] of both [redacted] (which were easily detected). The results showed no detection of [redacted] in any lot, but there was the presence of [redacted] at levels [redacted]
10. For Cardura IR, the sample was spiked with [redacted] of [redacted] (which was easily detected). The presence of [redacted] was noted at levels [redacted]
11. Following teleconferences with sponsor on November 18 and December 9, 2004 and final review of all the submitted information, Dr. Agarwal concluded: "The amounts of [redacted] in each product, irrespective of day of analysis, were far [redacted]

3.2. In vitro Metabolism Study

During the Division's review of the proposed labeling, it became clear that the Metabolism section lacked up-to-date information on the metabolic pathway for doxazosin. The Division's search of the literature was not successful in locating updated information. The sponsor was asked to provide any and all information that would allow us to update this section. On February 3, 2005, the sponsor submitted a 15-page, 1998 report entitled "Identification of the Human Cytochromes P450 Involved in the In Vitro Metabolism of Doxazosin (UK-33,274)." Dr. Ortiz and Kim provided a brief review of this submission. Based upon this new information, revised labeling was proposed for the Metabolism and Precautions section, and was accepted by sponor.. Herein, I provide relevant excerpts from the sponsor's report:

1. The in vitro enzymology of 6-OH and 7-OH doxazosin formation was investigated using liver microsomes, human livers, and recombinant P450 systems.
2. Chemical inhibitors of the following specific enzymes were tested: CYP1A2, CYP2C9, CYP 2C19, CYP 2D6, CYP2E1, and CYP3A4. These were incubated with doxazosin in liver microsome preparations from a combination of 6 human livers.
3. A bank of 13 human livers were also used to assess doxazosin metabolism.
4. The data from the inhibitor studies "suggest a major involvement of CYP3A4 in the formation of the two metabolites, together with some evidence of involvement of CYP2C9" (page 6 of the report).
5. The data derived from the bank of 13 human livers "suggests a major involvement of CYP3A4, with some metabolism mediated by CYP2C9 and to a lesser extent CYP2D6" (page 8 of the report).
6. Data derived from microsome preparations engineered to produce only one type of CYPP450 enzyme revealed:
   a. CYP 3A4 produces equal amounts of the two metabolites.
   b. CYP 2C9 produces equal amounts of the two metabolites, but at a slower rate than CYP 3A4.
   c. CYP 2D6 appears to form more of the 6-OH metabolite than the 7-OH metabolite, but forms both at a lower rate than CYP3A4.
8. According to sponsor's conclusion, the relative contribution of CYP3A4 to doxazosin metabolism (in real-life) is expected to be much greater than any other P450 investigated.

3.3. Safety Update

This re-submission from August 20, 2004 (the "third cycle") contained a Clinical Safety Update. This Update consisted of a summary of deaths and serious adverse events (SAEs) from BPH and hypertension clinical trials covering the dates January 1, 2003 through December 31, 2003. Some of the deaths reported in this Update were previously reported to the NDA but at that time, the studies were still blinded. The primary MO, Dr. Willett, reviewed this Safety Update and found no evidence of new safety risks for the product. Herein, I provide relevant excerpts from this section of his review.

1. Three patients who were taking Cardura XL in a comparative study with tamsulosin died. None was considered to be drug-related (airplane crash, traffic accident and pneumonia sepsis).
2. There were 51 serious adverse events reported in BPH trials. Some of these are notable:
    a. There were 12 reports consistent with bladder outlet obstruction (e.g. TURP, urinary retention, worsening dysuria, etc). The reader should be aware that alpha-blocker therapy does not fully manage symptoms in all BPH patients and some are expected to go on to other therapies or surgery.
    b. There were 17 reports of other genitourinary or pelvic conditions which might simulate BPH or might be associated with BPH (e.g. prostatitis, prostate cancer, rectal cancer, uncontrolled diabetes mellitus, ureteral calculus, herniated vertebral disc, inguinal hernia, renal stone, etc). These are not unexpected in the care and management of BPH patients
    c. There were 10 reports of conditions not reasonably expected to be related to drug or to BPH (e.g. basal cell carcinoma, cataract surgery, bronchitis, choolecystectomy, aneurysm of femoral artery bypass, etc).
    d. Of the remaining 11 reports, all were cardiovascular in nature, including: atrial arrhythmia (n=3); stroke (n=2); MI , angina, or coronary artery disease (n=4); and syncope=1, vertigo=1. Based upon the age and co-morbidity of these patients, such events are not unexpected and any relationship to doxazosin cannot be determined.. Syncope and vertigo may be related to treatment with Cardura XL.
3. There were no new deaths in hypertension trials and 6 serious adverse events. These were one each of the following: cholecystectomy, worsening spinal stenosis, metastatic colon cancer, renal failure secondary to hepatic decompensation, stroke and chest pain. Dr. Willet's review states that none of these were attributable to drug.

4. Clinically Relevant Issues from Other Disciplines

4.1. Chemistry

In a draft review dated February 16, 2005, Dr. Agarwal concluded:

> *"This NDA is recommended for approval from the CMC perspective."*

The reader is referred to Section 3.1 of this TL's memo for details about the [redacted] analysis. The only other issues of note are in regard to the container/closure labeling and the professional samples. Sponsor ultimately agreed to and made the requested changes to the carton/container label as per the recommendations of DMETs and Chemistry. In addition, the sponsor successfully demonstrated that the product could be produced in blister packaging (as professional samples) with quality maintained over 24 months shelf-life. Finally, while the

[redacted] bottles have [redacted] the professional samples do not. The samples have been revised to have obvious package labeling informing users [redacted]. I find this a clinically acceptable resolution.

4.2. Pharmacology/Toxicology

In a final review dated November 30, 2004, Dr. Reid concluded:

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

The only of issue of note is that Dr. Reid commented on December 15, 2004 that Pharm/Tox requires no revision to portions of the Cardura XL label dealing with nonclinical findings.

4.3. Clinical Pharmacology and Biopharmaceutics

In a final review dated February 18, 2005, Dr. Ortiz concluded:

> *"A teleconference was held with sponsor on February 1, 2005 regarding the in vitro and in vivo metabolism of Cardura XL. In response to this teleconference, the sponsor faxed the Agency results of several in vitro metabolism studies involving Cardura XL on February 3, 2005....Analysis of these in vitro studies suggest that the primary metabolic pathway for elimination is via CYP 3A4; however, CYP2D6 and CYP2C19 metabolic pathways also exist to a lesser extent....Based on the results of these studies, appropriate changes have been made to the Metabolism section and PRECAUTIONS; Drug Interactions section of the label."*

The reader is referred to Section 3.2 of this TL's memo for additional details about the in vitro metabolism data. In addition, the reader may wish to read the entire summary report of the in vitro metabolism study as appended to Dr. Ortiz' memo. (*In Dr. Ortiz' review he notes that one of the minor pathways is by 2C19 – however, according to sponsor's report, the minor pathways are by 2D6 and 2C9, not 2C19. This has been accurately conveyed in the product label*). The only other issue of note is that Dr. Ortiz made a few minor changes to the package insert on February 16, 2005 and these were all formally accepted by sponsor. To my knowledge, therefore, there are no other outstanding or notable Clinical Pharmacology issues for this application.

4.4. Biometrics

Dr. Welch contributed to this third cycle review by conducting a review of the revised package insert labeling. On January 26, 2005, Dr. Welch provided an eMAIL with three labeling comments pertaining to the tables and figures in the Clinical Studies section. Sponsor formally accepted the three requested changes. To my knowledge, therefore, there are no other outstanding or notable Biometrics issues for this application.

4.5. Division of Drug Marketing, Advertising and Communiccations (DDMAC)

In a final review dated May 3, 2004, Corrinne Kulick of DDMAC provided a detailed review of the proposed package insert (PI) on May 3, 2004. Each of the DDMAC comments was carefully assessed and changes were made to the sponsor's proposed PI as deemed appropriate by the relevant review discipline in conjunction with the medical team leader. Most of the DDMAC suggestions and recommendations were fully enacted and accepted by sponsor. Those that were

not enacted were either enacted in part, or if not enacted, were deliberated upon by the review team and felt not to be necessary. The reader is referred to Section 5 of this TL's memo for additional details of the labeling review.

The only other issue of note from DDMAC pertains to the container and carton label. On January 19, 2005, DDMAC provided a recommendation to [redacted] the established name because [redacted] the established name. This was communicated to sponsor and in response, sponsor formally [redacted] from the container and carton labeling.

4.6. Office of Drug Safety/Division of Medication Errors and Technical Support (ODS/DMETS)

In a final memo dated December 17, 2004, Carol Holquist et al provided final comments about the tradename and the container/carton labeling. They concluded:

> *"The Division of Medication Errors and Technical Support has not identified any additional proprietary or established names that have potential for confusion with Cardura XL since we conducted the initial review that would render the name objectionable...DMETS has no objection to the use of the proprietary name, Cardura XL."*

Other notable issues in this final DMETS consult included the potential for confusion between Cardura (standard) and Cardura XL (extended-release tablets); and specific container/carton labeling comments.

In regard to the former issue, DMETS recommended that "sponsor ensure that healthcare practitioners are educated about Cardura XL before and during its launch into the marketplace." DMETS also advised differentiating the labels and labeling of the two formulations as much as possible. The sponsor and DDMAC are aware of these recommendations.

In regard to the latter issue, DMETS made specific and general comments. One general comment was to differentiate the container and carton labeling between Cardura IR and Cardura XL as much as possible because it may be expected that the two products will stand side-by-side on the pharmacy shelf. The Division worked with the sponsor on font size and color to meet this objection. Finally, all specific comments by DMETS on the container and carton labeling were enacted by sponsor.

5. Labeling Review

Labeling discussions with sponsor were successfully completed on February 17, 2005. Herein, I provide several key concepts from the labeling:

1. The Description and Clinical Pharmacology sections indicate that Cardura (doxazosin standard or "IR") and Cardura XL (doxazosin extended-release) are different formulations associated with different pharmacokinetic profiles. [redacted]

2. The Clinical Pharmacology section delineates the difference in exposure between the fed state (somewhat higher) compared to the fasted state. The variability in this exposure is

shown in a graph. The recommendation for dosing in the Dosage & Administration section is the same as in the Phase 3 trials – with breakfast.

3. The extend-release, OROS-based formulation depends in part on gut transport; therefore, marked changes in gut transit time can affect systemic drug exposure. Greatly increased gut transit (as in short bowel) can reduce exposure, whereas greatly reduced gut transit times (as in severe constipation) can increase exposure. This is noted prominently throughout the labeling.

4. The Clinical Pharmacology; Metabolism section has been updated to include the in vitro CYP P450 results. Despite the lack of specific human drug-drug interaction pharmacokinetic or pharmacodynamic studies, the Precautions; Drug Interactions section has also been updated to advise caution in patients taking concomitant potent inhibitors of CYP 3A4.

5. The Clinical Pharmacology; Special Populations section describes the increase in exposure in patients with hepatic impairment, even mild hepatic impairment. The Precautions section also advises that prescribers use caution in such patients.

6. The Warnings section describes the class-related risk of syncope and orthostatic hypotension, especially after the first dose or increase in dose. The Warning is consistent with other products in the class. The section has been revised to indicate that the risk of orthostatic hypotension exists even at times later than a few hours after dosing.

7. The Indications statement is the same as for other products in the class and indicates that Cardura XL is not indicated for treatment of hypertension.

8. The Precaution; Geriatric Use section contains age-specific information regarding syncope and orthostatic hypotension. This adverse event occurs more frequently in those older than age 70 years. This is delineated carefully in the label.

9. The Dosage & Administration section recommends that therapy be initiated at 4mg daily and after a 3 to 4-week trial, the dose may be increased to 8mg at the discretion of patient and prescriber.

10. The Adverse Reactions section provides a detailed table of adverse events for the placebo, Cardura XL and Cardura groups from the two pivotal BPH trials.

11. The Clinical Studies section provides results for the primary efficacy endpoints for the two pivotal BPH trials. [redacted] First, the titration schema for Cardura was slower than the per-labeled use. This could have had an effect on time-to-symptom relief in the Cardura IR group. Second, in Study 1, the design was not appropriate to [redacted] Third, in Study 2, while the results appear quite comparable between the two formulations, and the sponsor's definition of "equivalence" was met, this definition was not pre-defined in the protocol [redacted]

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

/s/

Mark S. Hirsch
2/22/05 04:00:35 PM
MEDICAL OFFICER

Daniel A. Shames
2/22/05 04:04:51 PM
MEDICAL OFFICER

Clinical Memorandum to File

Date: February 18, 2005
From: Gerald Willett MD, Medical Officer, DRUDP
Subject: NDA 21-269 (Cardura XL)

Summary Statement

Based on the clinical efficacy and safety data from the original submission (20-Apr-2001), the applicant's response to the approvable letter of 22-Feb-2002 and the resolution of the chemistry issues addressed in the approvable letter of 17-Jun-2004, I recommend approval for Cardura XL for the indication of treatment of the signs and symptoms of benign prostatic hyperplasia.

Background

This is the third review cycle for NDA 21-269. Two approvable letters have been sent to the applicant (22-Feb-2002 and 17-Jun-2004) regarding this NDA.

The principal concern with the original submission was the lack of adequate safety data in regard to potential hypotensive episodes in the first 24 hours following administration of 4mg Cardura XL compared to 1mg of Cardura immediate release, and a critical comparative analysis from all available databases for the occurrence of vasodilatory adverse events in the first 24 hours and the first seven days of use for both Cardura XL and Cardura IR. Please see the clinical reviews in DFS for the original submission.

The sponsor adequately addressed these key clinical issues and other minor points in their Dec 17, 2003 submission. Please see the clinical reviews in DFS for the full discussion of the sponsor's response to the approvable letter. However safety concerns related to the possible presence of [redacted] necessitated another approvable letter. The sponsor provided data in their August 20, 2004 submission that the [redacted] impurities in their products is [redacted] With this data in hand, chemistry is now recommending approval from a CMC standpoint (see Chemistry Review for full discussion)

Safety Update Information (August 20, 2004 submission)

In the August 20, 2004 submission, the sponsor provided some additional information covering deaths and SAEs from BPH clinical trials (Jan 1, 2003 – Dec 31, 2003). The deaths had been previously reported in the update covering Jan 1, 2001 through Dec 31, 2002 but the some of the studies were still blinded. In a comparative trial between doxazosin GITS versus tamsulosin, three men died who were taking doxazosin GITS. None of these were related to study medication (airplane crash, traffic accident and pneumonia sepsis)

The following table lists the doxazosin GITS SAEs reported in the August 20, 2004 submission.

Case Number	Age	SAE	Comment
2002058285	53	Atrial flutter	History of atrial fibrillation
2002059711	64	Aneurysm of femoral artery by-pass	
2002061276	75	Hypoglycemic coma	History of diabetes
2002061835	75	Hemorrhagic stroke	
2002061901	61	Basal cell cancer	
2002062256	65	Inguinal hernia	
2002062334	57	Acute urinary retention	
2002062335	62	Pudendal canal syndrome	
2002063612	63	Herniated vertebral disc	
2002063615	75	Worsening dysuria	
2002064096	51	Worsening dysuria	
2002068473	56	Inguinal hernia	
2002069828	66	Uncontrolled diabetes	
2002070507	69	Prostatic cancer	
2003004475	Unknown	TURP	
2003004805	55	Bladder tumor	
2003006962	66	Stroke	
2003006984	92	Urinary retention	
2003006985	63	Myocardial infarction	
2003008163	56	Urinary retention	
2003008966	76	Bladder tumor	
2003010005	76	Elevated PSA – negative for tumor	
2003011449	61	Prostatitis	
2003028625	66	Cataract surgery	
2003031789	63	TURP	
A111979	69	Inguinal hernia	
A118777	75	Urinary retention	
A121970	51	Finger trauma/ amputation	
A121971	71	Temporal arteritis	
A124320	53	Inguinal hernias	
A126270	63	Urinary retention	
A126579	80	Worsening BPH	
A126590	87	Vertigo	Developed after one month on doxazosin GITS 4mg, felt to be drug related
A127902	74	Urinary retention	
A128503	63	TURP	
A128504	58	Coronary stent for angina	
A200788	76	Pneumonia, atrial flutter	History of cardiac rhythm disorder
A201260	53	Left renal calculus	
A201463	73	TIA/ cardiomyopathy	
A202683	60	Coronary stenosis	
A204163	82	Atrial fibrillation	
A204345	71	Cholecystectomy	
A205161	64	Right hip surgery	
A205291	71	Sigmoiditis	
A206641	72	Rectal cancer	
A207183	81	Cholecystitis Angina	
A208214	58	Colon cancer	
A210053	53	Ureteral stone	
A210832	67	Syncope	Also taking sildenafil Taking doxazosin GITS (unspecified dose for 5.5 months) Felt to be drug related
A211905	76	Asthmatic bronchitis	
A213624	67	Prostatic adenoma	
A214652	60	Unstable angina	

Medical officer's comments: This update does not reveal any new safety signals for doxazosin GITS. The one case of vertigo and the one case of syncope which are felt to be drug related are known adverse events related to this class of drugs. The appearance of the symptoms at remote times following initiation of therapy (one month and 5 ½ months) are similar to findings in the safety database in the pivotal trials of the original submission. Cases of urinary retention, worsened dysuria and transurethral resections are not unexpected, since not all patients respond adequately to alpha-blocker therapy.

In the safety update for the hypertensive trials, there are no new deaths to report. Six additional SAEs were listed for doxazosin GITS under hypertension trials in the August 20, 2004 submission. These adverse events include the following:

- 71 year old woman with development of renal failure secondary to hepatic decompensation
- 54 year old man with multiples serious adverse events (uncontrolled diabetes, syncope, colon cancer with hepatic metastases
- 85 year old male with a stroke
- 69 year old female with worsening of lumbar canal stenosis
- 50 year old female who underwent cholecystectomy
- 52 year old man with chest pain of undetermined etiology

Medical officer's comments: None of these adverse events are directly attributable to treatment with doxazosin. Some of these events, including stroke and hepatic injury are already listed in the "Adverse Reactions" section of the Cardura label as rarely reported clinical adverse events with doxazosin.

Labeling

The key concepts in regard to labeling Cardura XL are the following:

- Although Cardura XL has advantages over the immediate release Cardura in terms of less titration steps and a smoother release profile [redacted]

- At our request the sponsor has supplied additional in vitro information regarding hepatic metabolism which should be incorporated into the label. This information is derived from a 1998 study of doxazosin performed in the UK (UK33274). This in vitro study established that the P450 enzyme responsible for the 6' and 7' hydroxylation of doxazosin is CYP3A4 with minor contributions from CYP2D6 and CYP2C9. Therefore, the label should indicate that caution is appropriate when using Cardura XL with potent inhibitors of CYP3A4.

- The label should state that hypotensive episodes with Cardura XL occur more frequently in those over 70 years of age.

- The dosing of Cardura XL should reflect the dosing employed in the pivotal clinical trials, with emphasis placed on an adequate trial of 4mg prior to increasing the dose to 8mg (e.g. 3-4 weeks dosing interval)

Medical officer's comments: The final draft label is acceptable and captures the key concepts.

Gerald Willett MD, DRUDP

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

/s/

Gerald Willett
2/18/05 12:55:57 PM
MEDICAL OFFICER

Mark S. Hirsch
2/18/05 03:49:43 PM
MEDICAL OFFICER
I concur.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
ODE 3
Division of Reproductive and Urologic Drug Products

Date: June 17, 2004

From: Mark S. Hirsch, M.D., Medical Team Leader, HFD-580

To: Dan A. Shames, M.D., Division Director, HFD-580

Subject: NDA 21-269
Cardura® XL (doxazosin mesylate) extended release tablets for the treatment of the [redacted] symptoms associated with benign prostatic [redacted] (BPH)

1. Executive Summary

The purpose of this memo is to provide the Division Director with my recommendation regarding regulatory action on this NDA. At this time, I recommend that license to market Cardura XL for BPH should not be approved. Instead, I recommend an **approvable action** for this NDA.

- *If within CDER there is a precedent for or an interim standard of, [redacted] and this interim standard is adopted by the Division for this NDA, then I propose the following deficiency and resolution items:*

Deficiency:

Although the drug substance, doxazosin mesylate, has been qualified in two-year carcinogenecity studies in rats and mice, there is no genotoxicity data available for the mesylate salt since the base was used in the standard genotoxicity battery. [redacted]

[redacted]

To ensure patient safety, the Division requires a limit on the total amount of [redacted], in Cardura XL. At this time, no agreed-upon standard exists in the scientific community for limits on these specific impurities. Therefore, for this NDA, we recommend an interim standard of [redacted] in the final drug product. You have not yet provided sufficient information to demonstrate that the total amount of [redacted] in Cardura XL will be less than this interim standard limit.

Resolution items:

1. Demonstrate that your analytical methodology for detecting [redacted] impurities and degradation products in Cardura XL is sufficient to detect [redacted]

[redacted] In order to provide a margin of safety, the lower limit of detection of the assay should be [redacted]

2. Using an analytical methodology that is acceptable to the Division (as in Resolution Item #1), demonstrate that the total amount of [redacted] impurities and degradation products in Cardura XL, in both fresh and aged batches, is [redacted]

- *If there is no interim standard or precedent within CDER [redacted] in final drug products, or if there is such a standard within CDER, but the Division has not adopted that standard for whatever reason, then I propose the following deficiency and resolution items:*

Deficiency

Although the drug substance, doxazosin mesylate, has been qualified in two-year carcinogencity studies in rats and mice, there is no genotoxicity information for the mesylate salt [redacted] in the manufacturing of the final drug product, Cardura XL. This [redacted] offers an opportunity for [redacted] degradation products to form. [redacted]

To ensure patient safety, the Division requires a limit on the total amount of [redacted] in Cardura XL. You have not yet provided sufficient information to allow the Division to set a specification limit for the total amount of [redacted] in Cardura XL. In addition, you have not provided sufficient information to show that the total amount of [redacted] in Cardura XL will be below that limit.

Resolution Items

1. Determine the lower limit of detection of your analytical methodology for [redacted] impurities and degradation products.
2. Determine the total amount of [redacted] impurities and degradation products in doxazosin mesylate (the drug substance) and in Cardura XL (the drug product), in both fresh and in aged batches.

2. Background

Benign prostatic hyperplasia (BPH) is a common disorder affecting middle-aged and elderly males. The symptom complex that has been associated with BPH includes both irritative and obstructive voiding complaints. These symptoms include urinary frequency, urgency, urge incontinence, nocturia, hesitancy, diminished urinary stream and straining to void.

Currently, there are two classes of drug product available for the relief of these symptoms. These include the 5-alpha-reductase inhibitors (including finasteride [Proscar] and dutasteride [Avodart]) and the alpha-1-adrenergic antagonists (including terazosin [Hytrin], doxazosin [Cardura], tamsulosin [Flomax], and alfuzosin [Uroxatral]).

The "alpha-blockers" serve to relieve symptoms by relaxing the smooth muscle of the prostate and bladder neck and thereby relieving both irritative symptoms and outflow obstructive type symptoms. The effective use of alpha-blockers is not dependent upon gland size. Despite

symptomatic benefit, the alpha-blockers have not yet been shown to reduce long-term negative clinical outcomes of BPH (e.g. urinary retention, need for surgery, renal failure, etc).

Alpha-blocker therapy for BPH has been limited by orthostasis and other undesirable systemic alpha-blocking adverse events (e.g. rhinitis, dizziness, asthenia). These are more notable in the more "non-selective" alpha-blockers compared to the potentially more selective ones for the alpha 1A receptor (e.g. tamsulosin). In addition, safe use of most alpha-blockers for BPH is predicated upon a step-wise titration to the individual's own effective dose. Thus, for terazosin and doxazosin immediate release (IR), the prescriber must inform the patient to begin therapy with the lowest available dose and titrate up slowly. As a matter of fact, it is widely accepted practice to instruct patients to begin therapy in the evening prior to bedtime and to arise slowly from bed. These measures are used to limit the sequelae of orthostasis-related adverse events (AEs).

The sponsor now proposes a novel formulation of Cardura (Cardura XL) which presented some theoretic advantages compared with standard Cardura IR. First, Cardura XL would allow for a patient to initiate therapy with an effective dose (4 mg) rather than going through two additional titration steps before attaining effective symptom relief (1 mg to 2 mg then up to 4 mg then to 8 mg). Second, the actual pharmacokinetics of the novel formulation could serve to limit clinical adverse events by "smoothing out" acute increases in exposure (e.g. lowering C_{max}).

Cardura XL is supplied as a GITS formulation (gastrointestinal therapeutic system). Specifically, these extended-release tablets consist of an active drug layer and a second osmotically active layer compressed into a single core. A semipermeable membrane surrounds the bilayer tablet and allows water to enter, increasing the osmotic pressure, and forcing active drug through a single laser-drilled hole in the semi-permeable membrane. Upon initial dosing, doxazosin is not detected in the blood until approximately 3 hours after ingestion. The peak concentration is reached after approximately 8 to 12 hours, and concentrations remain fairly constant from approximately 8 to 16 hours.

[redacted] original NDAs were submitted by the Pfizer Pharmaceuticals Group on April 23, 2001. [redacted] the sponsor applied for [redacted] treatment of the symptoms of BPH (under NDA 21-269). The sponsor believed that Cardura XL was [redacted] an effective symptom reliever for BPH at both 4 mg and at 8 mg. During the course of the NDA review, the Division of Cardio-Renal Drug Products (hereafter referred to as "CR Division") provided comments to the sponsor leading to the eventual withdrawal of NDA 21-269 from the CR Division. In the last few weeks of this review cycle, the sponsor elected to proceed with the application for BPH Only two other agents in this class, Flomax (tamsulosin) and Uroxatral (alfuzosin) are currently approved for BPH [redacted]

In NDA 21-269, the sponsor submitted two controlled, Phase 3, efficacy and safety trials in BPH, and one open-label extension trial. [redacted]

On February 22, 2002, our Division issued an approvable action for the BPH NDA (21-269). While the evidence for efficacy was convincing and the overall safety appeared adequate, there was a persistent safety concern in regard to safety of the very first day and first week of dosing. Since Cardura XL 4mg extended release tablet produce a pharmacokinetic profile similar to the

Cardura immediate release 2mg tablet, the clinical reviewers requested additional data to support the safety of first dose and the first week of therapy. The exact items that were requested were:

1) results from a dedicated study comparing blood pressure for 24 hours following dosing with Cardura XL and doxazosin IR and,
2) a critical analysis from the available controlled safety databases of all vasodilatory AEs occurring within 24 hours and 7 days for Cardura XL and doxazosin IR.

Finally, although not approvable issues, the sponsor was asked to provide information regarding: safety in back men, safety in men older than 75 years of age, clarifications of some data line listings, some pharmakinetic data relevant to intra-subject variability, and revised package insert and container/carton labeling.

The sponsor submitted a Complete Response to Approvable on December 17, 2003. This contained the two items required for Resolution of the Approvable Decision but not all the items related to minor deficiencies. Responses to these were ultimately submitted as amendments during the review.

3. Design of Original Controlled Clinical Trials to Support the BPH Indication

In support of the efficacy and safety of Cardura XL for the BPH indication, the sponsor originally submitted the results from two "pivotal" trials:

Study DAZ-N/S/DK-95-001 (henceforth "Study #1") was a randomized, double-blind, double-dummy, placebo-controlled, parallel-arm design trial comparing Cardura GITs to Cardura standard and to placebo in men with BPH. The study was conducted at 97 sites in Denmark, Sweden, and Norway. The inclusion and exclusion criteria were appropriate to define a group of men with at least moderate BPH symptoms and moderate reduction in maximum urinary flow rate.

Patients were randomized to GITS: standard: placebo in a 2:2:1 ratio. The design included a two-week wash-out phase, a two-week placebo run-in phase, and a 13-week active treatment phase.

In the Cardura GITs group, the starting dose was 4 mg. Assessments of maximum urinary flow rate (Qmax) and International Prostate Symptom Score (IPSS) were conducted. In the titration procedure, if after seven weeks of active therapy, Qmax increased by at least 3 mL/sec and IPSS decreased by at least 30% from baseline, then an individual patient was allowed to remain on 4 mg. If however, these criteria were not met, patients were up-titrated to the 8 mg dose.

In the Cardura standard group, the initial dose was 1 mg, which was automatically increased to 2 mg after one week of active therapy. Doses were increased to 4 mg after three weeks of active therapy and to 8 mg after seven weeks of active therapy, based upon the same titration criteria as described above for the GITS group.

In the assessment of efficacy, there were two primary efficacy endpoints: mean change-from-baseline to final visit in the IPSS and in Qmax. Secondary efficacy endpoints included the proportion of patients achieving "adequate response" for each endpoint and for both endpoints. Adequate response was defined as having an increase in Qmax of at least 3 mL/sec (for the Qmax endpoint) or a reduction from baseline in total IPSS of at least 30% (for IPSS), or both.

A total of 795 patients were randomized to active treatment, 317 to the GITS group, 322 to the standard group, and 156 to placebo.

In the GITS group, approximately 60% of patients ultimately wound up on the 8 mg dose and 40% on the 4 mg dose. In the standard group, approximately 57% of patients wound up on the 8 mg dose, approximately 32%, on the 4 mg dose, and approximately 11% on the 2 mg dose.

Study DAZ-NY-95-001 (henceforth "Study #2") was a randomized, double-blind, double-dummy, active-controlled, parallel-arm design trial comparing Cardura GITS to Cardura standard in men with BPH. The study was conducted at 69 sites in the U.K. (10 sites), Canada (11 sites), South Africa (12 sites), and six other European countries (36 total additional sites). Inclusion and exclusion criteria were identical to the aforementioned trial except that this trial specifically required "prostate enlargement by digital rectal examination".

Patients were randomized to GITS: standard in a 1:1 ratio. The design of this trial was identical to the aforementioned trial. Duration of treatment and parameters for titration were also identical Efficacy endpoints were identical except for an additional measurement of sexual function at the final visit.

A total of 680 patients were randomized to active treatment, 350 to the GITS group and 330 to the standard group.

4. Clinical Results to Support the Indication

4.1 Clinical Efficacy

The efficacy results from **Study #1** revealed that Cardura GITS was superior to placebo and clinically equivalent to Cardura standard in both relieving symptoms and improving maximum urinary flow in men with BPH. Tables 1 and 2 present the IPSS and Qmax data respectively, for Study #1.

Table 1. Total IPSS and Mean Changes from Baseline (± Standard Deviation) in ITT Analysis Population-Study #1

	Doxazosin GITS (N=310)	Doxazosin standard (N=316)	Placebo (N=152)
Total IPSS at baseline	17.74 ± 4.31	17.78 ± 4.48	17.95 ± 4.31
Total IPSS at end of study	9.71 ± 5.34	9.31 ±5.30	11.78 ± 5.49
Change from baseline	-8.02 ± 5.35	-8.47 ± 5.49	-6.17 ± 5.17
Change LS mean	-8.01 ± .30	-8.45 ± 0.29	-6.06 ± 0.41
P-value vs Placebo	<0.001	<0.001	

Table 2. Changes from Baseline in Maximum Urinary Flow Rate (Qmax in mL/sec) at Endpoint (± Standard Deviation) in ITT Analysis Population-Study #1.

	Doxazosin GITS (N=304)	Doxazosin standard (N-315)	Placebo (N=154)
Baseline Qmax	10.30 ± 2.63	9.98 ± 2.77	9.86 ± 2.63
Qmax at end of study	12.88 ± 4.54	12.26 ± 4.41	10.94 ± 3.95
Change from baseline	2.58 ± 4.12	2.27 ± 3.74	1.07 ± 3.83
Change LS mean	2.63 ± 0.24	2.24 ± 0.23	1.02 ± 0.32
P-value vs Placebo	<0.001	<0.001	

Reviewer's comment: Presenting p-values for between-active group comparisons would not be appropriate because the study was not prospectively defined to show non-inferiority between these two groups.

Secondary endpoint analyses were also supportive of efficacy. For example, "responder rates" for IPSS (>30% reduction in total score from baseline) were 74%, 75%, and 53% for the Cardura GITS, Cardura standard, and placebo groups, respectively. Responder rates for maximum urinary flow rate (at least 3 milliliter per second increase from baseline) were 39%, 39%, and 21%, respectively for GITS, standard, and placebo. For achieving both "responses" the combined rates were 31%, 32%, and 14%, respectively for GITS, standard and placebo.

The efficacy results from **Study #2** revealed that Cardura GITS was clinically equivalent to Cardura standard in both relieving symptoms and improving maximum urinary flow in men with BPH. Tables 3 and 4 present the IPSS and Qmax data respectively, for Study #2.

Table 3. Total IPSS and Changes from Baseline (± Standard Deviation) in ITT Analysis Population- Study #2.

	Doxazosin GITS (N=335)	Doxazosin standard (N=320)
Baseline total IPSS	18.37 ± 5.00	18.33 ± 4.84
Total IPSS at end of study	10.35 ± 5.73	10.58 ± 5.58
Change from baseline	-8.02 ± 5.57	-7.75 ± 5.45
Change LS mean	-8.00 ± .30	-7.78 ± 0.30
P-value (GITS v standard)	0.553	

Table 4. Changes from Baseline in Maximum Urinary Flow Rate (Qmax, mL/sec) at Endpoint (± Standard Deviation) in ITT Analysis Population for Study #2.

	Doxazosin GITS (N=337)	Doxazosin standard (N=319)
Baseline Qmax	10.46 ± 2.89	10.53 ± 2.64
Qmax at end of study	13.02 ± 4.61	12.95 ± 4.95
Change from baseline	2.57 ± 4.27	2.42 ± 4.61
Change LS mean	2.74 ± 0.24	2.61 ± 0.27
P-value (GITS v standard)	0.705	

Reviewer's comment: Again, although this trial did not specifically aim to show statistical non-inferiority of the two treatments, the sample sizes and the actual results provide good evidence that the treatments are clinically equivalent, if not statistically equivalent by strict definition. In fact, the results for GITS are numerically slightly better then those for IR.

Secondary endpoint analyses were also supportive of clinical equivalence. For example, "responder rates" for IPSS (>30% reduction in total score from baseline) were 69%, and 68% for the Cardura GITS and Cardura standard groups, respectively. Responder rates for maximum urinary flow rate (at least 3 milliliters per second increase from baseline) were 40% and 36% respectively for GITS and standard. For achieving both "responses" the combined rates were 33% and 28%, respectively for GITS and standard.

Finally, the sponsor analyzed the open-label extension trial [redacted] Despite the obvious lack of control data, and acknowledging that enrollment in this trial was voluntary and that some patients dropped out during the trial, the results from this trial provide some evidence of durability of response (Table 5 and 6).

Table 5. Total IPSS during extension – ITT Subjects

	Doxazosin GITS N=289 start N=256 end
Baseline mean total IPSS	18.78 ± 5.24
Mean total IPSS at final extension visit	9.51 ± 6.29
Change from baseline	- 9.27 ± 6.59

Table 6. Maximum Urinary Flow Rate (Qmax, mL/sec) during extension – ITT Subjects

	Doxazosin GITS N=289 start N=256 end
Baseline mean Qmax	10.50 ± 2.79
Mean Qmax at final extension visit	13.20 ± 4.62
Change from baseline	2.70 ± 4.27

4.1.1 Other Efficacy Issues

Other efficacy issues of relevance include:

- Because these trials were designed using a dose-titration regimen using 4 mg to 8 mg, it is not possible to ascertain the individual fixed-dose effects of 4 mg or 8 mg. Also, a 2 mg Cardura XL dose was not studied.

  Reviewer's comments:
  1. In my opinion, it is unlikely that a 2 mg GITS dose would be effective considering the relative bioavailability of the GITS formulation compared to standard. Two mg GITS would provide Cmax similar to or lower than a 1 mg standard dose, and such a dose is not generally believed to be efficacious.
  2. The trials were designed to compare dose-titration regimens, not fixed doses, because this is the way the drugs are used in practice. This reviewer considers this to be a reasonable clinical decision. The lack of fixed-dose comparisons does not preclude our overall understanding the efficacy of Cardura XL alone.
  3. [redacted]

- Cardura standard and Cardura GITS both require daily dosing. Therefore, there is no net benefit in terms of decreased frequency of daily dosing. There is a benefit in terms of fewer steps in titration and beginning therapy with an efficacious dose.

4.2 Clinical Safety

4.2.1 Extent of Exposure

The total number of patients who received the Cardura XL 4 mg to 8 mg regimen in the two BPH Phase 3 pivotal trials was 666. The overall number of patients treated in these two trials, including Cardura XL, doxazsoin IR and placebo was approximately 1400. The duration of treatment in these trials was 13 weeks. Of this total number of patients, 289 enrolled into the BPH open-label extension trial and 256 completed that 24-week extension treatment period.

In four clinical pharmacology studies, 123 healthy volunteers received Cardura XL. The maximum treatment period for these subjects was 21 days.

[redacted]

Overall, Dr. Willett, the primary medical officer (MO) for the BPH application, believes that 1854 patients received Cardura XL [redacted] Of these, approximately 1100 completed three months, approximately 380 completed 6 months, and 138 completed 9 months of treatment.

Of note, Cardura itself has been marketed for approximately 10 years with over two billion patient-days of clinical experience. At the time of submission, Cardura XL had been approved in 24 countries including Germany, France, Spain, among others.

4.2.2. Deaths, SAEs and Discontinuations Due to AEs

In the original NDAs, there were two deaths reported overall. One patient died of a stroke after an episode of sepsis in an HTN trial and one patient died after a severe stroke in a BPH trial. The BPH patient was taking Cardura standard 2 mg.

There were 48 serious adverse events reported in the two BPH pivtoal trials. Forty events occurred during the pivotal trials, 19 followed dosing with Cardura standard, 17 following GITS and 4 following placebo. Eight additional SAE reports were reported during the open-label GITS extension. Only two SAEs in the GITS group were reported as treatment-related; syncope in one patient and hypotension, lethargy, dizziness, slurred speech, and unsteady gait in one patient. One patient with chest pain was reported as an SAE in the standard group.

> **Reviewer's comment**: There clearly remains a risk of syncope and hypotension with Cardura XL, even at the low dose (4mg). This is not unexpected for this drug class regardless of formulation.

In the BPH pivotal trials, 38/666 (5.7%) discontinued due to AEs in the GITS group, versus 47/651 (7.2%) in the standard group, versus 4/156 (2.6%) in the placebo group. The most common reasons for discontinuation were dizziness, vertigo, asthenia, headache, hypotension, postural hypotension, and somnolence.

> **Reviewer's comments**:
> 1. Discontinuations due to AEs were actually less frequent in the Cardura GITS group compared to the doxazosin IR group in the pivotal BPH trials.
> 2. Additional deaths, SAEs and dscontinuations due to AEs were reported in the safety update submitted with the Complete Response. These are summarized in Section 5 below.

4.2.3 Adverse Events of Special Interest: Adrenergic Blocking Symptoms

In the pivotal BPH and hypertension trials [redacted] over the total treatment period of 3 months, there did not appear to be any significant difference between GITS and standard treatment in the reported incidences of known adrenergic-blocking related adverse reactions (see Tables 7 and 8 below). In fact, in the BPH trials, the overall reported incidences appeared somewhat lower in the GITS group compared to the standard group.

Table 7. Adrenergic blocking related side effects in Cardura XL® BPH trials

COSTART Preferred Term	Doxazosin GITS (N=666)	Doxazosin Standard (N=651)	Placebo (N=156)
Dizziness	35 (5.3%)	59 (9.1%)	3 (1.9%)
Headache	40 (6.0%)	33 (5.1%)	7 (4.5%)
Hypotension	11 (1.7%)	12 (1.8%)	0 (0.0%)
Vertigo	10 (1.5%)	27 (4.1%)	1 (0.6%)
Postural hypotension	8 (1.2%)	14 (2.2%)	1 (0.6%)
Syncope	4 (0.6%)	2 (0.3%)	0 (0.0%)

The four reported syncopal events in the GITS group occurred on Days 3, 19, 40 and 53. For the standard formulation, syncope occurred on Days 28 and 60.

> **Reviewer's comment**: Syncope was not just a first-dose phenomenon in either doxazosin group. This is important for prescribers and patients to know and should be included in labeling.

In the BPH trials, the incidences of dizziness and of postural hypotension were greater in the older population (≥65 years) compared to the younger population (<65 years) in both the GITS and the standard groups. These incidences are higher in those older than 70 and even higher in those older than 75 years of age. This was similarly true for the placebo group and may, in part, be a consequence of aging, sensitivity to alpha blockade in the elderly, or to modestly increased pharmacokinetic exposures in the elderly.

> **Reviewer's comment**: Approximately 50% of each treatment group in the BPH trials was at least 65 years of age, an appropriate demographic for this indication. However, relatively few were at least 75 years old.

In the first week of the BPH trials, the incidence rates of reported adrenergic-blocking adverse events was not significantly different between formulations.

> **Reviewer's comment**: Given the limited size of the BPH safety database, and the small number of such events that occurred in the first week of the BPH trials, the Division requested results from a dedicated first dose pk/pD study and from an additional analysis of orthostasis after the first dose and first week of dosing (see Section 5).

[redacted] Dr. Abraham Karkowsky of the CR Division, noted that in the first week of therapy in both pivotal hypertension trials more subjects in the GITS group reported cardiovascular or vasodilatory AES compared with the standard group regimen. He actually listed these events individually [redacted] By his count, in Study [redacted] there were 19 such events in the GITS group, nine events in the standard group, and five events in the placebo group. In [redacted] there were nineteen such events in the GITS group and 13 events in the standard group. Dr. Karkowsky found these differences between groups to be a potential safety concern for Cardura XL at the proposed regimen. He postulated that the reason for the difference might be that Cardura XL 4mg provided a Cmax more akin to doxazosin IR 2mg than to doxazosin IR 1 mg.

The DRUDP clinical review team sought to address this particular CR concern, both at the time of the original NDA and at the time of the Complete Response. At the time of the original NDA,

we assessed the orthostasis-related adverse events seen in the hypertension trials. Overall, if one looks at the entire dosing period in the hypertension trials, we found that the incidence of vasodilatory AEs did not look significantly different between groups (see Table 8).

Table 8. Adrenergic blocking related side effects in Cardura XL® hypertension trials

Study	Postural hypotension	Vertigo	Palpitation	Syncope
[redacted]	**GITS = 4** STD = 2 Plac = 0	GITS = 7 STD = 10 Plac = 2	GITS = 9 STD = 5 Plac = 0	**GITS = 0** STD = 2 Plac = 1
[redacted] (extension)	**GITS = 0** STD = 2	GITS = 3 STD = 4	GITS = 3 STD = 0	**GITS = 0** STD = 0

In the clinical pharmacology studies, there was one report of postural hypotension and two reports of syncope in Study 96-010 following single doses of GITS (albeit at the high dose of 8 mg) in healthy volunteers. There was also one report of syncope in Study 96-009 just prior to the Day 2 dose of GITS (4 mg).

Of particular interest was Study DAZ-NY-96-009. This study compared the pharmacokinetics of multiple doses of GITS 4 mg (7 days) in young normal men and women to elderly normal men and women. Syncope occurred in one young man. His only recorded blood pressure during the event was listed as normal (128/76 mm Hg). In this study, all subjects received 4 mg GITS. Five of the 10 total elderly males reported a clinical AE on Day 1 (headache x 3, asthenia x 1, and enlarged abdomen x 1). Three of 10 total young males reported a clinical AE on Day 1 (syncope x 1, dizziness and headache x 1, and palpitation x 1). In this study, actual blood pressure data was available for 21 men prior to dosing and at 12 hours after dosing. There were no obvious or gross changes in blood pressure in any patient.

> **Reviewer's comment**: To the best of my knowledge, at the time of the original NDA, these appear to be the only available actual blood pressure data measured at Tmax following the first dose of GITS 4 mg. There was no data comparing blood pressure response after the first dose of 1 mg standard versus 4 mg GITS in BPH patients. Such was provided in the Complete Response (see Section 5)

4.2.4. Overall Adverse Events

In the BPH trials, incidences of overall adverse events were similar between Cardura standard (54%), Cardura GITS (41%), and placebo (39%). The list of commonly reported AEs appears below in Table 9. Some items in Table 9 below are repeated from Table 7.

Table 9. Incidence of Commonly Reported Adverse Events - BPH Efficacy Studies

COSTART Preferred Term	Doxazosin GITS (N=666)	Doxazosin Standard (N=651)	Placebo (N=156)
Headache	40 (6.0%)	33 (5.1%)	7 (4.5%)
Dizziness	35 (5.3%)	59 (9.1%)	3 (1.9%)
Respiratory tract infection	32 (4.8%)	29 (4.5%)	3 (1.9%)
Asthenia	26 (3.9%)	45 (6.9%)	2 (1.3%)
Back pain	19 (2.9%)	11 (1.7%)	4 (2.6%)
Abdominal pain	12 (1.8%)	15 (2.3%)	1 (0.6%)
Hypotension	11 (1.7%)	12 (1.8%)	0 (0.0%)
Somnolence	10 (1.5%)	8 (1.2%)	0 (0.0%)
Vertigo	10 (1.5%)	27 (4.1%)	1 (0.6%)
Myalgia	9 (1.4%)	3 (0.5%)	0 (0.0%)
Dyspepsia	9 (1.4%)	8 (1.2%)	0 (0.0%)
Nausea	8 (1.2%)	15 (2.3%)	1 (0.6%)
Dyspnea	8 (1.2%)	8 (1.2%)	0 (0.0%)
Postural hypotension	8 (1.2%)	14 (2.2%)	1 (0.6%)

4.2.5 Other Safety Issues From the Primary MO's Review

In the original NDA review:

Dr. Willett commented that the label should adequately inform patients not to chew the GITS tablet.

Dr. Willett recommended revisions to the label to inform prescribers and patients that syncopal events have been reported to occur (albeit infrequently) days or weeks after the start of therapy.

The safety update in the original NDA was significant only for a single case of urticaria that may have been treatment-related. Sponsor acknowledged this finding and agreed to describe the case in labeling.

Dr. Willett noted that some data line listings for adverse events from the BPH pivotal trials listed 2 mg doxazosin standard as being dosed during the first week of therapy as opposed to the per-protocol 1 mg dosage strength.

> **Reviewer's comment**: The sponsor eventually clarified this simple transcription error in their Complete Response.

4.2.6 Other Safety Issues

Other safety issues of relevance from the original NDA included:

1. While the Cardura standard label encourages blood pressure measurements after initial dosing with 1 mg and other risk management measures such as helping patients arise from a supine position, the Cardura XL label dose not propose such measures.

   Reviewer's comment: Sponsor does not believe that such is necessary for the Cardura XL product.

2. There was no clear evidence that Cardura XL is actually "safer" than Cardura standard or than any other product in this class. It is true that some adverse events that relate to

tolerability were reported at a lower incidence in the Cardura XL group compared to the doxazosin IR group (e.g. dizziness and asthenia) but the incidence rates of hypotension and syncope were still similar.

5. Response to Approvable: Clinical Issues

5.1. Overview of Complete Response

In the Approvable letter dated February 22, 2002, the sponsor was asked to show that treatment with Cardura XL 4mg would be safe in the first day and first week of therapy. The major concern of the Division was that the new regimen be no less safe than the already approved doxazosin IR regimen. To this end, sponsor was asked to compare the novel formulation (GITS) at the proposed regimen (4mg starting dose) to the current standard Cardura regimen (doxazosin IR 1mg to 2mg to 4mg to 8mg) for safety in the first day and first week.

The actual items requested were: 1)a new pharmacodynamic study and 2) a critical analysis of all vasodilatory and cardiovascular AEs in the first week of therapy from all their relevant controlled clinical trials. Sponsor also asked to provide: 1) a safety update and 2) to respond to several lesser deficiencies (safety in the elderly, in African Americans, discrepancies in some line listings and some labeling issues).

Additional safety information was requested during the review of the Response (including effects on the QT interval, details on several specific patients, and an issue related to Tmax). Dr. Willett conducted the primary medical review of all this information and the reader is referred to his review for greater detail.

Therefore, in this section, the following clinical items will be briefly summarized:

1. Study A035-1061: the single dose pharmacodynamic study comparing GITS 4mg and standard 1mg.
2. The critical analysis of clinical adverse events at Days 1, 2-7, and 8 comparing GITS and standard.
3. Results from other studies conducted by Pfizer including:
    a. *DAZ-JP-97-501* – a single dose pharmacodynamic study in 12 Japanese males.
    b. *DAZ-NY-96-014* – a 4-week, comparative efficacy study of GITS 4mg and tamsulosin in 98 men with BPH, as published by Roger Kirby in the British Journal of Urology in 2003.
    c. A035-1027 – a 2-week, randomized, double-blind, placebo-controlled, time-to-onset study of GITS 4mg in 213 men with BPH.
    d. A035-1029 – a 6-week, randomized, placebo-controlled study in 177 men with poorly controlled hypertension.
4. Post-marketing experience with Cardura XL.
5. Two-Year Safety Update.
6. Responses to Other Minor Deficiencies and Review Issues (QTc, safety in elderly, safety in African-Americans, clarification of specific line listings, clarification of specific patients in Study A035-1061, and an issue regarding Tmax).

5.2. Study A035-1061

The study was entitled: "A Double Blind, Randomized, 3-Way Crossover Study To Investigate Supine and Standing Blood Pressure and Pulse During the 24 hours Following a Single Dose of Doxazosin GITS 4 mg vs Doxazosin Standard Formulation 1 mg vs Placebo."

The study enrolled 26 generally healthy male volunteers aged 40-75 years of age (mean age 52 years). Most were aged 45-64 years. The subjects had to show no evidence of orthostasis at baseline nor immediately prior to any dosing period. Supine and standing vital signs and pK were done frequently for 24 hours after dosing. The primary endpoint was the mean orthostatic change in BP at Tmax. Other endpoints included: the maximum orthostatic BP and pulse change regardless of Tmax, the percentage of patients with any orthostatic change at Tmax, any orthostatic change ≥20mmgHg systolic or 10mmHg diastolic, and the time to maxumimum orthostatic change. At baseline, the 3 randomized sequence groups were similar for vital signs.

For the primary endpoint, the results were as follows:

Table 10: Summary of Mean Orthostatic Change at Tmax

Vital Sign (units)	Statistics	Doxazosin GITS (N = 24)	Doxazosin IR (N = 24)	Placebo (N = 24)
Systolic BP (mmHg)	LSMean (SE)	-1.6 (1.92)	1.2 (1.92)	-0.9 (1.92)
Diastolic BP (mmHg)	LSMean (SE)	4.3 (1.34)	6.4 (1.34)	7.5 (1.34)
Pulse Rate (bpm)	LSMean (SE)	21.3 (2.14)	21.5 (2.14)	15.4 (2.14)

Source: Page 58 Study report A035-1061

For other important secondary endpoints, the results are presented below. The number and percentage of patients with *any* orthostatic drop are presented in Table 11

Table 11: Summary of the Subjects Who Experienced any Orthostatic Drop in Blood Pressure at Tmax

		Doxazosin GITS	Doxazosin STD	Placebo
Systolic BP	Proportion n/N (%)	14/24 (58.3%)	7/24 (29.2%)	10/24 (41.7%)
	Mean (SD)	-7.1 (7.77)	-9.7 (8.33)	-8.5 (7.33)
	Median	-4.0	-8.8	-4.5
	(Min , Max)	[redacted]		
Diastolic BP	Proportion n/N (%)	6/24 (25.0%)	4/24 (16.7%)	2/24 (8.3%)
	Mean (SD)	-6.2 (6.86)	-1.9 (2.10)	-2.5 (1.89)
	Median	-4.0	-1.0	-2.5
	(Min , Max)	[redacted]		

Source: Page 59 Study report A035-1061

The number and percentage of patients with of patients with *an orthostatic change ≥20mmgHg systolic or 10mmHg diastolic* is presented in Table 12.

Table 12: Summary of the Proportion of Subjects with a Drop ≥20mmHg in Systolic Blood Pressure or a Drop ≥10mmHg in Diastolic Blood Pressure upon Standing at least once in 24-Hour Period

Event	N	Doxazosin GITS	Doxazosin STD	Placebo
		24	24	24
Drop ≥20 mmHg in SBP	n (%)	6 (25.0%)	3 (12.5%)	3 (12.5%)
or ≥10mmHg in DBP	SE	0.09	0.07	0.07

The *mean maximum* orthostatic change is presented in Table 13 below:

Table 13: Summary of Maximum Orthostatic Change in Blood Pressure and Pulse Rate over 24-Hour Period

Vital Sign (units)	Statistic	Doxazosin GITS (N=24)	Doxazosin STD (N=24)	Placebo (N=24)
Systolic BP (mmHg)	LSMean (SE)	-13.8 (1.60)	-12.5 (1.60)	-11.3 (1.60)
Diastolic BP (mmHg)	LSMean (SE)	-1.7 (1.10)	-1.8 (1.10)	1.0 (1.10)
Pulse Rate (bpm)	LSMean (SE)	32.2 (2.61)	32.6 (2.61)	26.3 (2.61)

Source: Page 61 Study report A035-1061

The time to maximum orthostatic drop was similar between groups: 8-9 hours after dosing.

In terms of clinical adverse events, the standard and GITS groups were very similar. Eight subjects reported AEs while receiving doxazosin standard, of which 5 were judged by the PI to be treatment-related. Nine subjects had an AE while receiving GITS, of which 6 were judged by the PI to be treatment-related. Three subjects had AEs while receiving placebo, of which 2 were considered by the PI to be treatment-related. These are shown further in the table below.

Table 14: Treatment-Emergent Adverse Events By Patient Identifying Number in A035-1061

	Doxazosin STD	Doxazosin GITS	Placebo
No. of Subjects Dosed	25	25	25
No. of Subjects with AEs: ac/ tr (a) AE	8/5	9/6	3/2
WHOCODE AE Term	**Subject ID reporting AE (b)**		
Headache	[01] #02 #41	#18 #41	None
Dizziness	#10	[#42] #08 #44	None
Hypotension Postural	#01 #19	#09	None
Somnolence	[#27]	[#11] #08	None
Abdominal Pain	None	[#30] #02	None
Pain	[#08]	[#08]	None
Skin Cold Clammy	#10	None	None
Arrhythmia	[#12]	None	None
Nausea	#10	None	None
Fatigue	#02	None	None
Glycosuria	[#08]	None	None
Epistaxis	[#02]	None	None
Pallor	None	#08	None
Diarrhea	None	[#30]	None
Back Pain	None	[#08]	None
Dizziness Postural	None	None	#22
Dyspnea	None	None	#12
Accidental Injury	None	None	[#52]

(a) = ac/tr = all causalities/treatment-related.
(b) = Subject ID is in brackets if PI judged AE to be not treatment related.
Source: page 71 Study A035-1061

Reviewer's comment: In summary, this study was admittedly small and perhaps not powered to show statistical non-inferiority; however, Dr. Willet and I agree that the study still provides some useful information. While the percentage of patients with orthostasis was slightly higher with Cardura XL compared with doxazosin standard in this trial, the magnitude of the drop in BP, the maximum amount of BP drop, and the time to the maximum drop were very similar. The clinical adverse events were similar. Therefore, I

agree with Dr. Willet, that this study provides some useful information that the initial orthostasis seen after dosing (both in terms of BP and clinical AEs) following doxazosin standard and GITS are reasonably similar. In our opinion, GITS was not shown to be substantially worse.

5.3. Comparative safety analysis

Sponsor provided the requested safety analysis of the four pivotal trials (BPH and HTN) [redacted] These included a total of 2180 patients; 984 received doxazosin GITS, 964 received doxazosin standard, and 232 received placebo. The table below provides a tabular listing of all vasodilatory and cardiovascular AEs on Days 1, 2-7, and thereafter.

Table 15: Doxazosin Protocol DAZ-NY-95-001, DAZ-N/S/DK-95-001, [redacted] Treatment Emergent Vasodilatory and Cardiovascular Adverse Events by Onset Period

	Doxazosin GITS			Doxazosin STD		
Onset Day of Adverse Event	1	2-7	8+	1	2-7	8+
No. of evaluable patients for safety	984	979	969	964	962	956
No. of patients with adverse events	25	92	339	23	86	416
% of patients with adverse events	2.5	9.4	35.0	2.4	8.9	43.5
No. of adverse events	29	116	573	26	109	664
Individual categories						
Shock			3 (0.3%)			1 (0.1%)
Arrhythmia				1 (0.1%)		2 (0.2%)
Bradycardia						1 (0.1%)
Palpitations	2 (0.2%)	3 (0.3%)	8 (0.8%)		1 (0.1%)	13 (1.4%)
Cerebral Infarct						2 (0.2%)
Cerebral ischemia			1 (0.1%)			2 (0.2%)
Congestive Heart Failure			1 (0.1%)			1 (0.1%)
Hypotension	1 (0.1%)	1 (0.1%)	7 (0.7%)		3 (0.3%)	6 (0.6%)
Postural Hypotension			11 (1.1%)		2 (0.2%)	12 (1.3%)
Supraventricular extrasystoles					1 (0.1%)	
Supraventricular tachycardia						1 (0.1%)
Tachycardia		4 (0.4%)	2 (0.2%)			4 (0.4%)
Syncope		1 (0.1%)	3 (0.3%)			4 (0.4%)
Vasodilatation	1 (0.1%)		3 (0.3%)	1 (0.1%)	2 (0.2%)	2 (0.2%)
Dizziness	5 (0.5%)	13 (1.3%)	30 (3.1%)	5 (0.5%)	11 (1.1%)	61 (6.4%)
Vertigo	1 (0.1%)	4 (0.4%)	12 (1.2%)	2 (0.2%)	5 (0.5%)	29 (3.0%)

A patient can be counted more than once in the subtotal. Adverse Events with unknown start date are not included. Patients with more than one occurrence of an adverse event are only included in the onset period of the first occurrence of the event.

Table15 continued - for placebo subjects

	Placebo		
Onset Day of Adverse Event	1	2-7	8+
No. of evaluable patients for safety	232	232	231
No. of patients with adverse events	4	11	74
% of patients with adverse events	1.7	4.7	32.0
No. of adverse events	4	12	113
Shock			
Arrhythmia			2 (0.9%)
Bradycardia			
Cerebral Infarct			
Cerebral ischemia			
Cerebrovascular accident			1 (0.4%)
Congestive Heart Failure			
Hypotension			
Postural Hypotension			1 (0.4%)

Supraventricular extrasystoles			1 (0.4%)
Supraventricular tachycardia			
Syncope		1 (0.4%)	
Vasodilatation			
Dizziness	1 (0.4%)	2 (0.9%)	4 (1.7%)
Vertigo		1 (0.4%)	2 (0.9%)

Source: Pages 5-32 "Response Table 1" in the cd2.PDF

In the four studies combined, the rates of orthostatic events were 1 in approximately 1,000 for the doxazosin GITS treatment group and 2 in approximately 1,000 for the doxazosin standard treatment group.

> **Reviewer's comment**: The table demonstrates that the incidence rates of vasodilatory and cardiovascular events known to occur on Days 1, 2-7, and thereafter are similar between active treatment groups, and overall are fairly low in incidence in a very large controlled cohort. I agree with Dr. Willet that this is compelling evidence that the critical safety outcomes between active treatment groups are not different.

The sponsor's analysis of vasodilatory and cardiovascular events following dosing was extended to three other trials:

1. *DAZ-NY-96-014* – a 4-week, comparative efficacy study of GITS 4mg and tamsulosin in 98 men with BPH, as published by Roger Kirby in the British Journal of Urology in 2003.
2. A035-1027 – a 2-week, randomized, double-blind, placebo-controlled, time-to-onset study of GITS 4mg in 213 men with BPH.
3. A035-1029 – a 6-week, randomized, placebo-controlled study in 177 men with poorly controlled hypertension.

> **Reviewer's comment**: The results from the later two trials demonstrated slightly higher incidences of vasodilatory events for the GITS groups compared with GITS groups from previous studies. The reader is referred to the next section of this review for details (Section 5.3).

5.4. Results from other studies conducted and reported by Pfizer (4 studies)

5.4.1. *DAZ-JP-97-501*

This was a single dose, placebo-controlled crossover pharmacodynamic study in 12 young Japanese males. The study compared GITS 4mg and GITS 8mg to doxazosin IR 1mg and placebo. In this study, the GITS 4mg was associated with less orthostasis than doxazosin1mg. For this study, Dr. Willet commented that in this single dose study:

1. Mean Tmax was 13.7 hours for GITS 4mg.
2. No mean orthostatic effect at Tmax was observed for GITS 4mg.
3. For the 12 young Japanese men studied there were more episodes of systolic drops ≥20mmHg and diastolic drops ≥10mmHg in the doxazosin standard 1mg (n=5 patients) compared to GITS 4mg (n=3).
4. The graphs demonstrating mean blood pressures (supine and standing) show that GITS 4mg showed slightly lower pressures overall compared to doxazosin standard 1mg for these younger Japanese men.
5. There were no serious adverse events or discontinuations in this trial. Orthostatic dizziness (2 subjects) and orthostatic hypotension (2subjects) was reported with equal

frequency in all three doxazosin treatment groups (STD 1mg, GITS 4mg and GITS 8mg). There were no reported syncopal events.

Reviewer's comment: The Japanese study further supports the safety of GITS 4mg compared to standard 1mg.

5.4.2. *DAZ-NY-96-014*

This was a 4-week, comparative efficacy study of GITS 4mg and tamsulosin in 98 men with BPH. It was published in the British Journal of Urology in 2003 under the authorship of Dr. Roger Kirby (Kirby et al; BJU Int 2003; Jan 2003: 91[1]:41-44). The authors concluded that doxazosin GITS was *more* effective than tamsulosin in relieving urinary tract symptoms. In terms of safety, the adverse events reported included:

Table 16. Adverse events from DAZ-NY-96-014

	Doxazosin-GITS	Tamsulosin
Adverse event	% (n = 48)	% (n = 50)
Dizziness	8	8
Headache	6	8
Asthenia	6	12
Somnolence	4	2
Hypotension	4	2
Rhinitis	2	4
Retrograde ejaculation	0	2

In this study, there were no orthostatic events (syncope, postural hypotension or postural dizziness) on the first day or even in the first week of therapy with GITS. However, the following vasodilatory adverse events were reported on Day 8 and thereafter

Table 17: Vasodilatory events: Doxazosin GITS Study DAZ-NY-96-014

Subject	Symptom	GITS (mg)	On Rx Day	Severity	Action
10330035	Dizziness	8	37	Mild	None
10330079	Tachycardia	4	8, 29, 57	Mild	None
10330081	Hypotension	4	22, 23, 52	Mild	Not titrated upward
	Dizziness	4	8, 43	Mild	None
10360064	Dizziness	4	25	Mild	None
10360066	Hypotension	4	28	Mild	None
10430069	Syncope	4	27	Severe	Hospitalized

Source: Pages 33-62 "Response Table 2" in the cd2.PDF

Reviewer's comment: Vasodilatory events are possible with GITS 4mg as far out as days or weeks into therapy. This also appears true for doxazosin standard and may well be true for all alpha-blockers. This information is appropriate for the label.

5.4.3. *Study A035-1027*

This was a randomized, double-blind, placebo-controlled, "time-to-onset" study of GITS 4mg in 213 men with BPH. The treatment period was 2 weeks. In this study, submitted only with the Complete Response, the incidences of vasodilatory adverse events were higher than in other previous studies. In this study, patients received their tablets at bedtime.

There were no cases of syncope. Six patients (5.6%) in the doxazosin GITS arm experienced "postural hypotension" compared with two patients (1.9%) in the placebo arm. Of the six GITS patients with postural hypotension, two had postural hypotension on Day 2, one of whom permanently discontinued the study. Two patients had postural hypotension on Day 4, and an

additional two patients had postural hypotension after the first week.

The incidence of hypotension was 1.9% in the GITS arm and 0% in the placebo arm. The hypotension with GITS occurred on Day 2 (after one dose the previousevening) in two patients and resulted in study discontinuation for both patients.

The incidence of dizziness was 11.1% in the GITS arm compared to 1.9% in the placebo arm. The dizziness occurred on Day 2 in five patients receiving GITS, one of whom discontinued the study due to the dizziness, and one of whom also had a second occurrence on Day 5. Two GITS patients had dizziness on Day 3, three GITS patients had dizziness on Day 4, one GITS patient had dizziness on Day 6, and one GITS patient had dizziness on Day 7. Two placebo patients had dizziness, one on Day 2 and one on Day 4.

Reviewer's comments:

1. The incidences of postural hypotension (5.6%) and dizziness (11.1%) were increased in this study compared to other studies.
2. Some orthostatic adverse events were noted to occur within 24 hours of dosing. It is possible this was related to dosing at bedtime. The actual reason for the increased incidences is not clear. There was no syncope reported.
3. The overall incidence of hypotension as an adverse event (1.9%) was comparable to that seen in the pivotal BPH trials (1.7%).

5.4.4. ***Study A035-1029***

This was a randomized, double-blinded, placebo-controlled study in 177 men with poorly controlled hypertension, comparing doxazosin GITS 4mg to placebo.

There were no cases of syncope. Six patients (6.7%) in the GITS group experienced "postural hypotension" compared with 0 in the placebo group. Two of the GITS patients had postural hypotension on Day 1 but continued in the study. One patient had postural hypotension on Day 7 resulting in study discontinuation. The other three patients had postural hypotension after the first week of therapy with GITS.

There were no cases of hypotension within the first week with either GITS or placebo. The incidence of dizziness was similar between doxazosin GITS (7.9%) and placebo (7.0%). One case of dizziness in the GITS group occurred on Day 1 and one case occurred on Day 2 (leading to study discontinuation). The remaining five cases of dizziness in the GITS group occurred after the first week of therapy. One case of dizziness in the placebo group occurred on Day 1, one case occurred on Day 2, and one on Day 8. The remaining three cases of dizziness in the placebo group occurred after the first week.

One patient in the GITS group experienced vertigo which occurred on Day 1. The vertigo was reported to occur when rising from sitting to standing. There were no reported vertigo cases with placebo.

Reviewer's comments:

1. Again, the postural hypotension incidence (5.6%) is somewhat higher than previously reported. Still, there were no cases of syncope, no cases of hypotension, and only one case of vertigo with GITS.
2. The dizziness rates were similar between GITS (7.7%) and placebo (7.0%).

5.5. Postmarketing experience

The sponsor provided a summary of safety from the use of Cardura XL as marketed from October 1, 2002 through September 30, 2003. From the fourth quarter 2002 through second quarter 2003, there were worldwide sales of over [redacted] standard dosage units of doxazosin standard tablets, which corresponds to approximately 1,710,641 patient-years of exposure and over [redacted] standard dosage units of doxazosin GITS, which corresponds to approximately *468,060 patient-years of exposure.* During this reporting period there were no actions taken regarding doxazosin for safety reasons by either the health authorities or by Pfizer. There were no relevant clinical trials containing important new safety findings identified in a literature search during this reporting period.

Despite this extensive exposure, only 188 doxazosin standard adverse event "cases" and 73 GITS "cases" fulfilled the sponsor's criteria for inclusion in this update. According to sponsor, the majority of the reported AES were well-known for doxazosin. Some could be attributed to patient clinical history or concomitant medications. Dr. Willet provided three tables (Tables 21 and 22 of his review) showing postmarketing deaths for all forumations, vasodilatory AEs for doxazsoin standard and vasodilatory AEs for GITS, respectively. None of the deaths appeared directly related to doxazosin. There were only 10 vasodilatory events reported for GITS including: vertigo x2, dizziness x 2, orthostatic hypotension x2, syncope x2, blood pressure lowered and ischemic stroke, and "anaphylactic shock"/dizziness. Eight of these were with the 4mg dose. All recovered except one patient. Two of the patients were older than 75 years of age. The vasodialtory AEs with doxazsoin standard were more frequent and of similar quality.

> **Reviewer's comments**: There is no signal that doxazosin GITS is associated with more frequent vasodilatory AEs compared with standard doxazosin from this post-marketing review. However, such events can *and do* occur with GITS 4mg. Several adverse event reports in men older than 75 provide some concern in that age group.

5.6. Two-Year Safety Update

In the Complete Response, the sponsor submitted another Safety Update. This one covered the years 2001 and 2002. The sponsor provided death and SAE narratives for from all trials either ongoing or compelted during that time period. Sponsor also provided a list of non-serious AEs for the studies previously mentioned in Section 5.4 above.

In this safety update, fourteen patients died during a GITS clinical trial for BPH including 9 patients on GITS, 1 on doxazosin tablets and 4 on blinded therapy. Of these, 4 died from a myocardial infarct, 4 from cancer, and and one each from respiratory failure, sepsis, suspected pulmonary embolus, suicide, an airplane crash, and a traffic accident. In HTN trials, 7 patients died and 5 were receiving doxazosin GITS: one hanged himself, one died of a cerebrovascular accident, one died from from carcinoma of the lung, one from chronic obstructive pulmonary disease, and one from an unknown cause.

> **Reviewer's comment**: None of these deaths appeared related to doxazosin.

In doxazosin/GITS trials of BPH, 116 patients experienced non-fatal serious adverse events; including 52 patients on doxazosin GITS, 1 who received doxazosin GITS followed by tamsulosin in a crossover study, 13 patients on standard doxazosin tablets, 49 during blinded therapy and 1 on placebo.

Of the patients receiving doxazosin GITS, the following was noted: 15 suffered from cancer, 7 were hospitalized due to worsening of their BPH (including 3 with urinary retention), *3 with a TIA or stroke*, 3 with gall bladder/bile duct disease, 2 with chronic obstructive pulmonary disease,

2 with decompensated diabetes mellitus, 2 with inguinal hernia, 2 with arrhythmia (resulting in syncope), *1 with syncope (without arrhythmia)*, 1 with bradycardia and hypotension, and one each with *vertigo, unstable angina, palpitations*, hypoglycemic coma, urinary tract infection, presacral abscess, hospitalization for an unknown cause, multiple fractures following a traffic accident, enteritis, perforated duodenal ulcer, pulmonary inflammation, asthma like bronchitis, and a herniated vertebral disc.

Finally, individual case reports of syncope were sought from the update. One case was found as follows:

Case A214691 involved a 55 year-old white man with benign prostatic hyperplasia and asthma being treated with ipratropium and fenoterol. After the first dose of doxazosin GITS 4 mg, he was hospitalized with weakness, dizziness, pallor, tingling in the hands, cold sweating and epigastric pain. He was thought to have experienced syncope. His blood pressure in the hospital
was 130/100 mmHg with pulse 92 bpm. He was discharged the next day with a blood pressure of 120/80 mmHg and pulse 78 bpm. These events were considered related to the study drug, which was permanently discontinued.

> **Reviewer's comment**: Although reported infrequently in this 2-year safety update of clinical trials, hospitalization for syncope and vertigo are possible in association with doxazosin GITS. There were no new safety signals.

5.7. Responses to Minor Deficiencies and Review Issues

5.7.1. Effect on QT interval

Based upon an abstract from the literature that purported a possible effect of doxazosin on hERRG channel activity, and our understanding that another drug in this class (alfuzosin) modestly prolonged the corrected QT interval at suprapysiological exposures, the sponsor was asked to provide all the evidence they could in regard to the effect of doxazosin on the QT interval. In addition, they were also asked to provide an argument as to why a dedicated "thorough" QT study wasn't necessary. They provided this response in May 2004.

Sponsor did a comprehensive review of their databases for *all clinical trials of doxazosin* sponsored by Pfizer, Pfizer's early alert database for spontaneously reported adverse events, and the medical literature. First, the sponsor reviewed 276 completed doxazosin trials, including both placebo and open-label studies, including a total of 95,282 patients exposed to the drug. The databases were searched for a large number of terms relevant to QT prolongation. A total of 13 cases involving one or more of those terms were found. Most of these cases were related to sudden and unexplained cardiac death in the elderly or symptoms that persisted after drug was stopped. .

> **Reviewer's comments**: The clinical review team agrees that relationship to doxazosin for these is unlikely. Other factors are more contributory. None was a clear case of QT prolongation.

The *Pfizer early alert database for spontaneously reported adverse events* was searched for a large number of terms possibly associated with QT prolongation and doxazosin. Review of 15,191 cases received through January 31, 2004 revealed 102 possible cases. Of these 79 coded to possible sequelae of QT prolongation without any clear evidence of such. Of the remaining 23, 9 coded to ventricular arrhythmia, 6 to ventricular tachycardia, 5 to ventricular fibrillation, 3 to

ECG QT prolongation, and 2 to torsade de pointes (one with both QT prolongation and torsade). The four specific QT prolongation/torsade cases are presented below:

Table 18: Cases of QT prolongation and/or torsade

Case # (rep #)	Age/ sex	Treatment/dose	Comments
1. (971139)			QT Prolongation Case stated by sponsor to be poorly documented
2. (A039989)	79 Female	Doxazosin 2mg for hypertension Patient was on cisapride	QT Prolongation and torsade de pointes QTc = 718msec Potassium 3.3mEq/L She developed ventricular extrasystole and multiple ventricular tachycardia leading to torsade de pointes which disappeared after intravenous magnesium The prolonged QT was attributed to her use of cisapride and the decreased potassium level.
3. (2003022296)	82 Female	Prescribed doxazosin and amlodipine	QT Prolongation On the same day the patient had loss of consciousness, respiratory arrest and undetectable pulse. In the hospital she was found to have hypokalemia and QT prolongation but no arrhythmia. The event resolved the following day
4. (9514901)	63 Female	Doxazosin for hypertension	Torsade de pointes This patient was given azithromycin and ambroxol (expectorant) for persistent fever. A few hours after these medications she developed cardiac arrest and was defibrillated for a ventricular rhythm disorder. Later rhythm disorders included torsade de pointes. She also was found to be hypokalemic.

Reviewer's comment: One of these cases is poorly documented, one is confounded by concomitant cisapride, one had torsade only following cardiac arrest, and one had torsade only after respiratory arrest and loss of consciousness. In none of these is doxazosin suspected as the cause

The sponsor conducted an extensive *literature search* spanning 1964 to 2004. Search terms were similar to those used in the search of the clinical trial databse. Forty possibly relevant articles were identified. Of these, 27 references were general to the topic and contained no specific relevant information, 6 were review papers containing theoretical comments only, the other 7 were reviewed in detail by sponsor and medical officer. Two of these suggested beneficial effects on the QT in humans, and two suggested beneficial effects on humans as transposed from animal studies. Only one abstract suggested that doxazosin had an potential negative effect on the QT in humans by blocking hERG currents in Xenopus oocytes or human HEK 293 cells.

Reviewer's comments:

1. Aside from this abstract, the medical literature did not demonstrate any evidence of a QT effect.
2. I agree with Dr. Willet that the overwhelming clinical database for doxazosin, especially the 92, 000 patients treated with the drug in over 265 clinical trials, and the lack of a single case of torsade or QT prolongation in over a decade, is extremely compelling information.
3. Cardura XL is known to have lower exposure than doxazosin IR and is not likely to have clinically relevant drug-drug interactions that would increase exposure substantially.
4. I agree with the primary MO that a thorough QT study should not be required in this situation.

5.7.2. Safety in African-American Men

The pivotal trials for both BPH and HTN were conducted primarily in a Scandanavian and Canadian population. There were few black patients enrolled. Sponsor was asked to provide a justification why an additional study in this population should not be required. Sponsor stated that based on their review of safety information for black patients from the BPH pivotal studies and from all other trials involving doxazosin GITS, "there is no signal of any safety issue in black men using Cardura XL." The total number of black patients in the BPH trials was 7. Of these six had adverse events. Three of these were non-serious and not related. Two necessitated temporary drug discontinuation (headache/nasal congestion and angina/stomach ulcer) and one was a serious adverse event. The SAE was described as follows:

"A 63 year old black male, with a history of essential hypertension treated with nifedipine, who experienced six serious adverse events: hypotension, unsteady on feet, dizziness, headache, slurring of speech, and lethargy. The patient had been receiving doxazosin GITS 8mg/d at the time of onset of the events and he permanently discontinued the study due to these events. His screening sitting blood pressure was 130/90 mmHg and baseline sitting BP was 160/110 mmHg. On study day 92, the patient's sitting blood pressure was 105/67.5 mmHg. At the prior visit on study day 55, his BP was elevated at 160/90 mmHg."

> **Reviewer's comment**: In my opinion, the patient's SAE was related to poor control of hypertension and a fairly large drop in the BP following GITS 8mg. This is likely attributable to poor control of underlying hypertension.

An additional 6 black patients received GITS in the other smaller BPH trials. There were no notable AEs in these patients.

> **Reviewer's comment**: Since there is no evidence that black men are at an inherently increased risk from the drug, and since there is no reason to believe that their response will be markedly different for treatment of BPH, a Phase 4 study is deemed not required.

5.7.3. Safety in Men Older than Age 75

In the original NDA it was noted the number of men older than 75 years of age in clinical studies of BPH was small (approximately 30 such patients treated with GITS). Sponsor was asked to provide all available safety information on these elderly men, who constitute part of the target population. Further, sponsor was later asked to support safety of first dosing in men at least 70 years of age since the "first-dose" study had only 1 such patient.

In regard to men older than 75 years of age, sponsor's responses included the following:

In the two pivotal BPH studies combined, there were 75 men over age 75: thirty on GITS, 32 on doxazosin standard, and 13 on placebo. The incidence of *most* adverse events in this group with doxazosin standard and GITS was similar to younger men (<65 years and 65-75 years). However, the incidence of hypotension was higher in those older than 75 years for both formulations.

In the BPH trials, the incidence of hypotension with GITS in men>75 was 10%, compared to men aged 65 to 75 years (1.4%) or men younger than 65 (1.2%). The incidence of hypotension with doxazosin standard was similarly higher in men over age 75 (6.3%) compared to men aged 65 to 75 years (1.4%) or in men younger than 65 years (1.8%).

To place this finding in some perspective, the incidence of dizziness with GITS in men >75 was actually lower (6.7%) than with doxazosin standard (9.4%). There were no reports of "postural dizziness" or "postural hypotension" in men over 75 with either GITS or doxazosin standard. Of those 75 men over age 75, only three had a clinical adverse event on Day 1: two on GITS and one on doxazosin standard. These events were: hypotension and back pain in the two GITS patients, and vertigo in the doxazosin standard patient.

> **Reviewer's comment**: The increased incidence of hypotension in those older than 75 years should be noted [redacted] This occurred at similar or even lower incidences when comparing GITS to standard. The incidence of dizziness is actually lower for GITS than for standard in this age range. There were few clinical adverse events in the first day of treatment in this group.

In the HTN trials, there were only 9 total men aged 75 years and greater: 2 on GITS and 7 on standard. No adverse events were reported in these two GITS patients.

In three other Pfizer-sponsored GITS trials for BPH, there were a total of an additional10 men older than 75 years. Of those, seven reported adverse events and in three of these there was definitely no relationship to doxazosin. The other four are summarized below:

1. "Feeling faint" in an 81-year-old man beginning after the first dose of GITS 8mg after four weeks on 4mg. The dose was reduced back to 4mg, the event resolved, and patient continued the study without further incident.

   Reviewer's comment: Up-titration led to an orthostatic symptom is this patient which resolved with down titration. This is not unexpected with use of any alpha-blocker.

2. "Feeling shaky" in a 77-year-old man beginning on Day 8 of GITS 4mg. The patient continued in the trial without further incident.

   Reviewer's comment: This symptom was tolerated and may or may not be directly related to doxazosin.

3. "Orthostatic hypotension" reported in an 85-year-old man on Day 4 of GITS 4mg. This occurred prior to the fifth dose of 4mg. In this patient, the BP dropped from 141/92 mmHg sitting (repeat 155/82 mmHg sitting) to 130/78 mmHg standing (repeat 134/75 mmHg standing). This patient had a second occurrence of "orthostatic hypotension" on Day 15 wile taking GITS 4mg. On this occasion, his BP dropped from 140/85 mmHg sitting (repeat 116/88 mmHg sitting) to 101/64 mmHg standing (repeat 108/54 mmHg standing).

   Reviewer's comment: In my opinion, these blood pressure drops did not, unto themselves, pose a dangerous clinical situation in this patient.

4. "Hypotension" in a 76-year-old man beginning on Day 2, less than 24 hours after the first dose of GITS 4 mg/d the previous evening. This event resulted in study discontinuation for this patient. In this patient (#0006 0297) the BP dropped from 123/68 mmHg sitting (repeat 111/62 mmHg sitting) to 101/66 mmHg standing (repeat 90/66 mmHg standing); pulse also increased from 81 bpm sitting (repeat 79 bpm sitting) to 92 bpm standing (BP data on file).

   Reviewer's comment: This case demonstrates the potential for orthostatic hypotension within 24 hours of first dosing with GITS 4mg. It is possible that this case was related to

bedtime dosing. It is possible that this case is related to the patient's somewhat low sitting BP at baseline (lowest reading of 111/62 mmHg). The sitting BP went to down as low as 90/66 mmHg while standing. In this reviewer's opinion, the changes noted following dosing were not very large reductions in overall BP. Nevertheless, this case supports our position that the GITS label should have a strong warning about the potential for orthostatic hypotension and syncope.

Finally, in regard to first dosing in men older then 70, the sponsor stated that:

In the two pivotal BPH studies combined, there were 306 men over age 70: 136 on GITS, 126 on doxazosin standard, and 44 on placebo. The incidence of hypotension with GITS was higher in men>70 (2.9%) than in men 65-70 (1.6%) or in men <65 (1.2%). Similarly, the incidence of hypotension with doxazosin standard was also higher in men over age 70 (4.8%) than in men 65-70 (0%) or in men <65 (1.8%). Results were similar for the AE term "postural hypotension". Finally, comparing the two formulations for reported dizziness, the overall incidence in men >70 was lower (6.6%) for GITS than for doxazosin standard (12.7%). Therefore, the sponsor concluded that there is no signal of a safety concern in men over age 70 receiving GITS or doxazosin standard.

> **Reviewer's comment**: Despite the sponsor's conclusion, I believe that both GITS and doxazosin standard were less well tolerated in those older than 70 than those younger than 70 and were even less well-tolerated in those older than 75 years of age, based upon the reported incidences of *hypotension*. This may be related to slightly increased exposure of drug in these age groups, to a propensity to orthostasis in this group, or to an inherent sensitivity to vasodilators in this age group. This should be described in the label.

6. Major Issues From Other Disciplines Or Other Sources

6.1. Pharmacology/Toxicology

Complete Response:
During the review of the Complete Response to Approvable, a new issue arose in the Pharmacology review, that of clinical safety risk of drugs containing a mesylate salt. Dr. Thornton-Jones summarizes this issue in her final review dated June 10, 2004. I have selected certain passages from this review to illustrate the issue for the reader:

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

The possibility for these process impurities in the drug substance and product exists for Cardura XL because [redacted] is used during manufacturing."

Dr. Thornton-Jones continues:

"Two approaches to establishing a limit specification for the impurities are being explored with CDER and include: 1) limiting the amount in the drug substance to [redacted] (Division of Cardio-Renal Drug Products); or 2) limiting the amount based on the total daily intake (TDI) (Division of Anesthetic, Critical Care, and Addiction Drug Products). The [redacted] proposal uses benzene as the model compound with the caveat that benzene may not be the correct model for assessing mutagenic risks of genotoxic impurities because it and these impurities may act by different mechanisms. The EPA limit of benzene is 5ppb in drinking (water) or 5 micrograms benzene/L. The limit was established assuming a 2L intake of water daily which is equivalent to 10 micrograms/day of benzene with a probability of 1 in a million risk of cancer.

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

The summary for the primary Pharm/Tox review states:

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

The final recommendation from the primary Pharm/Tox review states:

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

Reviewer's comment: This reviewer acknowledges Dr. Thornton-Jones' safety concerns and agrees that they are potential clinical safety issues. However, following my initial assessment of this review I remained unclear about two issues:

1) What is meant by "measurable amounts of the impurity"? The process of measuring any substance is dependent on the methodology used to detect that substance. If one has a poor assay, then one would conclude that there are not "measurable amounts" even when there might be large amounts. On the other hand, if one has an exquisitely sensitive assay, then it is possible that "measurable amounts" will always be detected, even when the amounts are trivial. Has CDER set a standard for the limit of detection for this particular assay for this particular impurity?
2) Why would it be "more prudent" to potentially set the specification level [redacted] Is it possible to detect levels [redacted] using the currently available assay methodology? If it is possible, what is the scientific basis for setting the specification [redacted] Finally, what is the current standard within CDER for a specification for this particular impurity?

Based upon these questions, I went ahead and discussed the issue further with the supervisory toxicologist, Dr. Reid.

On June 11, 2004, Dr. Reid provided me with a draft supervisory toxicologist's memo. I have selected passages from the memo that I believe are relevant:

[redacted] impurities have been detected at greater than one part per million (ppm) in some mesylated drug substances and/or products. Consistent with other CDER divisions, DRUDP is adopting an interim standard of [redacted] in drug substances and drug products.

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

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

1) The drug substance and drug product should be evaluated for [redacted] impurities and degradation products.
2) To determine the sensitivity of the analytical method, we want the lower limit of detection (LOQ) defined.
3) If the assay is not robust, a sufficient number of batches available for analysis, or aged drug product is not available for analysis, it may be necessary to set a specification for the drug product until enough data has been generated to assure the Division that [redacted] impurities remain well [redacted] for the shelf life of the drug product.

Reviewer's comment: Dr. Reid's recommendations are quite reasonable. However, it still remains unclear to me why the sponsor should be required to define the lower limit of detection of their assay, if the Division has adopted an interim standard of [redacted] "consistent with other CDER Divisions." If there is an interim CDER policy on this particular specification, then the only requirement for sponsor would appear to be: To show that the lower limit of detection for their assay for [redacted] and that there is no [redacted] detected in fresh or aged drug product batches using that assay. If there is no interim CDER policy because of continued internal scientific deliberations, then Dr. Reid's recommendations are wholly acceptable to me.

Original NDA

In the original NDA, Dr. DeFelice's memo stated that there were no new preclinical pharmacology or toxicology studies submitted to this NDA. However, he did comment about one study in which Cardura XL 4mg was tested against Slow-K 8mg in terms of its erosive potential on the colon. Based upon these studies results which showed:

"The expected pre-clinical evaluation of effects of doxazosin GITS (4 mg) tablets vs. Slow K on rabbit colonic mucosa ex vivo was performed and revealed no macroscopic irritation at any of the 9 mucosal sites, and only minimal microscopic lesions at 5 of the 9 sites. Slow-K 8 meq, the positive control, eroded the submucosa to the level of the tunica muscularis. The doxazosin GITS 8 mg strength was not tested."

In regard to the effect of the GITS formulation on the gastrointestinal tract, the current PI contains a Precaution stating that administration to patients with iatrogenic or pathological bowel

narrowings should be approached with caution since obstruction related to the non-deformable shell has been reported with another product in this formulation category.

Reviewer's comment: I think this issue is described sufficiently in the label at this time.

6.2 Chemistry

Complete Response

The chemistry review team continued its review of this NDA during the review of the Complete Response and also conducted additional review relevant to the mesylate issue. I have not yet received a draft review from the primary chemistry reviewer. However, on June 8, 2004, I received a draft chemistry team leader's memo from Dr. Rhee.

Dr. Rhee provided calculations to support his presumed determination of the amount of [redacted] in doxazsoin mesylate. Lacking definitive data for this amount, Dr. Rhee made some assumptions in his calculations. Ultimately, Dr. Rhee estimated that the amount of [redacted] in doxazosin mesylate is [redacted]

Reviewer's comments:

1. I assume that this applies to the drug substance only, not to the final drug product.
2. It is not clear to me which substance is the concern for this NDA, [redacted] or both.
3. Dr. Rhee believes strongly, based upon the information he has at hand, that the amount of [redacted] in the drug substance will be [redacted] However, he does not comment upon Cardura XL, the drug product. As per Pharmacology/Toxicology, there is [redacted] making the final drug product where there is an opportunity for additional [redacted] to form, and the drug product itself is not "qualified" by gentoxicity nor carcinogenecity data, nor is a specification set for total amount of [redacted] in the final drug product.

The final conclusions and recommendation from Dr. Rhee's draft memo is as follows:

"Based (on) the foregoing analysis, the amount of [redacted] in doxazosin mesylate is expected to be far [redacted] and even (if) it exceeds [redacted] the TDI to each patient will be about 5% or less than what hypertension patient(s) take everyday from Tevetan.

[redacted]

1. Dr. Rhee's proposal would only be reasonable if the Center and the Division have already accepted an interim standard [redacted], and the Division concurs for this specific NDA.
2. Even so, Dr. Rhee's proposal is dependent upon the sponsor's commitment not to commercialize Cardura XL if the [redacted] are found in the commercial batches. This carries some risk, in that it is a voluntary agreement not to commercialize what could be an unsafe product.

[redacted]

Negotiations regarding the container/carton labeling are ongoing. The Division is making every effort to adhere to the recommendations of DMETS (see relevant section regarding DMETS consult in this memo).

Original NDA
In the original NDA review, there were several issues of note from the chemist's review:

1. [redacted]

2. The overall recommendation from the Office of Compliance regarding manufacturing site inspections was "acceptable".

6.3 Clinical Pharmacology
Complete Response
I received a draft clinical pharmacology and biopharmaceutics review from Dr. Ortiz on May 24, 2004. The recommendation for this NDA was "acceptable"

Dr. Ortiz states that his review of the Complete Response focused upon two clinical pharmacology issues and upon the dissolution specifications. The two issues were: 1) intra-subject variability seen in two completed clinical pharmacology trials from the original NDA (as noted in the original NDA by Dr. Kiefer) and 2) The differences in time to maximum concentrations between single and multiple dosing.

Regarding the intra-subject variability, Dr. Ortiz reviewed minimum serum doxazosin concentrations (Cmin) after multiple dosing of doxazosin GITS and of doxazosin standard in Study DAZ-NY-007. In the table on page 6 of his review, he broke these out by dose (4mg and 8mg) and provided coefficient of variations. He noted that higher intra-subject variability was noted for GITS compared to standard groups for both 4mg and 8mg. He stated that the intra-

subject CV%'s ranged from 7-23% in the GITS groups, with the highest CV% seen in the 8mg GITS group.

For Study DAZ-NY-96-009, the minimum serum doxazosin concentrations (Cmin) were again analyzed after multiple dosing, but in this study, the only dose was 4mg GITS and the comparisons were between young and elderly men and women. A table is provided on page 7 of Dr. Ortiz' review. Dr. Ortiz commented that greater intra-subject variability was noted in the younger subjects compared to the older, and overall ranged from 11-24%, with young female subjects experiencing the greatest intra-subject variability. Dr. Ortiz concluded that overall, there was considerable variability noted throughout all the clinical trials using the GITS formulation.

> **Reviewer's comment**: While of note, this issue does not appear to be a major safety risk for Cardura XL for the BPH indication.

In regard to the issue of time to maximum concentration (Tmax), Dr. Ortiz reviewed the data from Study DAZ-NY-007 and from Study A0351061. In the former study, steady-state Tmax was between 8 and 9 hours. In the later study, following single dose administration, the associated Tmax was 14-15 hours. In his draft review, Dr. Ortiz concluded that this issue should be noted in labeling in case there is an effect on blood pressure at Tmax.

> **Reviewer's comment**: The medical officer found no relationship between Tmax and the occurrence of syncope or hypotension. And, at the Clinical Pharmacology Briefing, it was decided that this issue was not a major safety concern and was not required for labeling.

Finally, Dr. Ortiz commented that the in-vitro dissolution specifications had been agreed-upon between sponsor and Division. However, as of June16, 2004, these had not been formally agreed to by sponsor. On June 16, 2004, we discussed this with sponsor who agreed to accept the Division's proposed specifications. A letter was to be forwarded to this end.

> **Reviewer's comment**: For purposes of completing this review, I am assuming that the sponsor will send this letter and that this issue is resolved. The reviewer is referred to the chemist's and clinical pharmacologist's review for confirmation.

The only other clinical pharmacology issue of note was labeling. Major clinical pharmacology labeling issues including the effect of food and GI transit times, the differences in pharmacokinetics in the elderly, recommendations on when to dose during the day, and comparisons to doxazosin IR pharmacokinetics. It was decided to highlight the following:

1. Variability in GI transit time will have an effect on pharmacokinetics.
2. There is a modest increase in exposures in the elderly which may be clinically meaningful.
3. Dose should be administered with the morning meal as per the clinical trial instructions.
4. There is an effect of food that may be clinically meaningful.
5. Comparisons to doxazosin IR pK [redacted]
6. Drug interaction studies with CYP inhibitors or substrates were not conducted; neither were pharmacodynamic interaction studies with other anti-hypertensives or vasodilators.

Original NDA

The clinical pharmacology reviewers in the Division of Cardio-Renal Drug Products found the data "acceptable provided labeling comments are adequately addressed." In brief, these were:

1. IV/IVC analysis data did not establish a correlation.
   Reviewer's comment: This does not jeopardize approval.

2. The sponsor should change the dissolution specifications to those recommended by the Agency.
   Reviewer's comment: Dissolution specifications are agreed-upon at this time.

3. The sponsor should submit pharmacokinetic data relevant to intra-subject variability from Phase 1 Study DAZ-NY-96-007 and from Study DAZ-NY-96-009.

   Reviewer's comment: These data were submitted and reviewed by Dr. Ortiz and they do not impact approval.

In the original NDA review, Dr. Kiefer made the following additional relevant comments:

1. For the 8 mg GITS tablets, Cmax and AUC increase by 32% and 18% in the fed state compared with the fasted state. Dr. Kiefer believed that the extent of these differences between fed and fasted states were not clinically relevant and thus, dosing instructions with or without food were appropriate.

   Reviewer's comment: In the pivotal clinical trials for BPH, subjects were instructed to take their medication at breakfast time. In general, I believe that dosage and administration for approved drugs should reflect the per-protocol clinical trial instructions. And, the differences in Cmax and AUC described above may be relevant. Therefore, we have advised dosing with the morning meal.

2. Dr Kiefer stated that the that the initial 4 mg dose of Cardura XL will cause a maximum plasma concentration similar to 2 mg of Cardura standard. She then noted that the starting dose for Cardura is 1 mg; which is known to be well-tolerated in the patient population.

   Reviewer's comment: This comment was acknowledged and in large part, led to the first approvable action. The sponsor has addressed this potential safety risk through a single well-controlled pharmacodynamic study comparing a starting dose of 1mg doxazosin IR and Cardura XL 4mg and a detailed, robust analysis of adverse events in the first day and first week of clinical trials. Based on this data, our Division is comfortable with the GITS starting dose of 4mg. We do not note worsened orthostasis at the onset of therapy with the 4mg GITS compared with previous.

3. Dose-proportionality was demonstrated for the 4 mg and 8 mg doses for both formulations (GITS and standard).

4. Cmax is reduced by approximately 40% with the GITS formulation compared to the same dose for standard and Cmin is maintained regardless of formulation. Dr. Kiefer felt that this would offer some safety if prescribers abruptly switched patients from standard to GITS formulations at the same dose.

   Reviewer's comment: I agree that the issue of "switch" needs further discussion during labeling negotiations. This is perhaps more of an issue if a patient on doxazosin standard for both BPH and HTN switches to GITS – [redacted]

5. There are notable differences between men and women in bioavailability. After dosing with 4 mg GITS, Cmax and AUC were higher in females compared to males. Young females had the most notable findings: an AUC 46% higher on Day 1 and 20% higher on Day 7 then young males. [redacted] commented that in Study 96-009, 48% of all adverse events in the young female group occurred on Day 1 at the time of maximum "spike" in doxazosin plasma concentrations. By Day 2, 71% of all AES in that group had occurred. By Day 4, 84% of AEs had already occurred. At the time, Dr. Kiefer believed that these data indicate that dose-titration at doses lower than 4 mg GITS may be necessary in young women.

   Reviewer's comment: It is possible that a 4mg GITS starting dose in young females is too high, especially in hypertensive patients and considering the increased intra-subject variability in young women. However, this is not directly related to BPH indication.

6. There were differences between the young and the old in bioavailability. After dosing with 4 mg GITS, plasma concentrations were higher in the elderly than in the young. Elderly males had the most notable findings: bioavailability was 33% greater in elderly males compared to young males. At the time of the original NDA, Dr. Kiefer agreed with sponsor that these differences did not mandate dose adjustment in the elderly.

   Reviewer's comment: While the Division agrees with Dr. Kiefer that dose adjustment isn't necessary in the elderly, we believe that the differences in pK between young and old may be clinically relevant and should at least be described in labeling. Our review found an increased incidence of orthostasis in the elderly compared to the young and this may be due, in part, due to differences in pK (or other physiological factors). Therefore, we have highlighted these differences in labeling.

6.4. Biometrics

Complete Response

The single additional Phase 2 pharmacodynamic study submitted in the Response to Approvable was not reviewed by Biometrics. Dr. Welch did however, participate actively in labeling negotiations.

Original NDA

Dr. Gebert provided a memo for the original NDA review in regard to the pivotal BPH trials. In his memo, Dr. Gebert found that BPH Study #1 showed both doxazosin GITS and standard to be statistically superior to placebo for both primary endpoints. He concluded that both Study #1 and #2 showed doxazosin GITS to be "comparable" to doxazosin standard.

Several issues are of note from Dr. Gebert's original NDA Biometrics review:

1. Dr. Gebert comments that the sponsor powered BPH Study #1 "with comparability of the two active treatment groups in mind". However, he notes that the sample size analysis was actually not designed properly for a true equivalence trial. Rather, it was appropriate for a superiority trial design. Therefore, the finding of no statistically significant difference between groups does not mean that the groups are statistically equivalent.

   Reviewer's comment: I believe this comment also pertains to Study #2.

2. Dr. Gebert's analysis of the data from the ITT population for BPH Study #1 revealed that the 95% confidence limits surrounding the difference between active treatment groups for the least squares mean change-from-baseline in total symptom score were (-0.32 and 1.21). He stated that this "fails the sponsor's definition of statistical equivalence".

   Reviewer's comments:
   1. In my opinion, failure to achieve post-hoc statistical equivalence is not an impediment to approval of this NDA. These products appear clinically comparable when dosed as in BPH Studies #1 and #2.
   2. Cardura XL actually gave slightly more reduction in Qmax than doxazosin standard in both studies and numerically more symptom relief in Study #2.

3. Dr. Gebert's analysis of the data from the ITT population for BPH Study #2 revealed that the 95% confidence limits surrounding the difference between active treatment groups for the least squares mean change-from-baseline in total symptom score were (-0.98 and 0.53). He stated that this "just meets the sponsor's definition of statistical equivalence".

   Reviewer's comment: Again, in this TL's opinion, the results for Cardura XL and doxazosin standard for IPSS and Qmax in this fairly large trial are numerically very, very similar. In my opinion, whether the treatments are found to be statistically equivalent or not, and whether this is a post-hoc versus pre-defined statistical comparison, in the context of the overall NDA package, this issue does not preclude approval.

4. Dr. Gebert ultimately concluded that the two doxazosin treatments can be said "to give comparable results" based upon the fact that the two studies differed in which treatment gave numerically better results and that they were of comparable size for the active treatment groups.

6.5. Division of Scientific Investigation (DSI)

Complete Response

DSI was not asked to audit the additional Phase 1 study submitted with this Complete Response to Approvable.

Original NDA

Previously, DSI had inspected three Canadian sites from the second pivotal BPH study and had concluded that the data generated at these sites could be used in support of the NDA.

6.6. Financial Disclosure

Complete Response

In the Response to Approvable, for the additional new Phase 1 study none of the 5 listed investigators from the [redacted] had financial information to disclose.

Original NDA

Review of financial certification information submitted on April 20, 2001, "complied" with 21 CFR 54; that is, there was no disclosure of financial interests that could bias the outcome of the trials.

6.7. Pediatrics

Original NDA
Since this indication is intended for the treatment of the signs and symptoms of BPH in adult men, a pediatric waiver is appropriate. A regulatory letter granting the pediatric waiver was signed by Dr. Shames on February 12, 2002.

6.8. OPDRA Tradename Review
Complete Response
OPDRA 's re- assessment of the proposed tradename, Cardura XL, was completed on April 9, 2004. In summary, OPDRA again had no objection to the use of the proposed tradename.

DMETS re-iterated its original concern related to confusion between the two Cardura formulations in the marketplace. They stressed that:

1) Sponsor should educate healthcare practitioners about the new formulation, and
2) The labels and labeling should clearly differentiate the two products.

OPDRA again proposed several changes to the container label. These included the following:

1. The sponsor should more clearly differentiate the label appearance of Cardura XL and Cardura standard. Different colors and different type or size font might help.
2. The Cardura XL 4 mg and 8 mg dosage strengths do not have the word "mg" next to the digit. This should be added.
3. OPDRA recommended slight re-wording in regard to the overage issue.
4. The proposed containers of 30 tablets should provide [redacted] OPDRA was unable to determine if the [redacted] was included as part of the container.

Reviewer's comments:
1. The proposed container utilizes a [redacted] so this is issue is likely to be resolved.
2. *As of Monday June 14, 2004, active container label negotiations were ongoing with sponsor, as led by the Chemistry review team.*

6.9. Division of Drug Marketing, Advertising and Communiccations (DDMAC)
Complete Response
DDMAC provide a detailed review of the proposed package insert (PI) on May 3, 2004. Corrinne Kulick provided 32 individual comments. Each of these comments was carefully assessed and changes were made to the sponsor's proposed PI as deemed appropriate by the relevant review discipline in conjunction with the medical team leader. Most of the DDMAC suggestions and recommendations were fully enacted. Those that were not enacted were either enacted in part, or if not enacted, were still seriously deliberated by the review team.

6.10. Division of Cardio-Renal Drug Products (CR Division)
Complete Response
The Complete Response to Approvable submission was not reviewed by the CR Division. Nevertheless, it is appropriate to provide some comments here from the CR review of the original NDA:

Original NDA

[redacted]

Reviewer's comments:

1. [redacted]
2. I believe that there is a "net benefit" in the management of BPH if the 1 mg and 2 mg standard dose levels could be avoided entirely. A patient could be initiated on Cardura XL 4 mg as an effective initial dose.

Dr. Karkowsky other major comments included:

1. In the pivotal hypertension trials, there were more subjects who had cardiovascular or vasodilatory AES among those treated with the GITS regimen (then the standard regimen) during the first week of therapy. He listed these actual events individually in Table 5 of his review.
2. There were relatively few frail elderly (at least 75 years of age) and even fewer blacks among those treated.
3. A larger safety database, in a potentially more vulnerable population, would be "more informative".
4. Since the release characteristics of this formulation are dependent on gut transit times, there is more intrasubject daily variability in blood levels.
5. The Cardura XL label should be separate from the Cardura standard label. [redacted]
6. Dr. Karkowsky makes mention of the ALLHAT trial; specifically to note that its results should not impact on the regulatory decisions [redacted]

In terms of the actual BP effects from the hypertension and BPH trials, Dr. Karkowsky comments that:

1. In Study [redacted] the BP-lowering effect of doxazosin IR was slightly greater than the GITS formulation.
2. The titration design of [redacted] precluded any assessment of dose-response in the 4 mg and 8 mg GITS strengths.
3. Aside from the 24-hour post-dose measurement, there were no other measurements of the BP effect at any other time during the dose interval.

4. [redacted]

5. Neither study explored the entire dose range of doxazosin IR (up to 16 mg).
6. The magnitude of the blood pressure effect was lower among those in the BPH trials compared with those in the hypertension trials. This was not surprising to him, since the hypertension trials [redacted] The effect in the BPH trials was actually "relatively small" and "somewhat inconsistent" between the two BPH trials.

Reviewer's comment: It is notable that the CR Division described the actual BP-lowering effect of Cardura XL seen in the pivotal BPH trials as "relatively small" and "inconsistent".

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

/s/

Mark S. Hirsch
6/16/04 05:40:03 PM
MEDICAL OFFICER

Daniel A. Shames
6/17/04 05:15:05 PM
MEDICAL OFFICER

Division of Reproductive and Urologic Drug Products

Clinical Review

NDA 21-269

Cardura XL

(doxazosin mesylate GITS 4 & 8mg)

Pfizer Pharmaceutical Group

June 17, 2004

CLINICAL REVIEW

NDA 21-269

Date of original NDA submission: April 23, 2001
Date of complete response submission: December 17, 2003
Review of original NDA completed: February 12, 2002
Review of complete response completed: June 17, 2004

Reviewer:
Gerald D. Willett MD
Division of Reproductive and Urologic Drug Products

Applicant:
Pfizer Inc
235 East 42nd St.
New York, NY 10017

Proposed Trade Name:
Cardura XL

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

Dosage forms:
Cardura XL (Doxazosin mesylate GITS) 4 mg tablet
Cardura XL (Doxazosin mesylate GITS) 8 mg tablet

Route of administration:
Oral

Proposed indication:
Indicated for the treatment of [redacted]
symptoms associated with benign prostatic hyperplasia (BPH) [redacted]

Related INDs:

[redacted]

32633 = doxazosin (1989) mild to moderate hypertension with symptoms of BPH

Related NDAs:
NDA 19-668 Cardura (hypertension)
NDA 20-371 Cardura (benign prostatic hyperplasia)

Table of Contents

Table of Tables

Clinical Review for NDA 21-269

Executive Summary

I. Recommendations

A. Recommendation on Approvability

Based on safety concerns related to the possible presence of [redacted] in the drug product, I recommend an approvable action on this NDA. The proposed steps for resolution of this issue are fully described in the medical team leader's memo.

Clinical safety issues that arose at the time of the first approvable action (02 Feb 2002) have been satisfactorily addressed in the sponsor's complete response (17 Dec 2003).

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

No additional clinical studies or clinical risk management steps are required.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The clinical development for Cardura XL consisted of the following components:

- Controlled and non-controlled clinical pharmacology studies to establish:
  - Single dose pharmacokinetics
  - Multiple dose pharmacokinetics
  - Food effects
  - Effect in hepatically impaired subjects
  - Pharmacokinetic effect based on gender and age
- [redacted]

- Controlled and non-controlled studies for benign prostatic hyperplasia
- Additional study of first dose effect on blood pressure and pulse (subsequent to approvable action)
- Additional analysis of early adverse events (subsequent to approvable action)

B. Efficacy

Efficacy summary comments (taken from the original review):

- In the pivotal study DAZ-N/S/DK-95-001, Cardura XL was clinically equivalent to the approved drug Cardura and statistically superior to placebo for decreasing BPH symptomatology and improving the maximum urinary flow rate in subjects with BPH.

- In the pivotal study DAZ-NY-95-001, Cardura XL was clinically equivalent to the approved drug Cardura for decreasing BPH symptomatology and improving the maximum urinary flow rate in subjects with BPH.

- In the open label extension study DAZ-NY-95-001B, Cardura XL appears to show a durable effect for BPH symptomatology and maximum urinary flow rate in subjects with BPH during the 24-week extension.

- The magnitude of the improvement in the I-PSS score and the magnitude of improvement in the maximum urinary flow rate with Cardura XL appear comparable to that found with other approved alpha-blockers for BPH.

C. Safety

There is a large safety database for the doxazosin GITS formulation. There is over 2800 months exposure in clinical trials and over 460,000 patient-years in postmarketing experience.

The sponsor has adequately addressed the agency's requests for safety information related to early dosing of Cardura XL.

There is no evidence that Cardura XL presents an increased safety risk compared to Cardura either with initial dosing or overall. This evidence is derived from the following:

- Combined safety data from the pivotal BPH and hypertension trials
- Safety data from the "initial" dosing blood pressure study A0351061
- Two year safety update (2001-2002)
- Postmarketing safety report (Oct 2002 through Sept 2003)

Review of numerous clinical studies, an extensive postmarketing safety base and the published literature has not shown any signal for either QT prolongation or torsade de pointes with doxazosin or doxazosin GITS.

Vasodilatory events occur with greater frequency in the elderly. There is no evidence that the risk for Cardura XL for elderly men is any different than the risk of taking Cardura in this age range. The label should reflect vasodilatory event differences in elderly men compared to younger men.

D. Dosing

One of the principal advantages for Cardura XL over Cardura in subjects with BPH is the ability to offer the patients less titrating steps. Cardura has four dosage strengths applied to the titration (1mg, 2mg, 4mg and 8mg). Cardura XL has two dosages (4mg and 8mg)

E. Special Populations

Cardura XL is designated for middle to elderly age men by its indication of BPH.

Pharmacokinetic studies have indicated increases of 27% in maximum plasma concentrations and 34% in the area under the concentration-time-curve were seen in the elderly (≥65 years old).

The use of Cardura XL was evaluated in 12 hepatically impaired (stable alcoholic cirrhosis). The clearance of doxazosin decreased by 30% in the impaired subjects compared with normal subjects. There was no significant difference in Tmax, Cmax, and T (half) between the two populations. The use of Cardura XL with severe hepatic disease has not been studied and Cardura XL should not be used in this population.

Although women were evaluated in the hypertensive and Phase 1 trials of Cardura XL, there are no gender considerations for the BPH indication.

The sponsor has very little clinical data on the effect of Cardura XL in African American men with BPH. However, there is no clinical information to suggest that this drug product will act any differently in African American men or men of any other racial origin.

The sponsor requested a full pediatric waiver. This is acceptable because benign prostatic hyperplasia is not typically found in the pediatric population.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

A. Drug name, class, indication, dosage, regimens, age groups, relevant facts

Doxazosin mesylate gastro-intestinal therapeutic system (GITS) is a modified-release formulation of doxazosin. The releasing mechanism for this formulation employs a semipermeable membrane that allows for osmotic pressure to release the drug through a small, laser-drilled orifice in the membrane on the drug side of the tablet. The proposed name for this drug is Cardura XL. Doxazosin (Cardura) is a selective alpha$_1$-blocker, approved for the treatment of hypertension and benign prostatic hyperplasia (BPH). Doxazosin is a quinazoline compound structurally related to prazosin and terazosin.

The approved dosage and regimen of doxazosin (Cardura) for benign prostatic hyperplasia begins at 1mg, daily. The dosage may then be increased to 2 mg and thereafter to 4 mg and 8 mg once daily, depending on the individual patient's tolerance and symptomatology. In comparison, the initial dose of doxazosin mesylate GITS (Cardura XL) is 4 mg given once daily and the dose may be increased to 8 mg, again based on tolerance and symptomatology.

The typical expected age group for Cardura XL use in benign prostatic hyperplasia is middle aged to elderly males.

Benign prostatic hyperplasia (BPH) is the most common neoplastic condition affecting men. Histologically BPH is characterized by the presence of non-malignant nodules arising in a small region around the proximal segment of the prostatic urethra. BPH can lead to varying degrees of bladder outflow obstruction and voiding problem symptomatology. Symptoms are split into obstructive and irritative types.

The obstructive symptoms include hesitation, intermittency, dribbling, weak urinary stream, and incomplete emptying of the bladder. Irritative symptoms include nocturia, daytime frequency, urgency and burning.

Clinicians commonly use an index derived from the American Urological Association (AUA) to guide therapy for symptoms. This index is employed in the pivotal trials for this application and is designated as the International Prostate Symptom Score (I-PSS).

Additional assessment in everyday clinical practice for BPH patients includes the digital rectal examination (DRE) to assess prostatic size and screen for evidence of prostatic cancer, urinalysis to assess other reasons for urinary symptomatology (i.e., urinary tract infection), and serum creatinine to assess renal function.

Uroflowmetry provides an electronic recording of the urinary flow rate throughout micturition. The maximum flow rate is considered to be the most informative measurement and is utilized in the pivotal trials of this study.

Two factors are considered necessary for BPH development – aging and intact testicular function. Growth factors and the cellular interactions between the stromal and epithelial components of the prostate may also contribute to BPH.

Previously, surgery was the only option for this condition. Medical therapy advances have allowed symptomatic improvement for many men. The medical therapy for BPH includes 5alpha-reductase inhibitors and alpha-adrenergic receptor antagonists. 5 alpha-reductase inhibitors block full expression of androgenic effect by reducing the conversion of testosterone to dihydrotesterone. Adrenergic receptor antagonists as described below improve the symptomatology and urodynamics of benign prostatic hyperplasia at least in part by reducing the tone of prostatic smooth muscle.

Both alpha-adrenergic and cholinergic receptors are present in the prostate. The alpha-adrenergic receptors have been subtyped into $alpha_1$ and $alpha_2$ receptors, with $alpha_1$ receptors mainly responsible for contractile function. Further typing of $alpha_1$ has identified $alpha_{1A}$ (previously known as $alpha_{1c}$) as the primary prostatic adrenergic receptor. Therapeutic adrenergic blocking agents vary from non-selective (phenoxybenzamine) through $alpha_1$ selective agents such as doxazosin up to $alpha_{1A}$ selective agents like tamsulosin. Doxazosin (Cardura) specifically is a long acting selective $alpha_1$-blocking agent.

The percentage of patients experiencing any degree of symptom improvement with alpha-blockers varies from approximately 75-93%. Mean improvements in maximum urinary flow rates have been reported to be about 45% for alpha-blockers.

The most common adverse events associated with selective $alpha_1$ blockers include dizziness, light-headedness and asthenia. For some of these patients bedtime administration appears to lessen the severity of these adverse events. Syncopal episodes are the most severe side effect of doxazosin. The present label for Cardura includes warnings in regard to these severe side effects.

B. State of Armamentarium for Indication(s)

The treatment of benign prostatic hyperplasia includes the following:

Surgical:

- Transurethral resection of the prostate (TURP)
- Transurethral incision of the prostate
- Transurethral electrovaporization
- Transurethral needle ablation
- Transurethral balloon dilation
- Hyperthermia
- High intensity focused ultrasound
- Intraurethral stents
- Open simple prostatectomy (suprapubic, retropubic)
- Laser therapies

Approved Medical:

- Selective long acting $alpha_1$-blockers
  - Terazosin (Hytrin, approved in U.S. for BPH)
  - Doxazosin (Cardura, approved in U.S. for BPH)
  - Alfuzosin (Uroxatral, approved in U.S. for BPH)
- Selective $alpha_{1A}$ blocker
  - Tamsulosin (Flomax, approved in U.S. for BPH)
- 5alpha-reductase inhibitors
  - Finasteride (Proscar, approved in U.S. for BPH)

C. Important Milestones in Product Development

- **November 2, 1990** = Approval of Cardura (NDA 19-688)
- **October 22, 1999** = Discussion about the modified release tablet (GITS) with the Division of Cardio-Renal Drug Products
- **February 24, 2000** = Discussion about the modified release tablet (GITS) with the Division of Reproductive and Urologic Drug Products

NDA 21-269

- **April 23, 2001** = Initial submission of NDA 21-269
- **February 22, 2002** = Approvable action on NDA 21-269 (deficiencies and recommendations specific to this application and conveyed to the sponsor are as follows):

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following deficiencies:

1. There is inadequate information to determine the direct effect of a first dose of Cardura XL 4 mg on blood pressure and pulse, versus Cardura 1 mg, versus placebo, around the time of maximum plasma concentration. (see Study A0351061)

2. There is inadequate information to directly compare the incidence of vasodilatory and cardiovascular adverse events between Cardura XL 4 mg and Cardura 1 mg after one day and after one week of therapy. (see comparative safety section)

To address the above deficiencies the following is required:

1. Submit actual blood pressure and pulse data at periodic intervals over 24 hours after first dosing with Cardura XL 4 mg, compared with Cardura 1 mg, and with placebo. Conduct orthostatic maneuvers with blood pressure and pulse measurements.

2. Submit a critical analysis comparing clinical adverse events (especially those relating to vasodilation and orthostasis) between Cardura XL 4 mg and Cardura 1 mg in the first day and first week of therapy. This analysis may use all currently available data or may require new additional data from clinical trials in order to demonstrate non-inferiority of Cardura XL.

Additionally, the following deficiencies have been noted during the review of your NDA. We also request your response to these:

1. Provide all available safety information for the use of Cardura XL in black men or provide a justification why such information is not necessary. (see Race under Special Populations)

2. Provide all available safety information for the use of Cardura XL in men older than 75 years of age. (see Age under Special Populations)

3. Clarify why some data line listings for adverse events from the BPH pivotal trials listed 2 mg doxazosin standard as the dosage strength administered during the first week of therapy as opposed to the per-protocol 1 mg dosage strength.

4. Clarify whether the package insert will advise any blood pressure measurements around the time of first-dosing of Cardura XL or at any other time during therapy.

5. Submit revised labeling, highlighting that patients should not chew the GITS tablet, and highlighting that syncopal events have been reported to occur (albeit rarely) days or weeks after the start of therapy.

6. Submit pharmacokinetic data relevant to intra-subject daily variability from Phase 1 Studies DAZ-NY-96-007 and DAZ-NY-96-009.

7. Provide revised container labels that clearly differentiate the tradenames Cardura and Cardura XL.

- **June 3, 2002** = Teleconference with sponsor regarding the applicability of blood pressure data on 12 young Japanese men. DRUDP did not agree with use of this study to address deficiency #1 in the approvable letter. The Division recommended that the sponsor conduct another study in the population age that the drug was intended for. Additionally the sponsor asked the division if the combined safety analysis for the pivotal BPH and HTN trials for Cardura XL would provide sufficient safety data to answer deficiency #2. The division felt that this approach would be acceptable. However, pooling of any and all additional information was recommended.

Medical officer's comments: The protocol from Japan provided by the sponsor was DAZ-JP-97-501. Noteworthy findings from this study include:

1. ***Mean Tmax was 13.7 hours for GITS 4mg.***
2. ***No mean orthostatic effect at Tmax was observed for doxazosin GITS 4mg.***
3. ***For the 12 young Japanese men studied there were more episodes of systolic drops ≥20mmHg and diastolic drops ≥10mmHg in the doxazosin STD 1mg compared to doxazosin GITS 4mg (see sections 3 and 4 of the appendix)***
4. ***The graphs demonstrating mean blood pressures (supine and standing) show that doxazosin GITS 4mg shows slightly lower pressures overall compared to doxazosin STD 1mg for these younger Japanese men.***
5. ***There were no serious adverse events or discontinuations in this trial. Orthostatic dizziness (2 subjects) and orthostatic hypotension (2subjects) was reported with equal frequency in all three doxazosin treatment groups (STD 1mg, GITS 4mg and GITS 8mg). There were no reported syncopal events.***

- **September 4, 2002** = DRUDP receives protocol A0351061 (study was submitted by the sponsor to the Cardio-Renal Drug Product Division the preceding week)
- **October 11, 2002** = Protocol A0351061 is started
- **December 17, 2003** = Complete Response submission

Medical officer's comments: The sponsor did not seek a 45-day special protocol assessment or further concurrence on protocol A0351061 at the time of submission in late August, 2002. The study was initiated approximately 42 days after the protocol was sent to the Cardio-Renal Division. DRUDP did review and comment on this study but the comments were sent to the sponsor after this short study had been completed. The comments are as follows:

1. ***The study range should be 50-80. One half of the study population should be greater than 65 years.***

2. ***Baseline exclusion criteria #3 should be revised so as to exclude subjects with supine systolic readings less than 90mm Hg and/or supine diastolic readings less than 60mm Hg.***

3. ***Provide statistical information that the number of subjects enrolled in the proposed study will demonstrate non-inferiority of the 4mg Cardura XL compared to the 1mg standard preparation with regard to orthostatic effects.***

The sponsor did respond to these comments even though they had completed the study. In regard to the first comment they explained that they had chosen the lower age limit of 40 due to evidence that the prostate begins to increase in size at that age. The study analyzed 5/26 subjects who were older than age 65. The sponsor felt overall that the age range selected (40-75) is typical of what would be seen in clinical practice.

In regard to the second comment the sponsor stated that the study excluded subjects whose supine blood pressure was less than 100/65 mm Hg. No subjects were excluded because of this criterion. Therefore, the sponsor felt that an exclusion criterion of blood pressure less than 90/60 mm Hg would not have impacted the patients who entered the study.

In regard to the third comment, the sponsor stated that the non-inferiority of 4mg Cardura XL relative to 1mg standard will be assessed by a one-sided 95% lower confidence limit. The sponsor further stated that the number of completed subjects (24) is typical for a PK/PD crossover study and was discussed with FDA in a teleconference on June 3, 2002. No formal power calculations were conducted.

Although only 5 of 26 enrolled subjects were over age 65, the sponsor provided additional information on elderly subjects from other studies. Therefore this "first dosing" study does not need to be repeated again. The explanations regarding exclusion based on the sponsor selected blood pressure and statistical considerations are acceptable.

D. Other Relevant Information

All the relevant information is found in the other sections.

E. Important Issues with Pharmacologically Related Agents

These issues were previously discussed in the introduction and background section.

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Pharmacology/Toxicology and Microbiology

The review from Pharmacology/Toxicology highlights an important problem that may occur in the drug manufacturing process. This is illustrated in the following excepted paragraph:

> "Although the drug substance, doxazosin mesylate, has been qualified in two-year carcinogencity studies in rats and mice, there [redacted] in the manufacturing of the final drug product, Cardura XL. [redacted] offers an opportunity for additional [redacted] degradation products to form. [redacted] are known genotoxins and carcinogens."

Medical officer's comments: The resolution of this issue is fully addressed in the team leader's memo. This problem is the reason for the approvable action taken on this NDA at the present time.

Chemistry

Medical officer's comments: Refer to the chemistry review. The principal issue for the chemistry team is also the resolution of the [redacted] analysis.

Biostatistical Review (from initial submission review)

Principal findings from the statistician include the following:

- Differences in the sponsor's results compared to the datafiles were minor and do not affect efficacy review conclusions.
- Study DAZ-N/S/DK-95-001 showed both doxazosin treatments to be statistically superior to placebo in the two primary endpoints (I-PSS and MUFR)
- Formal testing of equivalence between the two doxazosin treatments was found to be problematic secondary to the titration with different starting doses as well as the sponsor's definition of equivalence. However, the two doxazosin treatments, based on study results can be said to give comparable results.
- Doxazosin GITS gave slightly more reduction in maximum flow rate in both studies.

Division of Drug Marketing, Advertising, and Communications

The Division of Drug Marketing, Advertising, and Communications (DDMAC) submitted their labeling review. Some of the major recommendations regarding clinical aspects include the following:

- Remove promotional type wording from the label
- [redacted]

- Clarify the effects of food and GI retention time
- Revise the discussion on orthostasis

Medical officer's comments: The label was reviewed and edited by each of the disciplines and sent to the sponsor. The comments from DDMAC were incorporated into the label review. The sponsor returned the label with additional comments. Some sections of the label, especially the clinical section, still require resolution. These sections can be addressed once the [redacted] issue is fully resolved.

III. Human Pharmacokinetics and Pharmacodynamics

The principal clinical pharmacology issues related to the sponsor's complete response and to the product in general are the following:

1. Some intra-subject variability seen in two completed clinical pharmacology trials from the original NDA
2. Differences in time to maximum concentrations between single and multiple dosing
3. In-vitro dissolution specifications
4. Variability in GI transit time's effect on pharmacokinetics
5. Modest increase in exposure in the elderly
6. Dosing time and effect of food
7. Lack of formal drug interaction studies

Medical officer's comments: A full discussion can be found in the biopharmaceutics review. Items 1 and 2 are not felt to represent safety concerns. The sponsor agreed to the proposed dissolution specifications. Items 4 through 7 will be addressed in the product label.

IV. Description of Clinical Data and Sources

A. Overall Data

The original NDA 21-269 (April 20, 2001) submission consisted of the following sections in the paper submission:

- Labeling
- Background

- Foreign Marketing
- CMC
- PharmTox
- Human pharmacokinetics and bioavailability (5 studies)
- Clinical Data Summary and Statistical Analysis (2 pivotal studies, one extension study)
- Benefit/Risk Relationship
- Additional Information [redacted]
- Appendices

The original NDA 21-269 (April 20, 2001) submission consists of the following electronic data:

- Datasets for studies:
  1. NSDK95001 (13 week pivotal trial BPH –GITS v. Std v. Placebo)
  2. NY95001 (13 week pivotal trial BPH – GITS v. Std.)
  3. NY95001B (open label extension)
  4. NY96007 [PK of GITS (4 and 8 mg) vs. Standard (4 and 8 mg)]
  5. NY96008 (Comparative bioavailability under fasted and fed conditions)
  6. NY96009 (PK of 4 mg GITS in young and elderly volunteers)
  7. NY96010 (Comparative bioavailability of two 4mg GITS vs one 8 mg GITS)

- CRFs for studies:
  1. NSDK95001 (13 week pivotal trial BPH –GITS v. Std v. Placebo)
  2. NY95001 (13 week pivotal trial BPH – GITS v. Std.)
  3. NY96007 [(PK of GITS (4 and 8 mg) vs. Standard (4 and 8 mg)]
  4. NY96009 (PK of 4 mg GITS in young and elderly volunteers)

- Labeling

On June 15, 2001 the sponsor sent an electronic submission of dataset definitions.

On June 28, 2001 the sponsor sent a compilation of the participating investigators and number of subjects for each of the study sites.

Additional data requested by the statistics reviewer was sent in an electronic file on August 3, 2001.

The 4 month safety update was sent by the sponsor on September 6, 2001 (covered the time period form January 1, 2000 through December 31, 2000).

Revised labeling for Cardura XL was submitted February 11, 2002.

On December 17, 2003, the sponsor sent in a complete response to the Division's February 22, 2002 approvable letter. The data submitted included the following in an electronic submission:

- Response to Critical Deficiency 1 (study A0351061)
- Response to Critical Deficiency 2 (comparing AEs for Cardura XL vs. Standard)
- Comment 1: Safety overview of Cardura XL in Black Male Population
- Comment 2: Safety overview of Cardura XL in Males > 75 years of age
- Comment 3: Clarification of Dosage strength in first week: 2mg vs. 1mg
- Comment 4: Clarification of Package Insert: Blood Pressure Measurements
- Comment 5: Revised Labeling
- Comment 6: Intra-subject Daily Variability PK Data
- Comment 7: Revised Container Labels
- Two Year Safety Update 2001-2002
- Literature Review 2001-2002
- Publications 2001-2002
- Financial Disclosure
- CMC
- Case Report Forms from study A0351061
- Case Report Tabulations from study A0351061

Based on initial review of this complete response submission some additional clinical comments were conveyed to the sponsor on February 17, 2004:

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

- 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.

- 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 and the lack of information for elderly subjects [redacted]

- 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.

- 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.

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

- Provide additional clinical information and CRF for subject 10010050 who was noted to have an intraventricular conduction delay.

- Provide information on the mean time of Cmax for the first day of use of Cardura XL and justify why [redacted] Cmax at steady state.

The sponsor responded to the previous information requests on May 14, 2004. These responses are assessed in Part C, section 6.

B. Tables Listing the Pivotal Clinical Trials for BPH

The pivotal clinical trials supporting NDA 21-269 are listed in Table 1.

Table 1: Pivotal studies for Cardura XL in benign prostatic hyperplasia.

BPH Studies	Design	Country	# ITT Safety	GITS	Std	Placebo
DAZ-N/S/DK/95-001	Placebo-controlled, parallel-group study, 13 weeks active treatment (GITS vs. Std vs. Placebo) For BPH	Denmark Norway Sweden	795	317	322	156
DAZ-NY-95-001	Parallel-group study, 13 weeks active treatment (GITS vs. Std) For BPH	Belgium Canada Germany Hungary Ireland Italy Poland South Africa UK	678	349	329	0
DAZ-NY-95-001B	Open label phase of DAZ-NY-95-001 (6 months) For BPH	Belgium Canada Germany Hungary Ireland Poland S Africa UK	295	149	146	0
A0351061	Double-blind placebo controlled 3-way crossover single dose of GITS 4mg, Std 1mg or placebo For Safety – Blood Pressure and Pulse with first day dosing	UK	26	crossover		

Source: Original NDA submission Vol 32, page 9; Vol 38, page 9; Vol 46, page 6
A0351061 electronic submission report page 2

A listing of additional studies is found in section 2 of the appendix.

C. Postmarketing Experience

The postmarketing experience that provides specifics for Cardura XL in addition to doxazosin standard is provided in the sponsor's response to filing request #1. The information on approvals

and launches of 4mg and 8mg Cardura XL in foreign countries is found in Appendix, sections 5 and 6.

D. Literature Review

The following are sponsor submitted literature references in the December 17, 2003 submission with key findings:

NIH NEWS RELEASE

Two drugs commonly used to treat benign prostatic hyperplasia (BPH) are more effective in combination than alone to prevent progression of this condition, according to results of a multi-center National Institutes of Health clinical trial being presented at the American Urological Association (AUA) meeting in Orlando on May 28, 2002.

The Medical Therapy of Prostatic Symptoms (MTOPS) Trial found that compared to placebo the 5 alpha-reductase inhibitor finasteride (Proscar) and tx-1 receptor blocker doxazosin (Cardura) together reduced the risk of BPH progression by 67 percent. The risk of progression was reduced by 39 percent with doxazosin alone and by 34 percent with finasteride alone.

Medical officer's comments: Although this combination therapy has been recently approved, Pfizer has not presented any formal submission of this data nor proposed [redacted]

Kirby R.S. BJU Int. 2003 Jan: 91(1): 41-4. **A randomized, double-blind crossover study of tamsulosin and controlled-release doxazosin in patients with benign prostatic hyperplasia**
(52 patients randomized)
Conclusion:
Treatment with doxazosin-GITS was significantly more effective than tamsulosin in relieving lower urinary tract symptoms. The adverse events reported are as follows:

Adverse event	Doxazosin-GITS % (*n* = 48)	Tamsulosin % (*n* = 50)
Dizziness	8	8
Headache	6	8
Asthenia	6	12
Somnolence	4	2
Hypotension	4	2
Rhinitis	2	4
Retrograde ejaculation	0	2

TABLE 3
A summary of common treatment-emergent, treatment-related adverse events

Medical officer's comments: This study was not proposed as a superiority study under NDA 21-269. The sponsor is not proposing superiority of doxazosin GITS over tamsulosin in their proposed label. The study does not appear to have any new safety signals.

NDA 21-269

Chrischilles E, Rubenstein L, Chao J, Kreder KJ, Gilden D, Shah H.
Clin Ther. 2001 May; 23(5): 727-43. **Initiation of nonselective alpha1-antagonist therapy and occurrence of hypotension-related adverse events among men with benign prostatic hyperplasia: a retrospective cohort study.**
CONCLUSIONS: Initiation of nonselective alpha1-antagonist therapy for the treatment of BPH increases the risk of a cluster of clinical events consistent with vascular alpha-adrenoreceptor antagonism. This effect is seen during a 4-month period around the initiation date. Prior initiation of other antihypertensive medication increases this effect. Urologists should consult with a patient's primary care physician about use of other antihypertensive agents before initiating nonselective alpha1-antagonist therapy for BPH.

Medical officer's comments: Including information about asking patients concerning other antihypertensive use appears appropriate for the label.

Benign enlargement of the prostate is a malady of older males, reaching an estimated prevalence of 90% in patients aged over 70 years. Many of these patients are treated with alpha blockers, which can lower blood pressure significantly. We report on a 64-year-old man who developed a right hemiparesis after taking one dose of doxazosin 4 mg for prostatic symptoms. A CT scan of the brain and carotid ultrasound studies were normal. He recovered most of his neurological function within a few days. Ambulatory blood pressure rnonitoring on doxazosin 2 rng revealed a striking sleep blood pressure reduction. (*J Natl Med* Assoc, 2002;94:1-4,)

Medical officer's comments: This patient had been treated with the 2mg dose of doxazosin for a number of months prior to this event. After taking one 4mg tablet at bedtime the patient awoke with findings of a right hemiparesis. Three weeks after this event the patient was found to have a nocturnal decline in blood pressure while resuming doxazosin 2mg. Doxazosin was then discontinued. Subsequent to discontinuation the patient has remained free of neurological symptoms for three years while taking aspirin.

The circadian variation in blood pressure is described in the following abstract from Elliot WJ in Am J Hypertens 1999 Feb; 12:43S-49S:

In most people, blood pressure (BP) displays a characteristic diurnal pattern, with a decline during sleep and a sharp increase around the time of awakening. The early morning surge in BP is synchronous with an increase in the risk of catastrophic cardiovascular events, including acute myocardial infarction, sudden cardiac death, and stroke. Although most clinical investigations have centered on modulating or even preventing the morning surge, emerging data suggest that it may be important to avoid nocturnal hypotension, especially in elderly patients and in those with established atherosclerotic disease. Considerable evidence has been accumulated to suggest that excessive lowering of BP at night (whether naturally or through the use of antihypertensive medications) can result in untoward ischemic phenomena, including silent cerebral damage (Binswanger's disease) or ophthalmologic symptoms (eg, anterior ischemic optic neuropathy). Controlled-onset extended-release verapamil, through its

unique delivery system, tends to diminish the morning BP surge, whereas it preserves a normal nocturnal BP decline; its effect on preventing early morning cardiovascular catastrophes (while preserving relatively normal nocturnal BP) is currently being tested in a large, international clinical trial.

No other cases of this adverse event were noted in the clinical studies or postmarketing safety reports of doxazosin or doxazosin GITS.

V. Clinical Review Methods

A. How the Review was Conducted

The review was conducted utilizing the following:
- Review of the electronic submission
- Independent data analysis utilizing JMP software
- Independent review of the literature
- Safety review utilizing the AERS database
- Consultative meetings regarding the data findings and clinical issues
- Interactions with sponsor for clarification and additional data

B. Overview of Materials Consulted in Review

Materials consulted in review include:
- Electronic submissions for NDA 21-269 (17 Dec 2003 complete response)
- Sponsor's responses to requests sought at the time of the filing meeting
- Consultation reports from the other disciplines
- Pubmed searches and journal review

C. Overview of Methods Used to Evaluate Data Quality and Integrity

Methods used to evaluate data quality and integrity include
- Checking the electronic database with JMP analysis
- Seeking additional safety information from the sponsor (noted at time of filing review)

D. Were Trials Conducted in Accordance with Accepted Ethical Standards

Study A0351061 was conducted in compliance with the ethical principles originating from the Declaration of Helsinki, Edinburgh version 2000, and with local laws and regulations relevant to the use of new therapeutic agents in the country of conduct.

The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of the participating clinical site approved the protocol, consent documents, and protocol amendments. IRB/IEC approval was received prior to shipping drug to the clinical site. The Investigator was required to keep his IRB/IEC informed of the progress of the study and the occurrence of any serious and/or unexpected events. The IRB/IEC responsible for monitoring this study is:

E. Evaluation of Financial Disclosure

In the original submission adequate documentation was submitted to comply with 21 CFR 54. There was no disclosure of financial interests that could bias the outcome of the trials in NDA 21-269.

In the supplemental NDA (Dec 17, 2003 submission, protocol A0351061) none of the 5 listed investigators from the [redacted] had financial information to disclose.

VI. Integrated Review of Efficacy

A. Efficacy Conclusions

See the executive summary (derived from original submission)

B. General Approach to Review of the Efficacy of the Drug

See the medical review for the original submission.

C. Detailed Review of Trials by Indication

A detailed review of the following trials is found in the medical reviews filed in DFS at the time of the approvable decision on the original submission. The two pivotal clinical trials on which efficacy is based are listed in Table 2. Summary statements for efficacy derived from the prior review are included in the executive summary.

Table 2: Studies for Cardura XL in which BPH efficacy was determined

BPH Studies	Design	Countries	# Randomized	GITS	Std	Placebo
DAZ-N/S/DK/95-001	Placebo-controlled, parallel-group study, 13 weeks active treatment (GITS vs. Std)	Denmark Norway Sweden	795	317	322	156
DAZ-NY-95-001	Parallel-group study, 13 weeks active treatment (GITS vs. Std), followed by six month open-label phase (GITS only)	Belgium Canada Germany Hungary Ireland Italy Poland S Africa UK	680	350	330	0

VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Medical officer's comments:

There is a large safety database for the doxazosin GITS formulation. There is over 2800 months exposure in clinical trials and over 460,000 patient-years in postmarketing experience.

The sponsor has adequately addressed the agency's requests for safety information related to early dosing of Cardura XL.

There is no evidence that Cardura XL presents an increased safety risk compared to Cardura either with initial dosing or overall. This evidence is derived from the following:

- ***Combined safety data from the pivotal BPH and hypertension trials***
- ***Safety data from the initial dosing blood pressure study A0351061***
- ***Two year safety update (2001-2002)***
- ***Postmarketing safety report (Oct 2002 through Sept 2003)***

B. Description of Patient Exposure to Study Drugs

The standard formulation of doxazosin has been marketed for approximately 13 years with over two billion patient-days experience. The safety database for the GITS formulation consists of over 2800 months of exposure in clinical trials and over 460,000 patient-years exposure in post-marketing information.

C. Methods and Specific Findings of Safety Review

Medical officer's comments: Most of the following information found in the sections 1 through 6 of Part C are directly taken from the sponsor's submission. This reviewer's comments are found in bolded italicized text.

1. Overview of safety in the treatment of BPH

See the overview discussion in section I (Introduction)

2. Safety Information From the Blood Pressure Trial (Study A0351061)

Medical officer's comments: In this section the sponsor's response to critical deficiency #1 will be presented. Study A0351061 was designed and submitted to address the following deficiency:

"There is inadequate information to determine the direct effect of a first dose of Cardura XL 4mg on blood pressure and pulse, versus Cardura 1mg, versus placebo, around the time of maximum plasma concentration."

a) Study Title:
A Double Blind, Randomized, 3-Way Crossover Study To Investigate Supine and Standing Blood Pressure and Pulse During the 24 hours Following a Single Dose of Doxazosin GITS 4 mg vs Doxazosin Standard Formulation 1 mg vs Placebo

b) Principal Investigators:
Philippe Bareille (Original PI, replaced during study)
Emanuel Engmann (Originally a subinvestigator who became PI as replacement)
[redacted]

c) Primary Objective:
To investigate supine and standing blood pressure and pulse at the time of maximum plasma drug concentration and during a 24-hour period following a single dose of doxazosin GITS 4 mg vs doxazosin standard formulation 1 mg vs placebo

Medical officer's comments: The sponsor considered the supine and standing blood pressure and pulse to be efficacy evaluations. This reviewer considers these findings as primary safety endpoints in regard to first day of use for Cardura XL 4mg.

d) Secondary Objective:
To investigate the safety and toleration of a single dose of doxazosin GITS 4 mg vs doxazosin standard 1 mg

e) Study Design:
A Phase IV double blind, placebo controlled, randomized, 3-way crossover study administering single doses of doxazosin GITS 4 mg, doxazosin standard 1 mg, and placebo at one week intervals.