f) Study Population:
Twenty-four (24) male subjects are to be enrolled in this study at one center in the United Kingdom.

g) Inclusion Criteria
Male subjects meeting all criteria listed below are to be included in the study.

- Age 40 to 75 years.
- Volunteers with no unstable clinically significant medical conditions after review of pre-study laboratory data, medical history review, and full physical examination.
- Weight between 60 and 100 kg and within the permitted range for their height (i.e., between 18-29), using Quetelet's index-weight (kg)/height^2 (m).
- Supine blood pressure less than 140/90 mmHg.
- Written informed consent obtained.

h) Exclusion Criteria:
Subjects presenting with any of the following are not to be included in the study.

- Supine blood pressure ≥ 140/90 mmHg; subjects could continue antihypertensive medications provided supine blood pressure was < 140/90 mmHg.
- Supine blood pressure < 100/65 mmHg [or orthostatic hypotension (change of ≥20mmHg systolic blood pressure or ≥10mmHg diastolic blood pressure upon standing) at screening or at any pre-dose blood pressure measurement]. ***Medical officer's comments: The segment in brackets was added as an amendment on November 4, 2002. The change is acceptable.***
- Donation of blood or blood products for transfusion during the 30 days prior to initiation of treatment with study drug (if applicable), at any time during the study or within 1 month after completion of treatment.
- Participation in any other studies involving investigational or marketed products, concomitantly or within 30 days prior to entry in the study.
- Ongoing treatment with doxazosin or doxazosin treatment within the last 30 days.
- Treatment with concomitant medication if its dosage was not stable for at least 30 days prior to study entry and throughout the study.
- History of clinically significant allergies, especially drug hypersensitivity.
- Significant gastrointestinal stricture or any disease which may have affected absorption.
- Unable and/or unlikely to comprehend and/or follow the protocol.

- Alcohol abuse and/or any other drug abuse.
- Smoke more than 5 cigarettes (or equivalent amount of tobacco) per day.
- A previous history of intolerance or hypersensitivity to the study drug(s) (including comparator) or to drugs with similar chemical structures.
- Positive HbsAg and HbcAb results; positive anti-hepatitis C virus serology (as determined by a multi-antigen EIA).

i) Randomization (Treatment) Arms

Subjects are to be randomized to one of the following sequences:

Sequence	Period 1	Period 2	Period 3
I	A	B	C
II	B	C	A
III	C	A	B

Where the treatments administered are:
A = doxazosin standard 1mg
B = doxazosin GITS 4mg
C = placebo

j) Schedule of Events

The Schedule of Events for Study A0351061 are shown in Table 3

Table 3: Study Procedures

Study Procedures	Screening	Study Period			Follow -up
		1	2	3	
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Day -7	Days -1,0,1	Days 6,7,8	Days 13,14,15	Day 21
Obtain Written Informed Consent	X				
Medical History	X				
Concomitant Medication	X	X	X	X	X
Physical Exam	X				X
Height	X				
Weight	X				X
Supine and Standing Blood Pressure/Pulse Rate	X	X[a]	X[a]	X[a]	X
12-lead ECG	X				X
Laboratory Safety Tests (includes CBC,					
Clinical Chemistry, and urine dipstick)	X				X
Evaluate Inclusion and Exclusion Criteria	X				
Urine Drug Screen via [redacted]					
A and Urine Creatinine	X				
Urine Drug Screen via [redacted]		X[b]	X[b]	X[b]	
Creatinine					
HbsAG, HbcAb, Antihepatitis C Virus	X				
Serology, HIV					
Study Drug Dosing		X	X	X	
PK Blood sampling[a]		X	X	X	
Schedule Next Visit	X	X	X	X	
Adverse Events		X	X	X	X
Clinical Summary					X

a = 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12,14, 16, and 24 hours post dose
b = Pre-dose only
Source: Page 40 Study report A0351061

k) Prior and Concomitant Therapy

A reasonable effort is to be made to document any medications the subject took for at least 30 days prior to study entry (first dose). Subjects are prohibited from participating in any other studies involving investigational or marketed products, concomitantly or within 30 days prior to study entry. Subjects are prohibited from ongoing treatment with doxazosin or doxazosin treatment within the last 30 days. Subjects are to be allowed treatment with concomitant medication if its dosage is stable for at least 30 days prior to study entry and throughout the study. Subjects are to be advised not to consume caffeine, methylxanthines, grapefruit, grapefruit juice and alcohol during the 48 hours prior to each dose and throughout each study confinement period. All subjects are to be questioned about concomitant medication use at each clinic visit.

l) Primary Endpoint

The primary endpoint is the mean orthostatic change in blood pressure at the time of peak plasma drug concentration (tmax). Orthostatic changes in blood pressure are to be calculated by subtracting supine blood pressure (BP) from standing BP for each subject. Negative orthostatic changes in blood pressure indicate a drop in blood pressure upon standing. Orthostatic changes in pulse rate are calculated by subtracting supine pulse rate from standing pulse rate. Positive orthostatic changes in pulse rate indicate an increase in pulse rate upon standing. The analysis timepoint of interest is the timepoint to attain Cmax.

Supine and standing blood pressure and pulse are to be measured at the following times: 0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, and 24 hours post dose. Supine blood pressure and pulse are to be measured after the subject had been supine for 10 minutes. Two measurements are to be taken. If the difference between the two measurements is greater than 10/5 mmHg, a third measurement is to be taken. Standing blood pressure and pulse are measured after the subject has been standing for 2 minutes. Two measurements are to be taken. If the difference between the two measurements is greater than 10/5 mmHg, a third measurement is to be taken.

At each scheduled (nominal) timepoint, the mean systolic BP, diastolic BP, and pulse rate are calculated as the average of the collected readings at that timepoint.

All blood pressure and pulse measurements are to be made using automated [redacted] monitors.

m) Secondary Endpoints

- Maximum orthostatic change in systolic BP and diastolic BP over a 24-hour period. This is calculated as the maximum drop (negative orthostatic change) or, the smallest increase (if no drop in blood pressure is observed over the entire 24 hours) occurring at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, and 24 hours post dose.

- Time to maximum orthostatic change in systolic BP and diastolic BP. The time of interest is that time among 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, and 24 hours post dose at which maximum orthostatic change occurs.

- Mean orthostatic change in pulse rate at the time of Cmax. The orthostatic change is to be calculated by subtracting supine pulse rate from standing pulse rate for each subject. The analysis timepoint of interest is the timepoint to attain Cmax.

- Maximum orthostatic change in pulse rate over a 24-hour period. This maximum is to be calculated as the maximum of orthostatic change occurring at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, and 24 hours post dose.

n) Statistical Methods

The sample size chosen for this study was not based on formal power calculations. The number of subjects, 24, is typical for a PK/PD study and was discussed with the FDA in a teleconference on 03 June 2002.

o) Pharmacokinetic Parameters
Cmax and tmax are the only two pharmacokinetic parameters that will be determined for doxazosin over the 24-hour period after a single dose of study medication. These parameters are to be determined directly from the observed plasma drug concentration. Cmax is to be calculated as the maximum observed plasma drug concentration. Tmax is to be calculated as the nominal time at which Cmax occurs. If Cmax occurs at more than one timepoint, Tmax is to be assigned as the time of first occurrence of Cmax. For statistical analysis purposes, Tmax for placebo is to be designated as the Tmax of the doxazosin standard 1 mg.

p) Safety Assessments

Medical officer's comments: Safety assessments were to include:
- ***Hematology***
- ***Clinical chemistry***
- ***Urine drug screen***
- ***Hepatitis and HIV screening***
- ***Monitoring for adverse events, abnormal laboratory tests and abnormal physical findings***

As mentioned earlier the sponsor considered blood pressure and pulse findings as efficacy results but I have included these finding under safety in this review

q) Protocol amendments

The following protocol amendments were submitted to protocol A0351061 under IND 32,633:
- Serial #s 243, 245 = New investigator or investigator revision to form 1572
- Serial # 247 = Change in protocol (Amendment date November 4, 2002)

Medical officer's comments: The change in protocol entailed adding orthostasis to the exclusion at screening and adding additional toxicology for drugs of abuse at screening. These changes are acceptable.

r) Study Findings

(1) Subject Disposition
Twenty-four (24) of 50 screened subjects completed the study. There were two replacements (Subjects # 30 and # 44) for two subjects who were withdrawn. One subject (#12) was

withdrawn (after receiving his second treatment) due to a protocol violation (unstable cardiac condition made known to the investigator after randomization). The other subject (# 9) was withdrawn prior to receiving his second treatment due to an adverse event (orthostatic hypotension prior to scheduled dosing- deemed not related to study drug). The study dates extended from 11 October 2002 to 19 December 2002.

Medical officer's comments: Subjects # 9 and #12 are discussed further in the sponsor's response from filing meeting requests.

(2) Demographic Findings
Of the 26 subjects in this study, 25 (96%) were white and 1 (4%) was black.

The age breakdown is as follows:
40-44 years 8 subjects
45-64 years 13 subjects
65-70 5 subjects

Medical officer's comments: The mean age derived by this reviewer from the demographic dataset (DEMOG) using JMP analysis was 52.4 years. The mean weight derived by this reviewer from the demographic dataset (DEMOG) using JMP analysis was 78.2 kilograms. Although having more subjects over the age of 65 would have been better, this reviewer does not feel that the sponsor needs to repeat the study with more elderly subjects.

(3) Study Drug Discontinuations
As mentioned in the disposition section, two subjects were discontinued from the study drug:
- Subject 9 (orthostatic hypotension prior to scheduled second dose)
- Subject 12 (protocol violation, unstable cardiac condition)

(4) Protocol Deviations

The protocol deviations include the following categories:
- **Fewer than 2 BP or HR readings at each assessment post dose** (33 instances recorded - of these 33 time points of fewer measurement, 7 time points had no measurement taken)
- **Timing of BP measurement last supine reading <2 minutes before first standing reading** (4 instances recorded)
- **Mean BP <100/65 or >140/90 at screening** (one instance, mean supine BP was 147/92)
- **Weight not in 60-100kg range or not in BMI 18-29 range** (one instance, wt = 58kg)
- **Disallowed medications <= 30 days before enrollment** (5 instances – paracetamol, multivitamins, Viagra, antacid and cod-liver oil)
- **Inclusion/Exclusion crit**eria (one instance, subject with unstable cardiac condition)
- **Subject screened for entry into study more than once** (two instances –subject 50 and 17 are the same patient – subject 36 and 14 are the same patient)
- **Time of dosing not 8-9AM** (one instance recorded, dose at 9:30AM)

Source: Pages 518 to 520; Study report A0351061

Medical officer's comments: The protocol deviations reported are not felt by this reviewer to have a significant outcome on the study. There were only 7 instances where no blood pressure was obtained. There should be no residual effect of the Viagra on blood pressure once the subject began the study.

(5) Number of subjects per study sequence

The 2 subjects added (Subject Id #s 30 and 44), as replacements for Subject ID #s 9 and 12, were not assigned the treatments of the subjects they replaced but were instead assigned to a Sequence based on the pre-established randomization schedule. Table 4 below specifies the number in each sequence.

Table 4: Number of subjects assigned per sequence

	Sequence 1*	Sequence 2**	Sequence 3***	Total
Randomized to a sequence (received at least one treatment)	9	8	9	26
Completed study (administered all three treatments)	9	7	8	24

* Sequence I: Doxazosin STD→Doxazosin GITS→Placebo

** Sequence II: Doxazosin GITS→Placebo→Doxazosin STD

*** Sequence III: Placebo→Doxazosin STD→Doxazosin GITS.

(6) Comparison of the Three Sequences in Regard to Baseline Blood Pressure and Pulse

Table 5 below shows that the systolic blood pressure, the diastolic blood pressure, and the pulse rate measured at baseline (Hour 0, Period 1) do not differ significantly among the 3 randomized sequences for both supine and standing positions. The mean baseline diastolic blood pressure increased 7 to 10mmHg from supine to standing positions and mean baseline pulse rate increased 13 to 19bpm from supine to standing positions. Overall, the results validate that the baseline measures in blood pressure and pulse rate among the 3 groups of subjects (randomized sequences) are similar and comparable.

Table 5: Baseline Blood Pressure and Pulse

		MEAN (SD)			
Vital Sign (Units)	Position	Sequence I[1] (N=9)	Sequence II[1] (N=8)	Sequence III[1] (N=9)	P-Value[2]
Systolic (mmHg)	Supine	118.8 (14.32)	119.5 (11.45)	119.9 (14.78)	0.987
	Standing	122.0 (17.36)	120.3 (11.43)	120.7 (11.35)	0.966
Diastolic (mmHg)	Supine	73.0 (6.23)	70.3 (5.31)	70.9 (10.49)	0.749
	Standing	83.4 (7.46)	77.2 (7.05)	80.3 (9.24)	0.292
Pulse Rate (bpm)	Supine	59.4 (10.30)	59.8 (8.63)	60.2 (8.49)	0.984
	Standing	72.4 (13.87)	74.3 (20.10)	78.9 (12.68)	0.666

Source: Page 53 Study report A0351061

Medical officer's comments: This reviewer concurs with the sponsor's assessment of the comparability of the three sequences at baseline.

(7) Assessment of Mean Orthostatic Change at the Time of Maximum Plasma Drug Concentration

The mean orthostatic change both in systolic blood pressure and diastolic blood pressure at the time of Cmax did not differ significantly among the 3 treatments (p-values = 0.359 and 0.176, respectively). All subjects experienced an increase in pulse rate upon standing at the time of Cmax. There was a difference detected when comparing both doxazosin regimens to placebo. Statistical comparison of doxazosin GITS 4 mg to doxazosin standard 1 mg was not significant in regard to pulse changes. The findings are presented in Table 6.

Table 6: Summary of Mean Orthostatic Change at the Time of Maximum Plasma Concentration

Vital Sign (units)	Statistics	Doxazosin GITS (N = 24)	Doxazosin STD (N = 24)	Placebo (N = 24)	P value
Systolic BP (mmHg)	LSMean (SE)	-1.6 (1.92)	1.2 (1.92)	-0.9 (1.92)	0.359
Diastolic BP (mmHg)	LSMean (SE)	4.3 (1.34)	6.4 (1.34)	7.5 (1.34)	0.176
Pulse Rate (bpm)	LSMean (SE)	21.3 (2.14)	21.5 (2.14)	15.4 (2.14)	0.009

Source: Page 58 Study report A0351061

Medical officer's comments: The GITS and STD formulations are comparable in this analysis.

To investigate any orthostatic ***drop*** at the time of Cmax in systolic blood pressure and diastolic blood pressure, descriptive statistics such as proportion of subjects who experienced any drop in blood pressure at the time of Cmax, mean, standard deviation, median, minimum, and maximum were generated and evaluated. Results from subgroup analysis of mean orthostatic ***drop*** in blood pressure at the time of Cmax are presented in Table 7 below.

Table 7: Summary of the Subjects Who Experienced any Orthostatic Drop in Blood Pressure at the Time of Maximum Plasma Concentration (tmax)

BP (mmHg)	Statistics	Doxazosin GITS	Doxazosin STD	Placebo	Treatment[1]
Systolic BP	Proportion n/N (%)	14/24 (58.3%)	7/24 (29.2%)	10/24 (41.7%)	0.050
	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%)	0.022
	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 A0351061

The proportion of subjects with any orthostatic drop in systolic blood pressure at the time of Cmax was significantly different among the 3 treatments (p-value = 0.050; doxazosin GITS: 58.3%; doxazosin standard: 29.2%; placebo: 41.7%). However the magnitude of the mean orthostatic drop was similar following all three treatments (approximately 7, 10, and 9mmHg with doxazosin GITS, doxazosin standard, and placebo, respectively).

The proportion of subjects with any orthostatic drop in diastolic blood pressure at the time of Cmax was statistically different among the 3 treatments (p-value = 0.022). Statistical comparison between doxazosin GITS and placebo was significant (p-value = 0.011) while that between doxazosin GITS and doxazosin standard and that between doxazosin standard and placebo was not significant (p-values = 0.720 and 0.100, respectively). The observed mean orthostatic drop was approximately 6, 2, and 3mmHg following doxazosin GITS, doxazosin standard, and placebo treatments, respectively.

Medical officer's comments: It is noteworthy that of the subjects with any orthostatic drop in blood pressure that the GITS arm showed a higher percentage. However, the mean magnitude of the drop was slightly less than that seen with doxazosin standard.

(8) Assessment of Maximum Orthostatic Change in Blood Pressure and Pulse Rate over a 24-Hour Period

The maximum orthostatic change in blood pressure and pulse rate over a 24-hour period was assessed and is presented in Table 8 below:

Table 8: Summary of Maximum Orthostatic Change in Blood Pressure and Pulse Rate over 24-Hour Period

Vital Sing (units)	Statistics	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)	0.396
Diastolic BP (mmHg)	LSMean (SE)	-1.7 (1.10)	-1.8 (1.10)	1.0 (1.10)	0.046
Pulse Rate (bpm)	LSMean (SE)	32.2 (2.61)	32.6 (2.61)	26.3 (2.61)	0.001

Source: Page 61 Study report A0351061

Medical officer's comments: The GITS and STD formulations are comparable in this analysis. Again there is a difference when comparing both doxazosin arms to placebo.

(9) Assessment of Time to Maximum Orthostatic Change in Blood Pressure and Pulse Rate

The time to maximum orthostatic change in blood pressure and pulse rate over a 24-hour period was assessed using non-parametric Friedman's test. The corresponding statistical results are presented in Table 9.

Table 9: Summary of Statistical Results of Time (Hours) to Maximum Orthostatic Change in Blood Pressure and Pulse Rate

Vital Sign (units)	Statistics	Doxazosin GITS (N=24)	Doxazosin STD (N=24)	Placebo (N=24)	P value
Systolic BP (mmHg)	Mean (SD)	8.3 (4.86)	8.4 (6.27)	7.1 (4.25)	0.879
Diastolic BP (mmHg)	Mean (SD)	8.9 (5.95)	7.1 (5.69)	7.7 (7.08)	0.368
Pulse Rate (bpm)	Mean (SD)	7.4 (3.15)	8.4 (6.24)	11.7 (6.16)	0.011

Source: Page 63 Study report A0351061

Medical officer's comments: From the information in the previous two tables, it appears that the maximum orthostatic changes occur around 8-9 hours following GITS administration. Individual patients can vary when symptoms occur.

(10) Assessment of 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 for ITT Population

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 a 24-hour period was assessed using a generalized linear model and utilizing generalized estimating equations to account for any correlations within a subject. The results are given in Table 10.

Table 10: 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 for ITT Population

Event	Statistics	Doxazosin GITS	Doxazosin STD	Placebo	Treatment[1]
	N	24	24	24	
Drop ≥20 mmHg in SBP	n (%)	6 (25.0%)	3 (12.5%)	3 (12.5%)	0.415
or ≥10mmHg in DBP	SE	0.09	0.07	0.07	

The six GITS subjects in the preceding table are subject #s 10, 24, 41, 44, 45 and 50. Table 11 shows the time of the occurrence, AEs and T max.

Table 11: GITS subjects with a Drop ≥20mmHg in Systolic Blood Pressure or a Drop ≥10mmHg in Diastolic Blood Pressure

Subject ID	Study	Time Postdose (hrs)	Supine SBP/DBP/HR (mmHg/mmHg/bpm)	Standing SBP/DBP/HR (mmHg/mmHg/bpm)	AE	Tmax (hrs)
10	GITS	16			No	16.0
24	GITS	0 (pre)			No	16.0
		1			No	16.0
		2			No	16.0
		3			No	16.0
		4			No	16.0
		5			No	16.0
		6			No	16.0
		7			No	16.0
		8			No	16.0
		9			No	16.0
		10			No	16.0
		12			No	16.0
		14			No	16.0
		16			No	16.0
		24			No	16.0
41	GITS	9			No	14.0
44	GITS	7			No	14.0
45	GITS	6			No	14.0
50	GITS	6			No	14.0

Source: Table 8.2.4B Study report A0351061

Medical officer's comments: There are no reported AEs associated with these changes in pressure. The Tmax for all six is in the 14-16 hour time frame. Subject 10 only had these blood pressure changes at Tmax while the rest either had multiple episodes (#24) or showed the blood pressure changes a number of hours before Tmax. Subject #9 was not included in the prior table since this subject was dropped. The blood pressure and pulse findings for subject #9 are shown in Table 12.

Table 12: Blood pressure and pulse changes for Subject #9

Subject ID	Study Treatment	Time Postdose (hrs)	Supine SBP/DBP/HR (mmHg/mmHg/bpm)	Standing SBP/DBP/HR (mmHg/mmHg/HR)	AE Present	AE WHOCODE Name	Tmax (hrs)
09	GITS	3			Yes	Hypotension Postural	5.0
		4			Yes	Hypotension Postural	5.0
		5			Yes	Hypotension Postural	5.0
		7			Yes	Hypotension Postural	5.0
		8			Yes	Hypotension Postural	5.0
		16			Yes	Hypotension Postural	5.0
		24			Yes	Hypotension Postural	5.0

The 3 subjects using standard doxazosin and encountering a drop ≥20mmHg systolic or a drop ≥10mmHg diastolic are listed below in Table 13.

Table 13: Relationship of Doxazosin STD Subjects with a Drop ≥20mmHg in Systolic Blood Pressure or a Drop ≥10mmHg in Diastolic Blood Pressure showing Orthostatic Change in Blood Pressure, Treatment-Emergent Adverse Event and Tmax

		Orthostatic Change in Blood Pressure					
Subject ID	Study Treatment	Time Postdose (hrs)	Supine SBP/DBP/HR (mmHg/mmHg/bpm)	Standing SBP/DBP/HR (mmHg/mmHg/HR)	AE Present	AE WHOCODE Name	Tmax (hrs)
01	STD	4			Yes	Hypotension Postural Pallor	1.0
10	STD	6			Yes	Dizziness Nausea	3.0
24	STD	0.5			No	No AE Present	4.0
		1			No	No AE Present	4.0
		4			No	No AE Present	4.0

Source: Table 8.2.4B Study report A0351061

Medical officer's comments: Subjects 10 and 24 also had similar blood pressure changes on the GITS formulation (≥20 mmhg SBP or ≥10 mmhg DBP). Subjects 01 and 10 were recorded as having AEs at the time of these blood pressure changes. Subjects 01 and 10 demonstrated the blood pressure changes a number of hours after Tmax. Subject 24 had the blood pressure changes before and at the time of Tmax.

Following administration of placebo 3 subjects (Subject IDs 11, 24 and 50) experienced a drop ≥ 20mmHg in systolic BP. None of the placebo subjects reported any adverse events at the time of the orthostatic change.

(11) Deaths and Serious Adverse Events

There were no deaths or serious adverse events in study A0351061

(12) Adverse Events Leading to Discontinuation from Study

Subject number 09 was randomly assigned to treatment Sequence II (doxazosin GITS 4 mg→placebo→doxazosin STD 1 mg) but only received doxazosin GITS 4 mg) because he was withdrawn prior to receiving his second treatment dose (placebo) due to orthostatic hypotension prior to scheduled dosing.

(13) Clinical laboratory safety findings

The significant lab changes per subject are noted in Table 14.

Table 14: Significant lab changes per subject

Subject No.	Age	Test	Baseline value	Final value
8	67	Urine glucose		
41	48	Urine Hgb		
46	43	Urine pH		
28	48	Total Bilirubin		

Medical officer's comments: There were no significant mean changes in baseline in any of the clinical lab safety tests aside from hematocrit (approximately –1.8). The hematocrit change can be explained by the blood draws. The sponsor did not explain the individual case of the bilirubin elevation. It is unlikely to be related to study drug.

(14) ECG Findings

Medical officer's comments: Subject 18 had an abnormal ECG compared to the screening ECG that was described in the comments as physiological atrial rhythm. ECG data on subject #12 who was discontinued for a history of an ongoing bradycardia evaluation had normal ECGs during the study. Subject #50 had a minor intraventricular conduction delay at the time of screening but a normal follow up ECG later in the study.

(15) Adverse Events

There were a total of 31 treatment-emergent adverse events (AEs) reported by 16 subjects during this study, of which 13 subjects had an AE of mild intensity, 5 subjects had an AE of moderate intensity, and 1 subject (#08) had an AE of severe intensity. The severe AE was glycosuria experienced by Subject # 08 after receiving doxazosin STD 1mg; the Investigator had actually not assigned a severity for this AE and therefore, severity was imputed as severe to be most conservative.

Eight subjects had had treatment-emergent AEs while receiving doxazosin standard of which 5 had an AE that was judged by the PI to be treatment-related. Nine subjects had treatment-emergent AEs while receiving doxazosin GITS, of which 6 had an AE that was considered by the PI to be treatment-related. Three subjects had treatment-emergent AEs while receiving placebo, of which 2 had an AE that was considered by the PI to be treatment-related. Treatment emergent adverse events are found in Table 15.

Table 15: Treatment-Emergent Adverse Events by Subject (Identification Numbers Listed)

	Doxazosin STD	Doxazosin GITS	Placebo
No. of Subjects Dosed	25	25	25
No. of ac/ tr (a) AEs	14/8	14/8	3/2
No. of Subjects with 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 deemed AE to be not treatment related.
Source: page 71 Study A0351061

(16) Timing of Orthostatic BP Changes Versus Treatment-Emergent (All Causality) Orthostatic Adverse Events Versus Time of Maximum Drug Levels (tmax)

Subjects with orthostatic adverse events are listed in Table 16 showing the blood pressure/pulse rate changes and the timing of the orthostatic adverse events in relation to the time of Cmax. Of the 5 subjects reporting treatment-emergent orthostatic AEs (i.e., hypotension postural and dizziness postural), 4 subjects (01, 09, 10 and 19) had concomitant drops in systolic and/or diastolic blood pressure and/or an increase in pulse rate. The fifth subject (22) had postural dizziness accompanied by a slight increase in blood pressure.

Of the 5 subjects with treatment-emergent orthostatic AEs, 4 did not have any relationship between time of treatment-emergent orthostatic AE and time of Cmax. One subject (19) had postural hypotension occurring at 2.9 hrs post dose with doxazosin standard, and a time of Cmax of 3.0hrs. There does not appear to be any clear relationship between the occurrence of treatment-emergent orthostatic AEs and the time to reach C_{max}.

Table 16: Orthostatic Adverse Events (Onset, Blood Pressure, Pulse and Tmax)

Subject ID	AE Name WHOCODE Term	AE Onset (hrs)	Study Treatment[a]	Supine SBP/DBP/HR (mmHg/mmHg/bpm)[b]	Standing SBP/DBP/HR (mmHg/mmHg/bpm)[b]	Tmax (hrs)
01	Hypotension Postural[c]	3.9	A			1.0
09	Hypotension Postural[c]	2.92	B			5.0
10	Dizziness[c]	5.9	A			3.0
	Nausea[c]	5.9	A			3.0
	Skin Cold Clammy[c]	15.9	A			3.0
19	Hypotension Postural[c]	2.9	A			3.0
22	Dizziness Postural[c]	0.37	C			NA

SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = pulse rate; NV = No value recorded/available.
a Study Treatments were: A = Doxazosin STD 1 mg, B = Doxazosin GITS 4 mg, and C = Placebo.
b Vital sign measurement for scheduled timepoint closest to time of AE onset.
c AE deemed by PI to be a treatment-related AE.
Source: Page 73 Study report A0351061

Medical officer's comments: Subjects 01 and 10 demonstrated the vasodilatory adverse events a number of hours after Tmax. Subject 19 showed vasodilatory adverse events at the time of Tmax.

Subject 09 is the only subject in the GITS arm with recorded vasodilatory adverse events. However this was the subject who was discontinued due to evidence that the subject also showed orthostatic hypotension at baseline with no treatment given. Subject 09 had vasodilatory events both before, during and after Tmax.

(17) Statistical Issues

Post hoc assessment of study power showed that with 24 subjects and a power of 80 %, with an alpha of 0.05 and an observed standard deviation of 5.88 for diastolic blood pressure and 6.94 for systolic blood pressure, a difference between active treatments in the orthostatic change in diastolic blood pressure of 4 mmHg and difference of 5 mmHg in orthostatic change in systolic blood pressure would be detected. There would be almost 100 % power to detect a 10 mmHg difference between active treatments in orthostatic change in diastolic and systolic blood pressure.

All hypothesis testing was carried out at the 5% level of significance (unless otherwise specified) using standard hypothesis testing methodology for the given null and alternative two-sided hypothesis. Results were declared statistically significant if the p-values resulting from these hypothesis tests were less than or equal to 0.05.

Pairwise treatment comparisons, namely doxazosin GITS 4 mg vs doxazosin standard 1 mg (primary comparison of interest), doxazosin GITS 4 mg vs placebo, and doxazosin standard 1 mg vs placebo, were performed using the least squares means from the ANOVA at 5% level of significance. Student's t-test was used for carrying out treatment comparisons. In addition, 95% confidence intervals (CIs) for these pairwise mean comparisons were obtained.

Medical officer's comments: Despite the small numbers in this trial and the post hoc statistical analysis, this reviewer feels that the data (frequent monitoring of blood pressure and pulse in the first 24 hours) is sufficient to address deficiency number 1 in the approvable letter and provide guidance in regard to the proper labeling of Cardura XL. The crossover design allowed a better comparison of doxazosin GITs vs. doxazosin STD vs. placebo.

3. Comparative Safety information from the First Week of Use

In this section the sponsor's response to critical deficiency #2 will be presented.

Critical Deficiency #2 stated the following:

"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."

Medical officer's comments: The sponsor's response includes the following:

Analysis of adverse events day 1, days 2-7 and days 8+ for doxazosin GITS, doxazosin STD and placebo (specific analysis of orthostatic events) in studies DAZ-NY-95-001, DAZ-N/S/DK-95-001, [redacted]

Analysis of adverse events in three other GITS studies (without STD comparator): DAZNY-96-014, A0351027, A0351029

a) Analysis of DAZ-NY-95-001, DAZ-N/S/DK-95-001, [redacted]

A pooled analysis of adverse events from the four doxazosin GITS pivotal trials (two BPH and two HTN) was conducted. This analysis included a total of 2180 patients: 984 received doxazosin GITS, 964 received doxazosin standard, and 232 received placebo. The listing of vasodilatory and cardiovascular events in found in Table 17. The timing of the adverse event is day 1, days 2-7 and 8days and beyond.

Table 17: 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.

Table17 (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

The sponsor analyzed those vasodilatory and cardiovascular events that they considered to be orthostatic in nature, i.e. syncope, postural hypotension, and postural dizziness. No orthostatic

events occurred on day 1 with either doxazosin GITS or doxazosin standard. One orthostatic event, syncope, occurred with doxazosin GITS in the first week (day 3). Two orthostatic events occurred with doxazosin standard in the first week (postural dizziness on day 4 and orthostatic dizziness on day 2; both events coded to the COSTART Term of postural hypotension). One orthostatic event, syncope, occurred with placebo on day 7. 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.

Medical officer's comments: The overall incidence for postural hypotension in the BPH efficacy studies was 1.2% for doxazosin GITS, 2.2% for doxazosin STD and 0.6% for placebo. Postural hypotension lead to discontinuation in 3 subjects taking doxazosin GITS and 1 subject taking doxazosin STD.

The sponsor looked at the incidence of hypotension, vertigo, and dizziness by onset day. The rates of hypotension were similar between doxazosin GITS and standard, and were less than 1% with each formulation regardless of onset day, although most of the cases of hypotension began after the first week of therapy. There were no cases of hypotension with placebo.

Medical officer's comments: These events could potentially be related to orthostasis also.

The rates of vertigo on day 1 were similar between doxazosin GITS (0.1%) and standard (0.2%). The rates of vertigo on days 2-7 were also similar between doxazosin GITS (0.4%) and standard (0.5%). After day 7, the incidence of vertigo was less with doxazosin GITS (1.2%) than with standard (3.0%). There were no cases of vertigo on day 1 with placebo. The incidence of vertigo on days 2-7 with placebo (0.4%) was similar to that of doxazosin GITS (0.4%) and standard (0.5%). The incidence of vertigo after day 7 with placebo (0.9%) was similar to that of doxazosin GITS (1.2%).

Medical officer's comments: The overall incidence for vertigo in the BPH efficacy studies was 1.5% for doxazosin GITS, 4.1% for doxazosin STD and 0.6% for placebo. Vertigo lead to discontinuation in 1 subjects taking doxazosin GITS and in 5 subjects taking doxazosin STD.

The rates of dizziness on day 1 were similar between doxazosin GITS (0.5%), doxazosin standard (0.5%), and placebo (0.4%). The rates of dizziness on days 2-7 were also similar between doxazosin GITS (1.3%), doxazosin standard (1.1%), and placebo (0.9%). After day 7, the incidence of dizziness with doxazosin GITS (3.1%) was about half of that with doxazosin standard (6.4%) and about double that with placebo (1.7%).

Medical officer's comments: The overall incidence for dizziness in the BPH efficacy studies was 5.3% for doxazosin GITS, 9.1% for doxazosin STD and 1.9% for placebo. Dizziness lead to discontinuation in 7 subjects taking doxazosin GITS and in 8 subjects taking doxazosin STD.

b) Analysis of DAZ-NY-96-014
In this trial, 48 patients received doxazosin GITS and 50 patients received tamsulosin in a BPH crossover study comparing doxazosin GITS with tamsulosin. This study has been published by Kirby, RS. (see literature review section) In this study, there were no orthostatic events (syncope, postural hypotension, or postural dizziness) on the first day or first week following treatment with doxazosin GITS. The listing includes a patient (#1043-0069) with an adverse event of "collapse" which coded to the COSTART Term "syncope". This "collapse" occurred in a 64-year-old patient on study day 27, three days after doxazosin GITS 4 mg/d had been discontinued. The collapse was attributed to fever and urinary tract infection following cystoscopy. The vasodilatory events by patient number are listed in Table 18.

Table 18: 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

Medical officer's comments: This study again illustrates that vasodilatory adverse events are not limited to a short time after initiation of therapy.

c) Analysis of A0351027
Study A0351027 was a randomized, placebo controlled study to evaluate the onset of action of doxazosin GITS in BPH. This study involved a two week treatment phase with either doxazosin GITS 4mg/d or placebo; 108 patients received doxazosin GITS and 105 patients received placebo. Dosing of study medication occurred at bedtime in this study.

There were no cases of syncope in study A0351027. 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 doxazosin GITS patients with postural hypotension, two had postural hypotension on study day 2 (after one dose the previous evening), one of whom permanently discontinued the study. Two patients had postural hypotension on study day 4 (before that evening's dose), and an additional two patients had postural hypotension after the first week. There was one additional patient (0006 0297) who had postural hypotension based on blood pressure changes upon standing on study day 2 (after one dose of doxazosin GITS 4mg the previous evening) however, the adverse event for this patient was reported as "hypotension", not "postural hypotension" and this patient is included in the incidence of hypotension. Postural hypotension in the placebo patients occurred within the first week (on day 6) in one patient.

The incidence of hypotension was 1.9% in the doxazosin GITS arm and 0% in the placebo arm. The hypotension with doxazosin GITS occurred on study day 2 (after one dose the previous evening) in two patients and resulted in study discontinuation for both patients. One of these patients (0006 0297) actually had postural hypotension (based on blood pressure changes upon

standing) although the adverse event was reported as "hypotension".

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

Vertigo occurred in one patient in the doxazosin GITS group (0.9%) on study days 2 and 8. Vertigo was not reported during placebo treatment.
The line listing of subjects in study A0351027 in Table 19

Table 19: Vasodilatory adverse events for Doxazosin GITS 4mg in study A0351027

Subject / Age	Symptom	On Rx Day	Severity	Action
00010004 77	Feeling shaky	8	Mild	None
00010349 63	Dizziness	4	Mild	None
00020361 58	Dizziness	7	Mild	None
00030045 68	Dizziness	2	Mild	None
00030054 61	Postural Hypotension	15	Mild	None
" "	Dizziness	6, 13	Mild	None
00030342 57	Dizziness	4	Mild	None
00030453 73	Dizziness	4	Mild	None
00030454 68	Dizziness	2,5	Mild	None
00060289 51	Reduced reaction ability in traffic	3	Mild	None
00060295 65	Orthostatic hypotension	4	Mild	None
00060297 76	Hypotension	2	Moderate	Discontinued
00160280 85	Orthostatic hypotension	4,15	Mild	None
00180589 59	Dizziness	2	Mild	Discontinued
00190405 65	Orthostatic hypotension	2, 15	Mild	None
00190409 66	Dizziness	2	Mild	None
00200417 66	Vertigo	2, 8	Mild	None
00200422 60	Dizziness	3	Mild	None
00200424 53	Dizziness	2	Mild	None
00300583 65	Orthostatic hypotension	2	Moderate	Discontinued
00310441 52	Orthostatic hypotension	15	Moderate	None
" "	Dizziness	3	Mild	None

Source: Pages 67-92 "Response Table 41" in the cd2. PDF

Medical officer's comments: This study showed higher percentages of dizziness and orthostatic hypotension than the integrated analysis of the pivotal BPH and hypertensive trials. The severity for most, however, is listed as mild and there is no comparator doxazosin IR arm. No syncopal episodes were recorded. The larger number of events listed as day 2 could be related to the dosing of a controlled release product at bedtime. The bedtime dosing is different from the pivotal BPH trial where doxazosin GITS was taken with breakfast. The labeling should specify to take doxazosin GITS at breakfast.

d) Analysis of A0351029

Study A0351029 was a randomized, placebo controlled study involving hypertensive patients whose blood pressure was not well controlled on their current antihypertensive regimen. This

study involved a six week treatment phase with doxazosin GITS 4mg/d or placebo; 89 patients received doxazosin GITS and 86 patients received placebo.

There were no cases of syncope in study A0351029. Six patients (6.7%) in the doxazosin GITS group experienced postural hypotension compared with 0 in the placebo group. Two of the doxazosin 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 doxazosin GITS.

There were no cases of hypotension within the first week with either doxazosin GITS or placebo. The incidence of dizziness was similar between doxazosin GITS (7.9%) and placebo (7.0%). One case of dizziness in the doxazosin 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 doxazosin 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 doxazosin GITS group experienced vertigo which occurred on day 1 of treatment. The vertigo was reported to occur when rising from sitting to standing. There were no reports of vertigo in the placebo group.

The line listing of subjects in study A0351027 in Table 20.

Table 20: Vasodilatory adverse events for Doxazosin GITS 4mg in study A0351029

Subject	Age	Symptom	On Rx Day	Severity	Action
0002 0002	71	Dizziness	17	Mild	None
0002 0006	54	Orthostatic hypotension	7	Mild	Discontinued
0002 0015	53	Dizziness	1	Mild	None
0002 0043	60	Orthostatic hypotension	28	Mild	Discontinued
0002 0048	61	Orthostatic hypotension	28	Mild	Discontinued
0003 0031	58	Orthostatic hypotension	14, 42	Mild	None
0006 0197	51	Dizziness	15	Mild	None
0007 0134	68	Orthostatic hypotension	1	Mild	None
" "		Dizziness	2	Moderate	Discontinued
0007 0137	31	Orthostatic hypotension	1	Mild	None
0014 0310	69	Vertigo on rising	1	Mild	None
0014 0409	58	Dizziness	13	Moderate	Discontinued
0014 0414	49	Dizziness	42	Mild	None
0015 0306	51	Dizziness	34	Mild	None

Source: Pages 98-127 "Response Table 41" in the cd2.PDF

Medical officer's comments: This study also showed slightly higher percentages of dizziness and orthostatic hypotension than the integrated analysis of the pivotal BPH and hypertensive trials. However the amount of dizziness in the treated group was similar to placebo. Most of the orthostatic hypotensive episodes were described as mild and no syncopal episodes were described. Since this study did not have a comparator arm of subjects well controlled with antihypertensives, I think it is difficult to derive any additional safety labeling comments for use of this product in uncontrolled hypertensives.

4. Clarification of Dosage Strength in BPH pivotal trial

The sponsor was asked to:

"Clarify why some data line listing 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."

Sponsor's Response:

Programming errors in adverse event line listings were corrected to reflect the 1 mg dose during first week of doxazosin standard therapy. However, due to a data entry error for patient 0397 at Investigator site 773, the line listing for study DAZ-NY-95-001 reflects 2mg during the first week; the case report form for this patient documents that the patient took 1mg during the first week, and we have noted this as a footnote to the listing.

Medical officer's comments: The sponsor's response is acceptable.

5. Two Year Safety Update 2001-2002

The original NDA submitted on 20 April 2001 contained a three-year safety update covering the period 31 December 1996 through 31 December 1999. A second safety update was submitted on 06 September 2001 covering the full year 2000. We are now submitting a third safety update covering the years 2001 and 2002. Consistent with the original NDA three year safety update and the second safety update, this safety update for years 2001-2002 contains listings of deaths and other serious adverse events from all BPH and HTN studies that were ongoing during this two-year period as well as from studies that were completed during the two-year period. Narratives for all patients that died or had other serious adverse events from these studies are included in this two year safety update for years 2001-2002.

Studies for which we are providing nonserious adverse event safety information are protocols A0351027, A0351029, and DAZ-NY-96-014 as these are Pfizer New York sponsored studies with readily accessible databases.

a) Deaths in BPH trials

Fourteen patients died during a doxazosin/GITS clinical trial for benign prostatic hyperplasia. Nine patients were receiving doxazosin GITS, 1 doxazosin tablets and 4 were on blinded therapy. Of these, 4 died following a myocardial infarct, 4 from cancer (renal, bladder, pancreas and lung), and one each from respiratory failure, sepsis, suspected pulmonary embolus, suicide, an airplane crash, and a traffic accident.

Doxazosin GITS

1. Case 2002057969 involved a 57 year-old male with benign prostatic hyperplasia, who was being treated with doxazosin GITS 4mg daily when he was killed in an airplane crash in Italy.

2. Case 2002071868 involved a 56 year-old Asian man who received doxazosin GITS 4 mg daily for benign prostatic hyperplasia. He also had hypertension, diabetes mellitus and hyperlipidemia and was being treated with thiazides, atorvastatin and insulin. Beginning on the 17th day of therapy with doxazosin GITS, he developed a common cold followed by pneumonia and sepsis and died in hospital. The investigator considered the event not to be related to study drug.

3. Case A113077 involved a 70 year-old white male with benign prostatic hyperplasia and a history of nephrolithiasis, who received 50 days of therapy with doxazosin GITS 4 mg daily. The next day he suffered a myocardial infarct which led to his death in hospital. The investigator did not consider the event to be related to study drug.

4. Case A116140 involved a 59 year-old white male with benign prostatic hyperplasia and asthma who was receiving theophylline, ipratropium, salmeterol and prednisone. After almost 6 months of therapy with doxazosin GITS 4 mg daily, he was hospitalized with respiratory insufficiency and died the next day. The investigator attributed the patient's death to his asthma.

5. Case A122264 involved a 64 year-old white male with benign prostatic hyperplasia and metastatic hypernephroma who was being treated with tramadol, lorazepam, aceclofenac, ketorolac clodronic and morphine. He had received therapy with doxazosin GITS 4 mg daily for six months. On an unspecified date after discontinuation of study drug, he died as the result of the hypernephroma. The investigator did not consider the event to be related to study drug.

6. Case A126268 involved an 88 year-old white man with benign prostatic hyperplasia, diabetes mellitus, hypertension, carcinoma of the colon and ictus. He also had a history of asthma, hyperlipidemia, hyperuricemia, congestive heart failure, coronary artery disease, orthostatic syndrome, cerebral hemorrhage and renal failure. Treatment included glyceryl trinitrate, aspirin, fenofibrate, glibenclamide, digoxin and buformin. After about 5 weeks of therapy with doxazosin GITS 4 mg daily, he suffered a heart attack and died. The investigator did not consider the event to be related to study drug.

7. Case A126355 involved a 73 year-old white male with benign prostatic hyperplasia, hypertension, and bladder cancer that had been resected about five months prior to initiation of doxazosin GITS. After about 2 months of therapy with doxazosin GITS 4 mg daily, he was hospitalized with worsening of his bladder tumor. Study drug was permanently

discontinued and 5 days later, the patient died due to "generalization of the bladder cancer." The investigator did not consider the event to be related to study drug.

8. Case A126360 involved a 57 year-old white man with benign prostatic hyperplasia, who after an unspecified duration of therapy with doxazosin GITS 4 mg daily, developed cachexia. Study drug was discontinued after a total of 54 days. One month later he died due to pancreatic cancer. The investigator did not consider the event to be related to study drug.

9. Case A205085 involved a 77 year-old white male with benign prostatic hyperplasia, hypertension, coronary disease, hyperlipidemia, diabetes mellitus, congestive heart failure and a history of recurrent strokes, who was receiving insulin, digoxin, aspirin, isosorbide mononitrate, atenolol, nifedipine and gliclazide. After two months of therapy with doxazosin GITS 4 mg daily, he died at home. Pulmonary embolus was the suspected cause of death. The investigator did not consider the event to be related to study drug.

Medical officer's comments: This reviewer agrees that the deaths listed do not appear to be related to doxazosin GITS.

Doxazosin standard

Case 9606211 involved a 71 year-old white male with benign prostatic hyperplasia and hypertension treated with lisinopril, diltiazem and lomefloxacin. He was treated with increasing doses of doxazosin from 1 to 4 mg daily over a 2 month period when he experienced dizziness and the dose was reduced to 2 mg daily for an additional 2 months. Doxazosin was then discontinued because the study had ended. Four days later the patient suffered a myocardial infarction and died. Just two days prior to the event, the patient was asymptomatic with BP 170/90 mmHg and heart rate 60 bpm. The event was considered as not related to study drug.

Medical officer's comments: This reviewer agrees that the death does not appear to be related to doxazosin Std.

Blinded Therapy

1. Case A118778 involved a 69 year-old man with benign prostatic hyperplasia, hypertension, angina pectoris, hypercholesterolemia, a duodenal ulcer and diabetes (with retinopathy and nephropathy) who was receiving atenolol, candesartan, nicorandil, clopidogrel, atorvastatin, furosemide, omeprazole and insulin. He was enrolled in a comparative study of doxazosin GITS vs tamsulosin and after about 2 months of blinded therapy, he was hospitalized for stabilization of his diabetes. He also had hypertriglyceridemia, global cardiac failure crisis, and worsening edema. Some 5 months after starting study drug he died from a myocardial infarct. All of these events were considered as not related to study drug by the investigator, but due to underlying disease.

2. Case A126390 involved a 61 year-old Asian man with benign prostatic hyperplasia, insomnia, anxiety, and a history of depression being treated with lorazepam who was enrolled in a double-blind comparative study of doxazosin GITS vs standard doxazosin tablets. After 10 weeks of blinded study drug he committed suicide by hanging. He was being treated by a psychiatrist at the time and had attempted suicide on a previous occasion. The event was not considered to be related to study drug.

3. Case A200789 involved a 58 year-old man with benign prostatic hyperplasia and a history of pulmonary cancer treated with prednisone and clobutinol. He was enrolled in a comparative study of doxazosin GITS vs tamsulosin. After about 20 weeks of double-blind therapy he developed bronchospasm and respiratory insufficiency related to his lung cancer and 'was dead after sedation'. The event was not considered to be related to study drug.

4. Case A212360 involved an 82 year-old man with benign prostatic hyperplasia being treated with lorazepam, who was enrolled in a comparative study of doxazosin GITS vs tamsulosin. He had been on study drug for 27 weeks when he was killed in a traffic accident.

Medical officer's comments: The first three events do not appear to be related to drug therapy. The traffic accident is not fully explained. A syncopal episode could result in a traffic fatality.

b) Deaths in hypertensive trials

Seven patients died while participating in doxazosin/GITS clinical trials. Five of these patients were receiving doxazosin GITS: one hanged himself, one died of a cerebrovascular accident, one from carcinoma of the lung, one from chronic obstructive pulmonary disease, and one from an unknown cause. One patient was murdered while taking doxazosin tablets. One patient died of cardiac failure while receiving quinapril.

<u>Doxazosin GITS</u>

1. Case A039413 involved a 46 year-old Asian man who was treated with doxazosin GITS for essential hypertension. About two months after initiation of treatment with doxazosin GITS 4mg daily, the patient was found dead as a result of hanging. His death was not considered by the investigator to be drug related. * Initially reported in Safety Update covering 01Jan00 – 31Dec00.

2. Case A118420 involved an 81 year-old obese white male with hypertension and chronic obstructive pulmonary disease being treated with omeprazole, theophylline, budesonide and enalapril. After about 3 months of therapy with doxazosin GITS 4 mg daily, he was hospitalized with obstructed airflow due to a respiratory infection. The study drug was permanently discontinued and the patient was withdrawn from the study. One week later the patient died due to chronic occlusion of airflow from the respiratory infection. The investigator did not consider the event drug related.

3. Case A118599 involved a 77 year-old hypertensive female with arthrosis and diabetes mellitus being treated with acetaminophen, zolpidem, amiloride, ibuprofen and ranitidine. After about 3 weeks of therapy with doxazosin GITS 4 mg daily, she was admitted to hospital with cholecystitis complicated by thromboembolism and an acute cerebrovascular accident. The patient died due to the cerebrovascular accident. The investigator did not attribute these events to the study drug.

4. Case A118602 involved a 58 year-old white man with hypertension and chronic obstructive pulmonary disease being treated with candesartan. After an unknown duration of therapy with doxazosin GITS 4 mg daily, he was diagnosed with pulmonary carcinoma and lost to follow-up. The patient died on an unknown date due to the pulmonary carcinoma. The investigator did not consider the event to be related to study drug.

5. Case A204070 involved a 70 year-old white male with hypertension, benign prostatic hyperplasia, diabetes mellitus and chronic obstructive pulmonary disease, and a history of a stroke with residual paresis treated with captopril, gliclazide, ranitidine and furosemide. After about three months of therapy with doxazosin GITS 4 mg daily, the patient was hospitalized with painful testicular inflammation, at which time he was withdrawn from the study. Several months later he developed worsening of his pulmonary condition that required several hospital admissions. He subsequently died; the cause of death and date of death are unknown. The investigator assessed the events as not related to study drug.

Doxazosin standard

Case A030853 involved a 68 year-old hypertensive Asian man treated with standard tablets of doxazosin 4 mg daily. After 50 days of therapy he was murdered, having died from massive blood loss due to a stab wound to the left flank. * Initially reported in Safety Update covering 01Jan00 – 31Dec00

Medical officer's comments: None of the deaths in the hypertensive studies appear to be doxazosin related.

c) Serious Adverse Events

A total of 116 patients in doxazosin/GITS trials for BPH experienced nonfatal serious adverse events. These included 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, 15 suffered from cancer (9 carcinomata of the prostate, 2 of the bladder, 1 basal cell, 1 bile duct, 1 renal and 1 adenoma of the prostate), 4 were hospitalized due to worsening of their symptoms of benign prostatic hyperplasia, 4 were hospitalized with urinary retention, 3 with a transient ischemic attack 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 (one of which resulted 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.

Of the 13 patients receiving doxazosin tablets, 2 suffered from cancer (prostate and abdominal), 2 had elevated blood pressure (one of which also had encephalopathy), and one each of amebic hepatitis, alcoholic gastritis and varices, intestinal occlusion, paresthesia of the face, urinary retention, erosive duodenitis, diplopia due to stroke, chronic obstructive pulmonary disease, and peripheral arterial obstruction.

Of the studies that remained blinded as of the end of the reporting period, 49 patients had nonfatal serious adverse events (50 case reports in the listings because 2 reports were for the same patient), including 3 with urinary retention, 2 with worsening of their benign prostatic hyperplasia, 6 with cancer (2 rectal, one each prostate, colon, lymphoma and prostatic adenoma), 6 with inguinal hernia, 4 with renal calculi, 4 with a cerebrovascular event, 3 with syncope, 8 with cardiovascular events (myocardial infarction, 2 with chest pain [one of which was also accompanied by palpitations and shortness of breath], 2 with coronary artery stenosis, 1 unstable angina and 2 arrhythmia [with pneumonia]), 2 suffered accidents, 2 with hip replacements, 2 with peripheral arterial disease, 1 with prostatic biopsy (which was negative) and one each with detached retina, pudendal canal syndrome, temporal arteritis, erysipelas, diarrhea, diverticulitis, and arthritic flare.

Medical officer's comments: Individual cases of syncope were sought in this 2-year safety update related to use of doxazosin GITS. The following case was found.

Doxazosin Gits Serious Adverse Events (Syncope)

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.

6. Filing Meeting Requests – Sponsor's Response

Medical officer's comments: Based on initial review of the December 17, 2003 complete response submission, additional clinical information was requested of the sponsor on February 17, 2004. The requests and the sponsor's responses (dated May 14, 2004) are as follows:

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

Sponsor's Response:
This periodic safety update report for doxazosin presents information for the reporting period 01 October 2002 through 30 September 2003. During fourth quarter 2002 through second quarter 2003, there have been worldwide sales of over [redacted] standard dosage units of doxazosin 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.

A total of 188 doxazosin tablet cases (containing 454 events) and 73 doxazosin GITS cases (137 events) fulfilled criteria for inclusion in this one-year safety update report. The majority of the most frequently reported events for both formulations were listed in the current core data sheets. Of the most frequently reported unlisted events, many could be attributed to the patients' concurrent medical disorders and/or treatment indication and appeared to be unrelated to doxazosin therapy.

Retrograde ejaculation and Cardiac failure were selected for review because continued monitoring of these events had been recommended in the previous one-year PSUR. An association with doxazosin GITS could not be excluded in the one case of retrograde ejaculation reported currently, therefore continued monitoring is still warranted. There were no cases of retrograde ejaculation reported with doxazosin tablets during the current period. Overall cases of cardiac failure did not suggest a causal association with doxazosin tablets or doxazosin GITS since most cases reported cardiac histories, significant underlying illnesses, concomitant cardiac medications, and/or advanced age, factors that could signal patients' predisposition to heart failure. However, continued monitoring of this event is still warranted because of the nature of the event.

Continued monitoring of photosensitivity skin reaction and esophageal stricture was also recommended in the most recent one-year PSUR; there were no cases reporting these events with either formulation during the current reporting period.

Medical officer's comments: The sponsor is monitoring retrograde ejaculation, heart failure, photosensitivity and esophageal stricture. These adverse events appear to be rare events. No causality for these events was suggested in the clinical trials and according to the sponsor no causality has been suggested in postmarketing analysis to date.

The following table (Table 21) has been derived from this reviewer by review of the sponsor's data regarding deaths recorded by the sponsor in the last quarter of 2002 and the first three quarters of 2003.

Table 21 Postmarketing safety report (deaths)

PSUR (Oct 1, 2002-Sept 30, 2003) Reports of Death for Doxazosin and Doxazosin GITS			
Patient	Age/ sex	Treatment/dose	Comments
2002 60834	86 male	Doxazosin 2mg	Unknown medical history Hematemesis, melena, stroke
2003 5288	82 female	Doxazosin 2mg Bendrofluazide 2.5mg	Hypokalemia, hyponatremia Pneumonia
2003 7286	76 male	Doxazosin 2mg Prochlorperazine 3mg Digoxin, enalapril, inapamide, nizatidine, salbuatamol and salmeterol	History of CAD Ventricular fibrillation Cardiac death
2003 13916	80 male	Doxazosin 2mg (for five years)	Weakness, tachycardia Died from unspecified cardiorespiratory disorder
2003 19221	18 female	Doxazosin 1mg (for two weeks)	Chronic renal failure on dialysis Developed pulmonary edema and congestive heart failure
2003 23061	39 male	Doxazosin, manidipine, carvedilol, temocapril and valsartan	Suicide Drug overdose
2003 26009	67 male	Doxazosin 2mg (for 6 months)	Probable myocardial infarction
2003 40219	56 female	Doxazosin 1mg (for 3 years)	Interstitial pneumonia (thought secondary to auranofin)
2003 16441	UNK	Doxazosin	Suicide (overdose) from 2000
2003 2684	84 sex?	Doxazosin	Suicide (overdose) from 2001
2003 39750	89 sex?	Doxazosin	Suicide (overdose) from 2002
2003 39751	95 sex?	Doxazosin	Suicide (overdose) from 2002
2003 14162	75 male	Doxazosin GITS 8mg or 16mg for hypertension for a number of years Bendrofluazide Warfarin (prior pulmonary embolism)	Ischemic heart disease and peripheral vascular disease Sudden cardiac death

Medical officer's comments: None of the deaths (except the suicides in which some are related to overdose) appear related to the use of doxazosin or doxazosin GITS. There are no cases of death related trauma secondary to syncope. Doxazosin use by prescription information is approximately 3.5 times that of doxazosin GITS in this recording time period. Only one of the preceding 13 deaths includes doxazosin GITS use.

The following table (Table 22), derived by this reviewer from the sponsor submitted line listings, enumerates the vasodilatory adverse events for doxazosin in the postmarketing safety reporting from October 2002 through September 2003. Cerebrovascular adverse events are also listed.

Table 22: Postmarketing safety report (doxazosin -- vasodilatory adverse events)

Doxazosin – Vasodilatory Adverse Events - Line Listings (Oct 1, 2002 through Sept 30, 2003)				
Subject (2002)	Age	Symptom	Rx and dose	Outcome
60560	64	Orthostatic hypotension / Fall	Doxazosin 1mg	Recovered
60834	86	CVA	Doxazosin 2mg	Death
61848	69	Syncope	Doxazosin 4mg	Recovered
63382	70	Cerebral infarction	Doxazosin 2mg	Unknown
63698	83	Syncope TIA	Doxazosin 0.5mg	Recovered
64098	72	Circulatory collapse Cerebral circulatory failure	Doxazosin 4mg	Recovered
64225	Unk	Hypotension Circulatory collapse	Doxazosin 2mg	Recovered
64229	65	Orthostatic hypotension Syncope	Doxazosin 4mg	Recovered
65947	64	Orthostatic hypotension	Doxazosin 4mg	Recovered
66197	89	Syncope	Doxazosin 4mg	Recovered
66455	81	Loss of consciousness	Doxazosin 4mg	Recovered
67295	47	Syncope	Doxazosin 4mg	Recovered
Subjects in 2003				
503	53	Vertigo positional	Doxazosin 8mg	Not recovered
1995	80	Blood pressure decrease Dizziness	Doxazosin 2mg	Unknown
2119	72	Blood pressure decrease	Doxazosin 8mg	Not recovered
4089	82	Dizziness	Doxazosin 1mg	Unknown
5290	80	Orthostatic hypotension	Doxazosin 1mg	Recovered
6816	33	Hypotension NOS	Doxazosin 2mg	Recovered
7081	72	Dizziness	Doxazosin 4mg	Recovered
8671	76	CVA	Unk	Recovered
8956	Unk	Dizziness	Doxazosin 2mg	Recovered
9871	80	Circulatory collapse Orthostatic hypotension	Doxazosin 1mg	Recovered
10062	45	Orthostatic hypotension Circulatory collapse Syncope	Doxazosin 4mg	Recovered
13321	62	Orthostatic hypotension	Doxazosin 4mg	Recovered
13704	70	Circulatory collapse Hypotension Dizziness	Doxazosin 1mg	Recovered
13706	75	Hypotension	Doxazosin 2mg	Recovered
16874	50	Orthostatic hypotension	Doxazosin 4mg	Recovered
17845	56	Dizziness	Doxazosin 2mg	Recovered
20533	75	Hypotension	Doxazosin 1mg	Unk
22296	82	Loss of consciousness Respiratory arrest	Doxazosin 4mg	Recovered or unknown
23301	85	Cerebral infarction	Doxazosin 2mg	Unk
23379	40	Orthostatic hypotension Dizziness	Unk	Recovered
30473	Unk	Blood pressure decrease Dizziness	Doxazosin 1mg	Unk
31313	82	Fall Balance impaired	Doxazosin 2mg	Unk
32056	78	Syncope Accidental overdose	Doxazosin 24mg	Recovered
32244	74	Loss of consciousness Dizziness	Doxazosin 4mg	Unk
37337	52	Dizziness	Doxazosin 2mg	Recovered
37802	69	Fall- Loss of consciousness Head injury	Doxazosin 2mg	Unk
39002	73	Dizziness	Doxazosin 2mg	Recovered
Total of 39 reference subjects with vasodilatory adverse events				

Medical officer's comments: These vasodilatory events are occurring at different dosage strengths of doxazosin.

The following table (Table 23) lists the vasodilatory adverse events from the same time period for doxazosin GITS. Cerebrovascular adverse events are also listed.

Table 23: Postmarketing safety report (doxazosin GITS – vasodilatory adverse events)

Doxazosin GITS – Vasodilatory Adverse Events - Line Listings (Oct 1, 2002 through Sept 30, 2003)				
Subjects in 2002	Age	Symptom	Rx and dose	Outcome
62338	61	Anaphylactic Shock Dizziness	Doxazosin GITS 8mg BID	Recovered
68633	66	Ischemic stroke Blood pressure decrease	Doxazosin GITS 4mg	Recovered
70511	Unk	Orthostatic hypotension Vertigo	Doxazosin GITS 8mg	Recovered Unknown
Subjects in 2003				
7468	78	Vertigo	Unk	Recovered
13917	58	Balance impaired Dizziness	Doxazosin GITS 4mg	Recovered Unknown
16720	56	Dizziness	Doxazosin GITS 4mg	Recovered
24649	82	Syncope	Doxazosin GITS 4mg	Recovered
25417	64	Orthostatic hypotension	Doxazosin GITS 4mg	Not recovered
27706	84	Vertigo	Unk	Recovered
31400	76	Syncope Orthostatic hypotension	Doxazosin GITS 4mg	Recovered
Total of 10 reference subjects with vasodilatory adverse events				

Medical officer's comments: As mentioned earlier the ratio of prescriptions of doxazosin compared to doxazosin GITS during this reporting period was 3.5 to 1. The overall ratio of vasodilatory adverse events (doxazosin/doxazosin GITS) Is 3.9 to 1. Based upon this analysis, there is no postmarketing signal that the GITS preparation is showing more vasodilatory problems than doxazosin.

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

Sponsor's Response:

As there are no known studies designed specifically to evaluate the effect of doxazosin on the QT interval, the question was examined by a comprehensive search for evidence of a relationship between doxazosin therapy and either prolongation of the QT interval or the sequelae of a prolonged QT interval.

The search took the form of a comprehensive review of the following: a) Databases of doxazosin clinical studies sponsored by Pfizer, b) Pfizer's early alert safety database, and c) Medical literature.

Databases of 276 completed doxazosin studies, including both placebo-controlled studies and open label studies, involving a total of 95,282 patients exposed to doxazosin were searched for the following COSTART preferred terms:

> *Electrocardiogram QT Interval, Electrocardiogram QT Corrected Interval Prolonged, Electrocardiogram QT Prolonged, Torsade de Pointes, Sudden Death Unexplained, Cardiac Arrest, Heart Arrest, Ventricular Arrhythmia, Ventricular Tachycardia, Ventricular Fibrillation, and Sudden Death.*

A total of 13 cases involving one or more of the terms listed was identified, 9 of which were reported as serious adverse events.

a) Review of Doxazosin Clinical Study Databases

Medical officer's comments: This reviewer compiled these 13 cases in the following table (Table 24):

Table 24: Potential QT related events

Case #	Age/ sex	Treatment/dose	Comments
9202758	58 Male	Doxazosin x 10 weeks then 4 week washout then 25mg atenolol	Sudden death 6 weeks after atenolol started
9000273	84 Female	Doxazosin for 67 days for hypertension Also on insulin, nifedipine, nitrates, diuretics and other antihypertensives	History of left ventricular hypertrophy and cardiac insufficiency Sudden death after 67 days of doxazosin therapy
9603133	84 Male	Doxazosin for 16 days	History of hypertension, coronary heart disease and chronic bronchitis Found dead after 16 days of doxazosin treatment
9622024	53 Male	Doxazosin for BPH	History of untreated hypertension, obesity and alcohol consumption Myocardial infarct 10 days after starting doxazosin
9709022	63 Male	Doxazosin for hypertension Concomitant meds were glybenclamide, felodipine and penbutolol.	History of diabetes and angina, dies suddenly after 231 days of doxazosin.
A035922	79 Male	Doxazosin for hypertension Also taking metoprolol	History of coronary heart disease and chronic renal insufficiency Died 328 days after starting doxazosin
9000138	60 Male	Doxazosin for hypertension Also on metoprolol and nifedipine	Developed ventricular extrasystoles after 7 days of doxazosin Doxazosin was discontinued and the symptoms abated
9305944	38 Male	Doxazosin 2mg in a hypertension study	Symptoms of heart consciousness, sweating, pain and dyspnea while on therapy. Symptoms persisted after stopping doxazosin. Diagnosed after withdrawal of doxazosin with 3rd degree AV block which required pacemaker
9000907	74 Male	Doxazosin for hypertension Also taking atenolol and nitrates	History of coronary heart disease and nephrolithiasis Developed right bundle branch block, ventricular extrasystoles and bigeminy after 31 days of doxazosin This did not abate after doxazosin discontinuation
Four other cases of arrhythmia, not specified by subject number			The sponsor described these four cases as nonserious Three of four stated to be ventricular arrhythmias

Medical officer's comments: Most of these patients have significant preexisting heart problems that could explain the clinical findings.

b) Review of Pfizer's Early Alert Safety Database

This safety database includes serious adverse events from clinical studies in addition to non-clinical study cases. It was searched for evidence of a relationship between doxazosin use and prolongation of QT interval or its sequelae using the following MEDRA terms: ECG QT corrected interval prolonged, ECG QT prolonged, long QT syndrome, long QT syndrome congenital, torsade de pointes, cardiac arrest, cardiac fibrillation, cardiorespiratory arrest, cardiac

death, sudden cardiac death, sudden death, ventricular arrhythmia, ventricular fibrillation, ventricular flutter, ventricular tachycardia, ECG U-wave abnormality, ECG U-wave biphasic, ECG repolarization abnormality.

Review of clinical study cases through 1/31/04 identified by this search in which either the investigator and/or the sponsor considered drug-related causality revealed 5 cases: sudden death, ventricular arrhythmia (2), ventricular tachycardia, and ventricular fibrillation. In each of these, the reporter considered doxazosin therapy as a possible causative factor, but in all except one, Pfizer reviewers attributed the event to other factors such as underlying disease, patient's history, and age. In one case, of ventricular arrhythmia, the sponsor felt that although other factors were most likely involved, it was not possible to rule out a causative relationship with doxazosin.

Review of the 15,191non-clinical study cases received in the database through 1/31/04 using these search terms identified 102 cases, which represents a reporting rate of 0.7% 23 of these cases coded to specific heart rate/rhythm abnormalities (9 to ventricular arrhythmia, 6 to ventricular tachycardia, 5 to ventricular fibrillation, 3 to ECG QT prolongation, and 2 to torsade de pointes). The majority of these either contained insufficient information to make meaningful assessment or also reported confounding factors that may have contributed to events. The remaining 79 coded to events relating to clinical sequelae of QT interval prolongation, and included 70 cases of cardiac arrest, 11 of cardiorespiratory arrest, and 2 of sudden death. 5 cases coded to more than one of these events. 88% were male, and 81% were aged over 65. Again, in the majority of cases either information was incomplete or else significant concomitant disease was present.

Medical officer's comments: The cases of QT prolongation and torsade de pointes are provided in Table 25(One case is listed with both)

Table 25: 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.

Medical officer's comments: Of the three preceding cases with more clinical information available, none of them shows a strong causality between doxazosin and QT prolongation/Torsade. In the second case Cisapride is the primary suspected culprit. Hypokalemia could have contributed to ECG changes in the third and fourth case, which occurred only after cardiac or respiratory arrest.

Case number 2 was also identified in the AERS database. This case was reported in a Japanese medical journal.

c) Literature Review

A literature search was done to look for evidence of a link between doxazosin therapy and prolonged QT interval or its sequelae in articles published from 1964 through early 2004. Search terms used were similar to those used in the clinical study database review, in combination with doxazosin or Cardura.

The searches identified a total of 40 references. These included reports of 4 clinical and 2 animal studies, 1 paper discussing case reports, and 6 review papers presenting theoretical comments on the relationship between doxazosin and various sequelae of QT prolongation (1 of which suggested a negative relationship and 5 a positive relationship). The remaining references were general reviews containing no information relevant to the issue under consideration.

Medical officer's comments:

The sponsor listed seven references. One of their referenced authors suggested a benefit for patients with long QT syndrome. Another author found less arrhythmias in CHF patients who were given doxazosin. The sponsor also referenced an analysis of five doxazosin BPH studies that had no arrhythmias. Two animal studies were also quoted that suggested beneficial effects of doxazosin on rhythm disorders. These studies do not provide any direct evidence of an adverse effect of doxazosin on QT interval.

An additional abstract was identified through PUBMED in regard to inhibition of human ether-a-go-go-related gene potassium channels by alpha1-adrenoceptor antagonists prazosin, doxazosin and terazosin. These drugs blocked HERG currents in Xenopus oocytes with IC (50) values of 10.1, 18.2 and 113.2 microM respectively. HERG channel inhibition in human HEK 293 cells were 1.57 microM, 585.1 nM and 17.7 micro M respectively. The full article* has been requested through the FDA library.

** Thomas D et al. Inhibition of human ether-a-go-go-related gene potassium channels by alpha1-adrenoceptor antagonists prazosin, doxazosin, and terazosin. Naunyn Schmiedebergs Arch Pharmacol. 2004 May;369(5):462-72.*

The clinical safety information on doxazosin since its original approval in 1990 does not indicate that there is a signal that this drug is associated with prolonged QT or torsade de pointes. Although sudden death that is postulated to be secondary to heart arrhythmia has

occurred in patients taking doxazosin, there is no indication that a cause and effect relationship is present. Most of these patients have had significant concomitant cardiovascular diseases and other medical illnesses.

Cardura XL has a lower Cmax than Cardura. Theoretically, even if there is a small QT interval increase associated with doxazosin use, the approved formulation should show a slightly greater change than the proposed GITS formulation. Cardura additionally has been used concomitantly with a number of different drug classes and shows no interactions.

Another member of this drug class, alfuzosin, has shown QT prolongation. Based on the correction method and dose the mean difference versus placebo varies from 4.9 to 13.9 msec.

Despite the above mentioned report of HERG inhibition (in abstract form) and the QT prolongation noted in another member of this drug class, the voluminous amount of safety information from clinical studies (92,000 subjects in 256 clinical trials) and worldwide use of doxazosin for over a decade provides a substantial argument that a formal QT study is not required for approval of Cardura XL.

Request #3:

Since the first dose blood pressure study had only one subject aged 70 or greater, justify use of Cardura XL in men over age 70 years and the lack of information for elderly subjects on [redacted]

Sponsor's Response:

In the two pivotal BPH studies combined, there were 306 men over age 70: 136 on doxazosin GITS, 126 on doxazosin standard, and 44 on placebo. The incidence of hypotension with doxazosin GITS was higher in men>70 (2.9%) than in men 65-70 (1.6%) or in men <65 (1.2%). The incidence of hypotension with doxazosin standard formulation was higher in men over age 70 (4.8%) than in men 65-70 (0%) or in men <65 (1.8%). The incidence of postural hypotension with doxazosin GITS was similar in men >70 (1.6%) and men 65-70 (1.5%) but higher than in men <65 (0.9%). The incidence of postural hypotension with doxazosin standard was higher in men>70 (3.2%) than in men 65-70 (2.2%) or men<65 (1.2%). The incidence of dizziness with doxazosin GITS in men >70 was lower (6.6%) than that in the same age category with doxazosin standard (12.7%).

Sponsor's Conclusion

Based on a review of adverse event and blood pressure data in men over the age of 70, there is no signal of a safety concern in men over age 70 receiving doxazosin GITS or doxazosin standard.

We propose to add the following statement to the label in the [redacted] section:

[redacted]

Medical officer's comments: The overall results in the combined BPH studies are similar to the sponsor's analysis for men over 75 (see age section) with more hypotensive effects in the elderly. The label should reflect the hypotensive effects seen in the elderly. [redacted]

Request #4:

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

Sponsor's Response:

The protocol indicated that we would include in the final PK & efficacy analysis only subjects with PK and efficacy data in all 3 periods. Subjects with PK and efficacy in only one or two periods were not to be included in the per-protocol population.

The decision to include only subjects with results in all 3 periods was included in the protocol and subjects who were discontinued early (regardless of their reason for discontinuation) were replaced to ensure that 24 subjects with complete data will be included in the final analysis.

Medical officer's comments: See the individual blood pressure readings for this patient in section VI. ***Although the sponsor's response is acceptable in light of the established protocol, the response of this patient is instructive in regard to labeling education regarding alpha blockers. This subject's initial baseline blood pressure indicated no orthostatic change prior to medication on one day but orthostatic changes prior to a crossover treatment at another visit. Patients intended for treatment with doxazosin should be questioned thoroughly about prior episodes of lightheadedness etc.***

Request #5:

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

Sponsor's Response:

This subject was an outlier only for the analysis of orthostatic change in SBP at Cmax when treated with DOX GITS and DOX STD. For all the other efficacy measures considered in this study, the observed results for this subject were consistent with the mean observed results for the other subjects included in the analysis.

The impact of outliers in any analyses based on "mean" is that the mean shifts towards the outlier and it may be misleading. However, summary tables present median values as well which are not impacted by outliers. At the same time, this subject is an outlier (same direction of change and almost the same magnitude) when treated with DOX GITS and DOX STD therefore the impact on the direct comparison of the mean change from baseline between the 2 treatment groups is minimal.

The results observed for this subject would not impact the overall conclusions of the study.

Medical officer's comments: After reviewing the submitted CRF it appears that this subject could have been excluded because there was a drop >20mmHg in the systolic pressure at screening. The inclusion of this subject's orthostatic changes balances the exclusion of subject #9's first treatment blood pressure results. As noted in an earlier table, this subject had no adverse events reported with his systolic pressure changes. The response from the sponsor on this subject is acceptable.

Request #6:

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

Sponsor's Response:

Subject 10010012 was under evaluation for episodes of bradycardia at the time of enrollment. The investigator was made aware of the subject's condition after randomization.

Medical officer's comments: The medical history in the CRF lists "episodes of bradycardia – investigations ongoing". It appears that the PI was not aware of these investigations by the subject's general practitioner. On [redacted] the subject reported shortness of breath and missing a heart beat several times. The ECG on [redacted] were all read as normal with normal QTc intervals. The subject was withdrawn from the study on [redacted] for "cardiac condition incompatible with study" There is no indication that this subject had cardiac symptoms secondary to QTc changes.

Request #7:
Provide additional clinical information and CRF for subject 10010050 who was noted to have an intraventricular conduction delay.

Sponsor's Response:

Subject 10010050 had past medical history of benign ventricular ectopic beats noted in 1993. His electrocardiogram at screening was significant for "minor intraventricular conduction delay" which was noted by the investigator to be not clinically significant. This subject had many episodes of orthostatic changes in BP during the trial, although all were asymptomatic.

Medical officer's comments: As noted above the subject had a history of benign ventricular ectopic beats. The ECG results at screening [redacted] were:
Ventricular rate 65 BPM
PR = 166 ms
QRS = 118 ms
QTc = 459
A follow-up ECG on [redacted] was read as normal:
Ventricular rate 45 BPM
PR = 144 ms
QRS = 106 ms
QTc = 416
No adverse events were recorded for this subject during the trial. There was only one blood pressure assessment for this subject that had a systolic drop of 20mmHg and/or diastolic drop of 10mmHg.

Request #8:
Provide information on the mean time of Cmax for the first day of use of Cardura XL and [redacted]

Sponsor's response:
Tmax data after single and multiple doses are presented in Table 26.

Table 26: Single and Multiple Dose Tmax

Study	Population	Dose	Tmax single Dose(h)	Tmax Multiple dose (h)
DAZ-NY-96-009	10 Healthy Young Females	4mg	13.4	10.4
	10 Healthy Young Males	4mg	16.6	7.8
	10 Healthy Elderly Females	4mg	15.1	13.8
	10 Healthy Elderly Males	4mg	15.6	13.0
DAZ-JP-98-502	12 Healthy Male Japanese Subjects	4mg	13.0	12.2

There are two studies where mean Tmax data were obtained after both single dose and multiple (7 day) dosing. DAZ-NY-96-009 was a 7 day study where pharmacokinetics of the GITS formulation were assessed after single and multiple doses in young and elderly male and female subjects. DAZ-JP-502 was a 7 day study where pharmacokinetics of the GITS formulation were assessed after single and multiple doses in young male Japanese subjects. In both of these studies, mean Tmax was 1-2 hours earlier after multiple dosing compared with single dose data, with one exception. The young male cohort tested in DAZ-NY-96-009 had a Tmax 9 hours earlier (7.8 vs 16.6h).

The reason for reduction in Tmax after multiple dosing is unclear. Food has been shown to also modestly decrease single dose Tmax (by 1-2 hours), however drug administration in relation to food was kept consistent in the two studies above.

In summary, the reduction in Tmax upon multiple dosing is modest and not considered to be of clinical relevance. As Cardura XL is dosed on a chronic basis, it was considered more relevant to present multiple dose Tmax data.

Medical officer's comments: Since it appears that vasodilatory adverse events can occur at times away from Tmax, the clinical relevance of including both single dose and multiple dose Tmax information in the label is not compelling. Further, the actual difference between Tmax after single and multiple dosing is fairly small.

D. Adequacy of Safety Testing

The additional safety information provided by the sponsor in their complete response (17 Dec 2003) and their responses to filing requests (14 May 2004) has provided adequate safety information to allow approval recommendation.

E. Summary of Critical Safety Findings and Limitations of Data

Medical officer's comments:

Study A0351061

Although study A0351061 was small in regard to the number of subjects and the number of elderly subjects, it is adequate to provide a safety analysis of the first dose effect of Cardura XL. The strengths of the study include a large number of blood pressure and pulse analyses, a crossover design to allow comparisons between Cardura XL 4mg and Cardura standard 1mg and a comparison to drug levels (especially Cmax and Tmax)

Although the GITS arm in study A0351061 showed a higher percentage of orthostatic drops than the standard arm, the mean magnitude of the drop was actually slightly less than that seen with doxazosin standard.

In study A0351061, Cardura XL 4mg and Cardura standard 1mg are comparable when evaluating the maximum orthostatic change in blood pressure and pulse rate over 24-hour period. The time to the maximum orthostatic change for both preparations is about 8-9 hours.

In study A0351061, six subjects in the GITS 4mg arm had one or more episodes of a systolic drop ≥ 20mmHg and/or diastolic drop ≥ 10 mmHg compared to three subjects in the standard 1mg arm. However there were no corresponding vasodilatory adverse events recorded for the subjects in the GITS arm compared to two recorded in the standard arm.

In study A0351061 there is no evidence of a correlation between time of maximum orthostatic change and first dose Tmax (approximately 8 hours compared to 16 hour). Vasodilatory adverse events, as shown in this study, can occur away from the time of Tmax.

Analysis of DAZ-NY-95-001, DAZ-N/S/DK-95-001, [redacted]

The combined safety data from the pivotal trials of Cardura XL (BPH and hypertension) do not show high percentages of vasodilatory adverse events for Cardura XL in the first day of use or the first week of use. The percentages are similar to that seen with Cardura standard.

Noteworthy in the analysis of these pivotal studies is the fact that vasodilatory events (including syncope) can occur at remote time periods after the first week of use. Patients and medical caregivers should be aware these adverse events are not limited to initiation or titration time periods.

Analysis of A0351027 and A0351029

Two additional smaller studies that included the 4mg GITS formulation showed a greater overall percentage of vasodilatory adverse events than seen in the larger pivotal studies. However most of the events were listed as mild and there was no comparison to the 1mg doxazosin standard in these studies.

Two Year Safety Update 2001-2002

This two-year safety update for doxazosin clinical trials did not show any new safety concerns. One syncopal serious adverse event was presented.

Postmarketing safety data specific to Cardura XL

There is no signal from postmarketing safety data that Cardura XL presents a greater safety risk than Cardura. The number of vasodilatory adverse events in countries where Cardura XL has been launched shows similar numbers of events in both products.

QT issues

Review of AERS database and the published literature has not shown any signal for either QT prolongation or torsade de pointes with doxazosin. Most reported cases of cardiac death reported in patients taking doxazosin have other potentially contributing preexisting medical conditions and concomitant medications with adverse events. Formal QT studies have not been performed with doxazosin. Another member of the alpha-blocker drug class, alfuzosin has shown QT prolongation. In one abstract, doxazosin has been shown to inhibit HERG channels.

Use in the elderly

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 that the risk of taking Cardura in this age range.

VIII. Dosing, Regimen, and Administration Issues

Medical officer's comments: The principal issues related to dosing, regimen and administration are the following:

- ***Patients should be informed that Cardura XL should be swallowed whole. Patients should not chew, divide, cut or crush tablets.***

- ***The timing of the dosing should be at breakfast.***

- ***The issue of switching from the immediate release formulation to the GITS formulation may require additional labeling recommendations.***

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

The evaluation of gender effect is not applicable since Cardura XL is intended for benign prostatic hyperplasia.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

Age
Please also see the section on age in the "demographic" section of the study findings. The sponsor also responded to a question regarding use in men over 70 years in section VII, 6.

In the "approvable" letter that sponsor was asked to:
"Provide all available safety information for the use of Cardura XL in men older than 75 years of age"

Sponsor response:

In the two pivotal BPH studies combined, there were 75 men over age 75: thirty on doxazosin GITS, 32 on doxazosin standard, and 13 on placebo. The incidence of most adverse events with doxazosin and doxazosin GITS in men over 75 was similar to that for each formulation in men <65 and 65-75. The incidence of hypotension with doxazosin GITS was higher in men>75 (10%) than in men 65-75 (1.4%) or in men <65 (1.2%). The incidence of hypotension with doxazosin standard formulation was higher in men over age 75 (6.3%) than in men 65-75 (1.4%) or in men <65 (1.8%). The incidence of dizziness with doxazosin GITS in men >75 was lower (6.7%) than that in the same age category with doxazosin standard (9.4%). There were no reports of postural dizziness or postural hypotension in men over 75 with either doxazosin GITS or doxazosin standard. Of the 75 men over age 75, three had an adverse event on day 1: two on doxazosin GITS and one on doxazosin standard. The events on day 1 were: hypotension and back pain in the GITS patients, and vertigo in the doxazosin standard patient.

Medical officer's comments: Labeling should reflect the increased incidence of vasodilatory adverse events in the elderly, especially for those over age 75.

In the two pivotal HTN studies combined, there were only 9 men over age 75: 2 on doxazosin

GITS and 7 on doxazosin standard (none on placebo). No adverse events were reported for the two doxazosin GITS patients over age 75.

The line listings from the BPH and hypertension trials for vasodilatory adverse events in men over 75 are found in Table 27 and Table 28.

Table 27: Vasodilatory adverse events for Doxazosin GITS use in men > 75 years (BPH and hypertension trials).

Subject	Age	Symptom	Dose (mg)	On Rx Day	Severity	Action
Study DAZ-NY-95-001 (BPH trial)						
7580019	79	Hypotension	4	22	Moderate	Discontinued
7800385	76	Hypotension	4	1	Moderate	Discontinued
Study DAZ-NY-95-001 (BPH trial)						
6410406	77	Dizziness	4	22	Mild	None
6610554	78	Dizziness	4	2	Mild	None
6840702	79	Hypotension	8	51	Moderate	None
Studies [redacted]						
None						

Source: Pages 56- "Response Table 10" in the c2.PDF

Table 28 Vasodilatory adverse events for Doxazosin Std use in men > 75 years (BPH and hypertension trials).

Subject	Age	Symptom	Dose (mg)	On Rx Day	Severity	Action
Study DAZ-NY-95-001 (BPH trial)						
7630597	76	Hypotension	?	?	Mild	None
7730397	79	Dizziness	2	6	Mild	None
8160533	83	Dizziness	8	58	Moderate	Reduced dose
Study DAZ-NY-95-001 (BPH trial)						
6470436	77	Vertigo	8	73	Mild	None
6570489	77	Dizziness	1	2	Moderate	None
" "		Dizziness	4	43	Severe	Discontinued
7200151	76	Vertigo	1	5	Mild	None
7200152	79	Hypotension, worsening angina, Vertigo	1	1,2	Moderate	Discontinued
Study [redacted]						
None						
Study [redacted]						
8390190	76	Vertigo, TIA	2	17	Moderate	Treatment given
" "		Syncope	4	46	Moderate	Treatment given

Source: Pages 56- "Response Table 10" in the c2.PDF

Medical officer's comments: For men >75 years there is no signal from these studies that the GITS formulation has more vasodilatory adverse events than the standard formulation or that these events occur disproportionately earlier.

In other Pfizer trials (protocols DAZ-NY-96-014, A0351027, and A0351029) involving a total of 10 men over age 75 who received doxazosin GITS, there were 7 men who had at least one adverse event. Three of these men had adverse events that were considered unrelated to doxazosin GITS, and did not include dizziness or orthostatic events. Four men over 75 had adverse events which were considered to be related to doxazosin GITS. These adverse events were as follows:

- "feeling faint" in an 81 year old; this adverse event began with the first dose of 8mg after the patient had been on 4mg for 4 weeks. The dose was reduced to 4mg and the event resolved.

- "feeling shaky" in a 77 year old; this adverse event began on study day 8 with doxazosin GITS 4mg/d - this patient was hypertensive at baseline and his BP continued to be elevated after one week of treatment

- hypotension in a 76 year old; this adverse event began on study day 2, after one dose of doxazosin GITS 4 mg/d the previous evening, and resulted in study discontinuation. This patient (0006 0297) had an orthostatic drop in systolic blood pressure of at least 20mmHg. His blood pressure 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).

- orthostatic hypotension reported in an 85 year old on study day 4 (before that evening's dose of doxazosin GITS 4mg/d) - blood pressure dropped from 141/92 mmHg sitting (repeat 155/82 mmHg sitting) to 130/78 mmHg standing (repeat 134/75 mmHg standing). This subject had a second occurrence of orthostatic hypotension on study day 15 (before that evening's dose with doxazosin GITS 4mg/d) - blood pressure dropped from 140/85 mmHg sitting (repeat 116/88 mmHg sitting) to 101/64 mmHg standing (repeat 108/54 mmHg standing) (BP data on file).

Race

Medical officer's comments: In **the "approvable" letter that sponsor was asked to:**

"Provide all available safety information for the use of Cardura XL in black men or provide a justification why such information is not necessary."

Sponsor's Response:

There were 7 black patients in the BPH pivotal studies combined. Six of the 7 patients reported adverse events. One of the six patients also experienced serious adverse events and the narrative is as follows:

Subject 7900179 was 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.

Medical officer's comments: The poor control of his hypertension may have additionally contributed to the adverse event.

Three patients had nonserious events involving the respiratory system: bronchitis (subject 8110107, GITS 4mg/d and subject 7700756, doxazosin standard 8mg/d) and upper respiratory tract viral infection and common cold (subject 7820200, doxazosin standard 4mg/d).

The remaining two patients had adverse events that necessitated temporarily stopping study drug. Subject 7900177 had angina and stomach ulcer from study day 20 to 21, and was receiving doxazosin standard 2mg/d at the onset of the events. Although doxazosin was stopped temporarily, the investigator did not attribute causality to study drug. Subject 7900736 temporarily discontinued study drug on two occasions due to headache with nasal congestion, which occurred with the 2mg/d dose of doxazosin standard. The investigator attributed causality to the study drug. This subject eventually permanently discontinued the study due to bradycardia which began on study day 64 and was not considered by the investigator to be related to study drug.

There were no black patients in the hypertension pivotal studies. These studies were conducted in Norway.

There was one black subject in study A0351061, the PK/PD study conducted to address critical deficiency #1. This black subject had no adverse events and no episodes of orthostatic hypotension or hypotension.

There were 5 black men in the doxazosin GITS group and 3 black men in the placebo Group of study A0351029. Of the 5 black men who received doxazosin GITS, two reported no adverse events; one reported runny nose; one reported headache, leg pain, shoulder numbness, and trouble sleeping; and one reported swelling of his toe. Of the 3 black men who received placebo, one reported no adverse events; one reported fatigue, fever, headache, feeling sleepy, and tonsillitis; and one reported fatigue and bilateral ankle swelling.

There were no black men randomized to doxazosin GITS in study A0351027.

The sponsor summarized this information with the following:

"Based on our review of safety information for black patients from the BPH pivotal studies and from additional trials involving doxazosin GITS, there is no signal of any safety issue in black men using Cardura XL."

Medical officer's comments:

Although one study found greater lower urinary tract symptom severity in black men compared with white men (Urology. 2003 Jun;61(6):1086-91); this study could not determine

whether this disparity was secondary to an underlying biologic difference or difference in the perception of symptoms, or both. The authors felt that additional studies were needed.

If additional studies confirm a true difference then efficacy studies may need to be tailored appropriately. There is no clinical information to suggest that blacks or other racial groups react differently to alpha-blockers either in regard to efficacy or safety. Therefore a phase 4 study to compensate for the low number of blacks in the doxazosin GITS trials is not required.

C. Evaluation of Pediatric Program

The evaluation of a pediatric population is not applicable since benign prostatic hyperplasia is not a disease that occurs in this population.

D. Comments on Data Available or Needed in Other Populations

Medical officer's comments:
Asian men generally have smaller prostate gland sizes than their Western counterparts. One study indicated that Asian men were less likely to have undergone BPH surgery although the relative risk for symptoms was similar to that of Caucasians (J Urol. 2000 Feb;163(2):490-5). There is no indication from the literature that a separate study of Cardura XL in oriental men with BPH is indicated or that labeling for this population should be different.

X. Conclusions and Recommendations

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 AERS database and the published literature has not shown any signal for either QT prolongation or torsade de pointes with doxazosin.

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

XI. Appendix

Section 1: Abbreviations

AE = Adverse event
Alk Phos = Alkaline phosphatase
ALT = Alanine aminotransferase
AMI = Acute myocardial infarction
ANOVA = Analysis of Variance
AST = Aspartate aminotransferase
AUA = American Urological Association
AUC = Area under the plasma concentration-time curve
BP = Blood pressure
BPH = Benign prostatic hyperplasia
bpm = beats per minute
C = Celsius
CBC = Complete Blood Count
CFR = Code of Federal Regulations
CHF = Congestive heart failure
CI = Confidence interval
$\mathbf{C_{max}}$ = Maximum plasma concentration
CRF = Case Report Form
CRU = Clinical Research Unit
DBP = Diastolic blood pressure
DRE = Digital rectal exam
DRUDP = Division of Reproductive and Urologic Drug Products
ECG = Electrocardiogram
EIA = Enzyme immunoassay
EMIT = Enzyme-multiplied immunoassay technique
GEE = Generalized estimating equations
GITS = Gastro-intestinal therapeutic system
HbsAG = Hepatitis B surface antigen
HbcAB = Hepatitis C core antibody
HPLC = High performance liquid chromatography
IEC = Independent Ethics Committee
IIEF = International index of erectile function
I-PSS = International Prostate Symptom Score (see Appendix for scoring table)
IRB = Institutional Review Board
ITT = Intent-to-treat
kg = kilogram
LSMean = least squares mean
m = Meter(s)
mg = Milligram(s)
ml = Milliliter(s)

mmHg = Millimeters of mercury
N = Number of observations or subjects
NA = Not applicable
MUFR = Maximum urinary flow rate
PBO = placebo
PD = Pharmacodynamic
PI = Principal Investigator
PK = Pharmacokinetics
PPA = Per protocol analysis
PSA = Prostate specific antigen
Ref = Reference
SAE = Serious adverse event
SBP = Systolic blood pressure
SD = Standard deviation
SE = Standard error
STD = Standard
TEAE = Treatment-emergent Adverse Event
Tmax = Time of maximum concentration
TURP = Transurethral resection of the prostate
UK = United Kingdom
UV = Ultraviolet
VTE = Venous thromboembolism
Vs = Versus
WHO-ART = World Health Organization – Adverse Reporting Term

Section 2: Listing of BPH Trials

Completed BPH Trials			
1	A0351010	Pakistan	Doxazosin In The Symptomatic Treatment Of Benign Prostatic Hyperplasia, An Open, Baseline Controlled Study In General Practice
2	A0351022	China	A prospective, randomized, open-labeled trial of the safety and efficacy of doxazosin GITS versus tamsulosin in patients with benign prostrate hyperplasia
3	A0351032	Pakistan	Doxazosin in the symptomatic treatment of benign prostatic hyperplasia. An open, baseline-controlled study in general practice
4	DAZ-COL-96-001	Columbia	Doxazosin in the treatment of benign prostatic hyperplasia open, multicenter, non comparative, baseline controlled study in ambulatory urological practice
5	DAZ-E-96-002	Spain	Postmarketing surveillance and pharmacoepidemiologic study to evaluate the effect of doxazosin on erectile function in patients with moderate to severe BPH
6	DAZ-EG-98-001	Egypt	A multicenter open, baseline controlled study of efficacy, safety and toleration of doxazosin in the symptomatic treatment of patients with benign prostatic hyperplasia concurrent with male erectile dysfunction
7	DAZ-I-94-002	Italy	Double-blind, comparative clinical study on the efficacy and safety of doxazosin GITS vs. placebo in the symptomatic treatment of benign prostatic hyperplasia
8	DAZ-JO-96-001	Jordan	An open study of the efficacy, safety, and tolerability of doxazosin in the symptomatic treatment of benign prostatic hyperplasia
9	DAZ-K-95-002	Korea	Drug use investigation [redacted] of Cardura in patients with benign prostatic hyperplasia
10	DAZ-K-95-003	Korea	Drug use investigation of Cardura by quick dose titration in patients with benign prostatic hyperplasia
11	DAZ-NY-92-004B	Korea	Doxazosin in the symptomatic treatment of benign prostatic hyperplasia. An open baseline controlled, study in general medical practice
12	DAZ-NY-92-008	Denmark, Netherlands	A double blind study comparing the efficacy and safety of doxazosin vs. alfuzosin in the treatment of benign prostatic hyperplasia
13	DAZ-NY-94-001	S. Africa, S. America, Eastern Europe	Doxazosin in the treatment of benign prostatic hyperplasia. An open baseline controlled, study in hospital urological practice
14	DAZ-SAU-96-001	Saudi Arabia	An open study of the efficacy safety, and toleration of doxazosin in the symptomatic treatment of BPH
15	DAZ-VEN-96-001	Venezuela	Doxazosin in the treatment of benign prostatic hyperplasia. An open, multicenter, baseline-controlled study in urological practice

Ongoing BPH Trials (continued)			
1	A0351013	Germany	Open, non- comparative drug monitoring program with doxazosin GITS in patients with benign prostate hyperplasia
2	A0351015	France	Double-blind, randomized, prospective evaluation of the efficacy and safety of Zoxan LP versus tamsulosin LP in the treatment of patients with symptomatic benign prostatic hyperplasia
3	A0351025	Spain	A pharmacovigilance study in patients with benign prostatic hyperplasia treated with doxazosin GITS to evaluate reduction of urinary symptoms ("HORUS" study)
4	A0351027	U.K., France, Germany, Poland, Norway, Spain, Hungary, U.S.	A double-blind, placebo controlled study to evaluate the onset of action of doxazosin gastro intestinal therapeutic system (GITS) in the treatment of BPH (SOARx)
5	A0351030	Hong Kong	Double-blind, randomized, prospective evaluation of the efficacy and safety of doxazosin standard versus doxazosin GITS in Chinese patients with symptomatic benign prostatic hyperplasia - a study to evaluate rate in achieving therapeutic effects
6	A0351038	Czech Republic	Cardura XL in patients with BPH - observational study
7	A0351039	Brazil	Multicenter, comparative, double-blind, double-dummy and randomized study to assess the safety and efficiency of doxazosin of controlled liberation against tamsulosin when treating patients with symptoms of benign prostatic hyperplasia
8	A0351040	Brazil	Multicenter, non comparative, open-label study of the efficacy and safety of doxazosin extended release tablets on the reduction of prostatic and urinary symptoms in patients with benign prostatic hyperplasia
9	A0351044	Spain	Transcultural adaptation into Spanish of a specific related quality of life questionnaire (BPH-PIM) for men with benign prostatic hyperplasia
10	A0351052	Czech Republic	Cardura XL in the treatment of BPH

Completed BPH studies (continued)			
11	A0351057	Korea	Post-marketing surveillance study to evaluate
			the safety and effectiveness of doxazosin GITS
			in patients with benign prostate hyperplasia
12	A0351058	Slovakia	Non-interventional study in BPH patients
13	DAZ-D-99-003AB	Germany	Open, non-comparative drug monitoring
			program with doxazosin GITS in BPH patients
14	DAZ-NY-96-014	U.K.	Prospective, randomized, double-blind, cross-
			over trial of the safety and efficacy of
			doxazosin versus tamsulosin in patients with
			benign prostatic hyperplasia

Section 3: Number of episodes where orthostatic change induces decrease in systolic blood pressure by ≥ 20mm Hg in study DAZ-JP-97-0501.

Subject #	1mg STD	4mg GITS	8mg GITS	Placebo
1	5	1	4	0
2	1	0	1	0
3	0	0	0	0
4	0	0	0	0
5	0	0	0	0
6	0	0	0	0
7	0	0	0	0
8	0	0	0	0
9	0	0	0	0
10	0	0	0	0
11	0	0	0	0
12	0	1	0	0
Total	6	2	5	0

Section 4: Number of episodes where orthostatic change induces decrease in diastolic blood pressure by ≥ 10mm Hg in study DAZ-JP-97-0501.

Subject #	1mg STD	4mg GITS	8mg GITS	Placebo
1	7	3	10	4
2	3	3	3	1
3	0	0	1	0
4	0	0	4	0
5	0	0	0	0
6	0	0	0	0
7	0	0	0	0
8	1	0	0	2
9	1	0	2	0
10	0	0	0	0
11	1	0	2	1
12	0	1	1	0
Total	13	7	23	8

Section 5: Approval and Launch Information for 4mg GITS preparation.

Market	Trade Name	Status	Approval Date	Launch Date	Withdrawal Date
GERMANY	CARDULAR PP 4MG	LAUNCHED	4-Dec-97	1-Mar-98	Not Applicable
NORWAY	CARDURAN CR	LAUNCHED	12-May-98	1-Aug-98	Not Applicable
SWEDEN	ALFADIL	LAUNCHED	15-May-98	15-Jun-98	Not Applicable
BRAZIL	CARDURAN XL	LAUNCHED	19-Jun-98	6-Apr-00	Not Applicable
TURKMENISTAN	CARDURA XL	LAUNCHED	22-Jun-98	22-Jun-98	Not Applicable
DENMARK	CARDURAN RETARD	LAUNCHED	12-Nov-98	28-Dec-98	Not Applicable
HUNGARY	CARDURA XL	LAUNCHED	2-Dec-98	28-Feb-02	Not Applicable
UZBEKISTAN	CARDURA XL	APPROVED	8-Apr-99	[redacted]	
SPAIN	CARDURAN NEO	LAUNCHED	27-May-99	2-Feb-00	Not Applicable
POLAND	CARDURA XL	LAUNCHED	30-Jul-99	1-Jun-00	Not Applicable
CZECH REPUBLIC	CARDURA XL	LAUNCHED	4-Aug-99	15-Sep-00	Not Applicable
ICELAND	CARDURAN RETARD	LAUNCHED	11-Aug-99	1-Oct-99	Not Applicable
HONG KONG	CARDURA XL	LAUNCHED	12-Aug-99	1-Jun-00	Not Applicable
FRANCE	ZOXAN LP	LAUNCHED	13-Aug-99	1-Feb-00	Not Applicable
NETHERLANDS	CARDURA XL	LAUNCHED	30-Aug-99	1-Nov-99	Not Applicable
SWITZERLAND	CARDURA CR	LAUNCHED	27-Sep-99	4-Jan-00	Not Applicable
IRELAND	CARDURA XL	APPROVED	29-Oct-99	Unknown	Not Applicable
KYRGYZSTAN	CARDURA XL	APPROVED	19-Nov-99	[redacted]	
SINGAPORE	CARDURA XL	APPROVED	15-Dec-99		
PORTUGAL	CARDURA GITS	APPROVED	23-Dec-99		
VENEZUELA	CARDURAN XL	APPROVED	27-Dec-99		
CHILE	CARDURA XL	LAUNCHED	30-Dec-99	1-Jul-01	Not Applicable
LITHUANIA	CARDURA XL	LAUNCHED	28-Jan-00	Unknown	Not Applicable
SLOVAK REPUBLIC	CARDURA XL	LAUNCHED	7-Feb-00	15-Sep-01	Not Applicable
UKRAINE	CARDURA XL	APPROVED	24-Feb-00	[redacted]	
LATVIA	CARDURA XL	LAUNCHED	15-Mar-00	1-Apr-00	Not Applicable
COLOMBIA	CARDURA XL	APPROVED	4-May-00	[redacted]	
SOUTH AFRICA	CARDURA XL	LAUNCHED	28-Jun-00	1-Nov-00	Not Applicable
ARMENIA	CARDURA XL	LAUNCHED	20-Jul-00	19-Sep-00	Not Applicable
ITALY	CARDURA XL	APPROVED	2-Oct-00		
RUSSIA	CARDURA XL	APPROVED	11-Nov-00	[redacted]	
KOREA	CARDURA XL	LAUNCHED	30-Nov-00	1-Jun-01	Not Applicable
BULGARIA	CARDURA XL	APPROVED	15-Dec-00		
BELGIUM	CARDURA GITS	APPROVED	20-Dec-00	[redacted]	
UNITED KINGDOM	CARDURA XL	APPROVED	15-Jan-01	1-Mar-01	Not Applicable
MALTA	CARDURA XL	APPROVED	30-Mar-01		
ECUADOR	CARDURA XL	APPROVED	1-Jun-01	[redacted]	
CHINA	CARDURA XL	LAUNCHED	29-Jun-01	29-Sep-02	Not Applicable
LUXEMBOURG	CARDURA GITS	APPROVED	12-Jul-01		
ZIMBABWE	CARDURA XL	APPROVED	3-Oct-01		
GEORGIA	CARDURA XL	APPROVED	25-Mar-02	[redacted]	
ROMANIA	CARDURA XL	LAUNCHED	21-May-02	10-May-02	Not Applicable
KAZAKHSTAN	CARDURA XL	APPROVED	1-Jul-02		
SLOVENIA	CARDURA XL	APPROVED	10-Jul-02		
TAIWAN	DOXABEN	APPROVED	5-May-03	[redacted]	

Section 6: Approval and Launch Information for 8mg GITS preparation.

Market	Trade Name	Status	Approval Date	Launch Date	Withdrawal Date
GERMANY	CARDULAR PP 8MG	APPROVED	4-Dec-97		
NORWAY	CARDURAN CR	LAUNCHED	12-May-98	1-Aug-98	Not Applicable
SWEDEN	ALFADIL	LAUNCHED	15-May-98	1-Nov-98	Not Applicable
BRAZIL	CARDURAN XL	LAUNCHED	19-Jun-98	6-Apr-00	Not Applicable
TURKMENISTAN	CARDURA XL	LAUNCHED	22-Jun-98	22-Jun-98	Not Applicable
DENMARK	CARDURAN RETARD	APPROVED	12-Nov-98		
HUNGARY	CARDURA XL	LAUNCHED	2-Dec-98	28-Feb-02	Not Applicable
UZBEKISTAN	CARDURA XL	APPROVED	8-Apr-99		
SPAIN	CARDURAN NEO	LAUNCHED	27-May-99	21-Jan-02	Not Applicable
POLAND	CARDURA XL	LAUNCHED	30-Jul-99	1-Jun-00	Not Applicable
FRANCE	ZOXAN LP	LAUNCHED	3-Aug-99	1-Feb-00	Not Applicable
CZECH REPUBLIC	CARDURA XL	LAUNCHED	4-Aug-99	1-Sep-00	Not Applicable
ICELAND	CARDURAN RETARD	APPROVED	11-Aug-99		
HONG KONG	CARDURA XL	LAUNCHED	12-Aug-99	1-Jun-00	Not Applicable
NETHERLANDS	CARDURA XL	LAUNCHED	30-Aug-99	1-Nov-99	Not Applicable
SWITZERLAND	CARDURA CR	LAUNCHED	27-Sep-99	4-Jan-00	Not Applicable
IRELAND	CARDURA XL	APPROVED	29-Oct-99		
KYRGYZSTAN	CARDURA XL	APPROVED	19-Nov-99		
SINGAPORE	CARDURA XL	APPROVED	15-Dec-99		
PORTUGAL	CARDURA GITS	APPROVED	23-Dec-99		
VENEZUELA	CARDURAN XL	APPROVED	27-Dec-99		
LITHUANIA	CARDURA XL	APPROVED	28-Jan-00		
SLOVAK REPUBLIC	CARDURA XL	LAUNCHED	7-Feb-00	15-Sep-01	Not Applicable
UKRAINE	CARDURA XL	APPROVED	24-Feb-00		
LATVIA	CARDURA XL	LAUNCHED	15-Mar-00	1-Sep-00	Not Applicable
COLOMBIA	CARDURA XL	APPROVED	18-Apr-00		
SOUTH AFRICA	CARDURA	LAUNCHED	28-Jun-00	1-Nov-00	Not Applicable
ARMENIA	CARDURA XL	LAUNCHED	20-Jul-00	19-Mar-01	Not Applicable
RUSSIA	CARDURA XL	APPROVED	11-Nov-00		
KOREA	CARDURA XL	APPROVED	30-Nov-00		
BULGARIA	CARDURA XL	APPROVED	15-Dec-00		
BELGIUM	CADURA GITS	APPROVED	20-Dec-00		
UNITED KINGDOM	CARDURA XL	LAUNCHED	15-Jan-01	1-Mar-01	Not Applicable
MALTA	CARDURA XL	APPROVED	30-Mar-01		
ECUADOR	CARDURA XL	APPROVED	1-Jun-01		
CHINA	CARDURA XL	LAUNCHED	5-Jul-01	1-Jan-02	Not Applicable
LUXEMBOURG	CARDURA GITS	APPROVED	12-Jul-01		
ZIMBABWE	CARDURA XL	APPROVED	3-Oct-01		
GEORGIA	CARDURA XL	APPROVED	25-Mar-02		
ROMANIA	CARDURA XL	APPROVED	21-May-02		
SLOVENIA	CARDURA XL	APPROVED	10-Jul-02		
KAZAKHSTAN	CARDURA XL	APPROVED	17-Oct-02		

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/s/

Gerald Willett
6/17/04 08:46:34 AM
MEDICAL OFFICER

Mark S. Hirsch
6/17/04 09:30:43 AM
MEDICAL OFFICER
I concur.

NDA 21-269

Medical Team Leader's Memorandum

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

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

Date of memo: February 22, 2002

Regarding: NDA 21-269, Cardura XL 4 mg and 8 mg tablets for the treatment of symptoms of benign prostatic [redacted] (BPH)

Executive summary:
The purpose of this memo is to inform the Division Director that the final chemistry review of Cardura XL (NDA 21-269) has been received and reviewed by the medical team leader.

There are no new chemistry issues compared to my previous memo.

In my previous memo (dated February 21, 2002), I noted that 3 container label issues were still under negotiation. In the opinion of the chemist these are resolved. They include:

1. The container label has clear color differentiation of the 4 mg and 8 mg dosage strengths.
2. The sponsor has justified the reason for the encircled dosage strength as a standard "Pfizer" measure. The chemist has learned that this type of marking has been allowed for several other drug products manufactured by this sponsor. The chemist will allow this marking to remain based upon precedence and I concur that it is not a safety risk.
3. The sponsor has committed to change the color of the letters "XL" of the tradename Cardura XL to better differentiate Cardura from Cardura XL. This commitment is appropriate and we will await revised container labels to be assured that the objective is met.

Finally, the sponsor has committed to market Cardura XL [redacted] bottles. In doing so, there is no further concern regarding the inadequacies of [redacted]

Mark S. Hirsch, M.D.
Medical Team Leader
Arch NDA 21-269
Cc: HFD-580/Div File
HFD-580/DShames/GWillett/EFarinas

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
2/22/02 10:41:30 AM
MEDICAL OFFICER

Daniel A. Shames
2/22/02 01:37:57 PM
MEDICAL OFFICER

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 21, 2002

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.

Clinical issues
In brief, I believe that the evidence in this submission is adequate to support efficacy of the product for the BPH indication. I also believe that a substantial body of data suggests that Cardura XL is *probably* safe when used for BPH as directed in the proposed label. However, I am not able to recommend final approval at this time because, in my opinion, the following two **deficiencies** remain:

1. The sponsor has not adequately defined the blood pressure-lowering effect of a single starting dose of Cardura XL 4 mg, compared to Cardura standard 1 mg, and compared to placebo when used for BPH, and

2. The sponsor has not adequately described the clinical risk profile for a starting dose of Cardura XL 4 mg as compared to Cardura standard 1 mg in the treatment of BPH, with particular attention to orthostasis-related adverse events after the first dose and after one week of dosing.

Also, the sponsor has not adequately supported safety in black men. This particular deficiency, known to the Agency before filing of this NDA, would not of itself preclude approval and therefore, I do not see this issue as a so-called "approvable deficiency", but it certainly is of clinical importance.

In arriving at this regulatory decision, I considered the following:

1. The bioavailability of Cardura XL 4 mg most closely resembles that of Cardura standard 2 mg, not Cardura standard 1 mg. Currently, it is widely accepted clinical practice to always start alpha-blocker therapy for BPH with the lowest available dose, which in this case is 1

mg. The sponsor has not yet provided sufficient data to fully support the safety of "skipping" the 1 mg Cardura standard starting dose.

2. Data line listings for adverse events in both BPH trials suggested that Cardura standard 2 mg was administered during the first week, as opposed to the per-protocol 1 mg dose. If this is correct, the Cardura standard adverse event incidence would be expected to be artificially inflated. This must be clarified.

3. Dr. Karkowsky of the Division of Cardio-Renal Drug Products found an increased incidence of vasodilatory adverse events in the Cardura XL group compared to the Cardura standard group in the first week of therapy [redacted]
He believes that this represents a potential signal for post-marketing risk.

Chemistry issues
In a correspondence dated February 13, 2002, (received by DRUDP on February 19th), the sponsor formally accepted the Agency's recommended dissolution specifications and shelf-life duration. We are still awaiting the chemist's actual review to be sure that these responses were indeed acceptable to the Agency. The chemistry staff continues to negotiate several container label issues relevant to differentiating the 4 and 8 mg strengths and Cardura standard versus Cardura XL. At this time, pending no other chemistry issues raised in the review, the container label remains as the only outstanding chemistry issue.

In order to **resolve** these deficiencies, I propose the following:

Clinical
1. The sponsor should provide data to describe the absolute effect on blood pressure and pulse of a single starting dose of Cardura XL 4 mg, when compared to Cardura standard 1 mg, and to placebo. Blood pressure and pulse (including orthostatic maneuvers) should be measured around the time of maximum plasma concentrations.

2. The sponsor should provide a critical analysis of clinical adverse events comparing Cardura XL 4 mg, and Cardura standard 1 mg after the first day and after the first week of therapy. The focus of this analysis should be on orthostasis-related adverse events. The objective of this analysis should be to demonstrate that a starting dose of Cardura XL 4 mg is not associated with a significantly greater incidence of orthostasis-related clinical adverse events than a starting dose of 1 mg in either the first day or the first week of treatment. The sponsor may use all available relevant data to conduct this analysis or may need to study additional patients in clinical trials as necessary.

Chemistry
The sponsor should formally agree to the Agency-proposed container labeling revisions. Such agreement is not required at this moment if an approvable action is taken for clinical deficiencies. Labeling negotiations (including carton/container labeling) will continue after sponsor's submission of the clinical deficiency resolution items.

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) and the alpha-adrenergic antagonists (including prazosin [Minipress], terazosin [Hytrin], doxazosin [Cardura], and tamsulosin [Flomax]).

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 outcomes of BPH (e.g. urinary retention, need for surgery, renal failure, etc).

Alpha-blocker therapy for BPH has been limited somewhat by vasodilatory and other undesirable systemic alpha-blocking adverse events. These are more notable in the more "non-selective" alpha-blockers (e.g. prazosin) compared to the potentially more selective ones (e.g. tamsulosin). In addition, safe use of alpha-blockers for BPH is predicated upon a step-wise titration to the individual's own effective dose. Thus, for terazosin and doxazosin, 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 further warn that they receive help in arising from bed following dosing. These measures are used to limit the sequelae of vasodilatory adverse events (AEs).

In this NDA, the sponsor has proposed a novel formulation of Cardura (Cardura XL) which presents some theoretic advantages compared with standard Cardura. First, Cardura XL would allow for a patient to initiate therapy with a potentially 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. limiting Cmax).

Comment:

1. The reviewer agrees that removing the need for the 1 mg and 2 mg titration steps would be a benefit in therapy for BPH.
2. The reviewer agrees that limiting clinical AEs related to alpha-blocker therapy would be a benefit in therapy for BPH.

[redacted] treatment of the symptoms of BPH (under NDA 21-269). The sponsor believed that Cardura XL [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 ("CR Division") provided comments to the sponsor leading to the eventual withdrawal of NDA 21-269 from the CR Division. In the last two weeks of this review cycle, the sponsor elected to proceed with the application for BPH [redacted] Only one other agent in this class, Flomax (tamsulosin) is currently approved for BPH [redacted] In practice, having a unique "BPH [redacted] indication is believed to be a clinical benefit of Flomax over the other products in the class.

Pfizer Pharmaceuticals Inc., the sponsor of this new drug application (NDA), submits clinical data which they now believe support this "BPH· indication" for Cardura XL.

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], and one open-label extension trial to support the BPH indication. In NDA 21-269, the sponsor also submitted two controlled Phase 3 clinical trials and one open-label extension trial to support the [redacted] indication. [redacted] NDA, the sponsor also submitted five (5) phase 1 clinical pharmacology studies [redacted] This comprises the clinically relevant data from all trials [redacted]

3. Design of Clinical Trials to Support the BPH Indication
In support of the efficacy and safety of Cardura XL for the BPH indication, the sponsor submitted the results from the following 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 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: 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) and a reduction from baseline in total IPSS of at least 30% (for IPSS).

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 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.

> **Comment**: It is not clear how many patients wound up on the maximum doses in Study #2.

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	

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	

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 for purposes of exploring long-term efficacy. 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:

1. The efficacy results from the Cardura XL and Cardura standard groups in these trials appear similar qualitatively to those described for other once-daily products in this class for this indication (e.g. tamsulosin and terazosin).

   Comment: Such cross-study comparisons are exploratory at best and conclusions drawn from such comparisons are also exploratory.

2. 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 dose was not studied.

   Comment: 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 blood levels akin to a 1 mg standard dose, and such a dose is not believed to be efficacious.

3. Cardura standard and Cardura GITS both require daily dosing. Therefore, there is no net benefit in terms of decreased frequency of daily dosing.

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 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], 318 patients received Cardura XL in two pivotal Phase trials. The duration of treatment in these trials was 12 weeks. Of this total number of patients, 280 enrolled into the [redacted] open-label extension trial and 266 completed at least 24 weeks. In fact, 138 completed at least 36 weeks.

The sponsor submitted data from 5 additional "supporting studies" [redacted] that included a total of 177 additional patients dosed for 10 to 14 weeks. [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 and Spain (others unknown to this reviewer).

> **Comment**: The controlled safety database for Cardura XL 4 mg to 8 mg regimen, especially in regard to safety of the first dose of 4 mg is fairly limited.

4.2.2. Deaths, SAEs and Discontinuations Due to AEs

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 BPH 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.

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.

> **Comments**: Discontinuations due to AEs were actually less frequent in the Cardura GITS group.

4.2.3 Adverse Events of Special Interest: Adrenergic Blocking Symptoms
In the BPH and hypertension trials, 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%)
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 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.

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. This was similarly true for the placebo group and may be a consequence of aging.

> **Comment**: In this regard, approximately 50% of each treatment group in the BPH trials was at least 65 years of age. Additional information in a more vulnerable population (e.g. those at least 75 years of age) would be valuable in overall assessment of risk.

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

> **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, it is difficult to draw conclusions from this finding.

[redacted]), Dr. Abraham Karkowsky of the Division of Cardio-Renal Drug products, notes however, that in the first week of therapy in both hypertension trials [redacted] more subjects in the GITS group reported cardiovascular or vasodilatory AES compared with the standard group regimen. He actually lists these events individually in Table 5 of his review. He notes that in [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 finds this to be a safety concern and attributes the signal to a relatively higher dose of doxazosin in those given Cardura GITS 4 mg compared to those given Cardura standard 1 mg. Based upon differences in bioavailability, both Dr. Karkowsky and Dr. Lydia Kiefer (of OCPB) believe that the 4 mg GITS dose provides blood levels more closely akin to the 2 mg standard than the 1 mg standard Cardura dose.

> **Comment**: I agree with Dr. Karkowsky that this finding could represent a potential safety signal and should be further assessed prior to the granting of marketing approval.

Overall, if one looks at the entire dosing period in the hypertension trials, the incidence of vasodilatory AEs dose 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]	**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 (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.

> **Comment**: To the best of my knowledge, these appear to be the only available actual blood pressure data measured at Tmax following the first dose of GITS 4 mg. There are no data comparing blood pressure response after the first dose of 1 mg standard versus 4 mg GITS. I believe that such information should be made available to the Agency prior to granting marketing approval. I recommend withholding approval until such data is submitted, reviewed, and supports the safety of Cardura XL when administered as recommended by the sponsor.

2.2.4 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)
Dizziness	35 (5.3%)	59 (9.1%)	3 (1.9%)
Headache	40 (6.0%)	33 (5.1%)	7 (4.5%)
Asthenia	26 (3.9%)	45 (6.9%)	2 (1.3%)
Respiratory tract infection	32 (4.8%)	29 (4.5%)	3 (1.9%)
Flu syndrome	16 (2.4%)	22 (3.4%)	7 (4.5%)
Back pain	19 (2.9%)	11 (1.7%)	4 (2.6%)
Vertigo	10 (1.5%)	27 (4.1%)	1 (0.6%)
Bronchitis	7 (1.1%)	8 (1.2%)	4 (2.6%)
Abdominal pain	12 (1.8%)	15 (2.3%)	1 (0.6%)
Nausea	8 (1.2%)	15 (2.3%)	1 (0.6%)
Postural hypotension	8 (1.2%)	14 (2.2%)	1 (0.6%)

4.2.5 Other Safety Issues From the Primary MO's 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 rarely) days or weeks after the start of therapy.

The safety update was significant only for a single case of urticaria that may have been treatment-related and should be included in the labeling. Sponsor acknowledged this finding and agrees to such labeling.

Dr. Willett notes that 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.

> **Comment**: While this may be an error of transcription, it requires resolution by the sponsor. If 2 mg standard was actually being administered during Week 1, such would be a protocol violation and would bias the analysis of Week 1 safety in favor of Cardura GITS.

4.2.6 Other Safety Issues

Other safety issues of relevance include:

1. While the Cardura standard label encourages blood pressure measurements after initial dosing with 1 mg and such risk management measures as helping patients arise from a supine position, [redacted]

   > **Comment**: It could be argued that the risk management measures advocated for Cardura standard may actually make for a "safer" product than Cardura XL without such procedures.

2. Currently there is no clear evidence that Cardura XL is actually safer than Cardura standard or than any other product in this class.

5. Major Issues From Other Disciplines Or Other Sources

5.1 Clinical Pharmacology

The clinical pharmacology reviewers in the Division of Cardio-Renal Drug Products found the data "acceptable provided labeling comments number 1 to 4 are adequately addressed."

I reviewed these 4 "labeling comments". They are, in brief:

- IV/IVC analysis data submitted on January 4th did not establish a correlation. At the time of the February 11th OCPH Briefing, Dr. Lydia Kiefer commented that the IV/IVC correlation still had not been established.

- The sponsor should change the dissolution specifications to those recommended by the Agency.

  Comment: These two deficiencies were resolved by the sponsor's acceptance of the Agency-proposed dissolution specifications in a correspondence dated February 13, 2002. I am awaiting the chemist's review for final assurance that this matter is resolved.

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

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

  Comment: OCPB would like the sponsor to better assess the performance of the formulation in an individual from one day to another. While this is rational, I find it unclear why the lack of this information should preclude OCPB from finding the current NDA submission "acceptable". From my perspective, the lack of this specific information should not preclude approval but would be valuable to know.

Clinical pharmacology reviewed the results from 7 studies:

1) Four (4) Phase 1 studies in healthy volunteers

   a. Study DAZ-NY-96-008 compared the bioavailability of a single dose of 8 mg GITS (both fed and fasted) to a single dose of 2 mg standard (fasted only).
   b. Study DAZ-NY-96-010 compared the bioavailability of a single dose of 8 mg GITS to two single doses of 4 mg GITS.
   c. Study DAZ-NY-96-007 compared the pharmacokinetics of multiple doses of GITS 4 mg and 8 mg (placebo for 7 days, followed by 4 mg for 7 days, followed by 8 mg for 7 days) to multiple doses of standard (1 mg for 2 days, 2 mg for 5 days, 4 mg for 7 days, and 8 mg for 7 days)
   d. Study DAZ-NY-96-009 compared the pharmacokinetics of multiple doses of GITS 4 mg (7 days) in young men and women to elderly men and women.

2) One (1) comparative study of bioavailability in the hepatically-impaired versus the healthy volunteer using standard 2 mg (reviewed previously under NDA 19-668/SLR-009).
3) One (1) in-vitro study relevant to dissolution testing and method validation.
4) One (1) "sub-study" within the Phase 3 BPH trial DAZ-N/S/DK-95-001 in which sparse pK samples were obtained from subjects at Norwegian sites in order to explore the relationship between pK and pD (using maximum urinary flow rate).

The clinical pharmacology reviewer makes the following clinically relevant major points:

1. For the 8 mg GITS tablets, Cmax and AUC increase by 32% and 18% in the fed state compared with the fasted state. The elimination kinetics are the same in fed or fasted states. Thus the reviewer concludes that at steady state, the extent of differences between fed and fasted states should not be affected by food and thus, dosing instructions with or without food are appropriate.

   Comment: In the 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. However, in this case, I agree with Dr. Kiefer that at steady-state, food effect should be lessened and labeled dosing instructions should allow for dosing with or without food.

2. Dr Kiefer states that the "sponsor has concluded" that the initial 4 mg dose of Cardura XL will cause a maximum plasma concentration similar to 2 mg of Cardura standard. She then notes that "the starting dose for Cardura is 1 mg; which is known to be well-tolerated in the patient population and is used initially per current labeling prior to dose titration."

   Comment: I agree with Dr. Kiefer on this point. The use of the 1 mg starting dose to minimize orthostatic AEs is well-recognized standard of care. Based on this important observation, lack of relevant blood pressure data at Tmax, and fairly limited nature of the overall safety database, I recommend that approval of Cardura GITS be withheld until the sponsor submits information relevant to the direct effect of a starting dose of 4 mg GITS on blood pressure and a critical analysis comparing orthostatic adverse events between 4 mg GITS and 1 mg standard following a single first dose and following 1 week of dosing. This, I believe is the major clinical reason for not granting marketing approval at this time.

3. Dose-proportionality was demonstrated for the 4 mg and 8 mg doses for both formulations (GITS and standard). Thus, extrapolations from these two points are possible.

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. This is of benefit if prescribers choose to switch from standard to GITS formulations.

3. 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. Dr. Kiefer comments 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. Dr. Kiefer believes that these data indicate that dose-titration at doses lower than 4 mg GITS may be necessary in young women.

4. There were notable 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. The sponsor believes that this finding does not mandate a dose adjustment and Dr. Kiefer agrees.

Comment: It is relevant that to note here that the number of patients older than 75 in the safety database is limited. Because this is a more vulnerable population in terms of orthostatic-related adverse events, and because it is a large part of the actual target population, and because the bioavailability was higher in elderly males than in the young, I would consider additional data in this population valuable.

5.2 Chemistry

As of this moment, no chemistry review (either draft or final) is available for my assessment. I have spoken with Dr. Srinivasachar, Chemistry Team Leader in Division of Cardio-Renal Drug Products and with Drs Agarwal and Rhee here in DRUDP.

To my knowledge, there have been ongoing negotiations with the sponsor about the final dissolution release specification and the expiry data. Dr. Srinivaschar assured me that that the sponsor had verbally accepted the Agency's proposed specification and shelf-life duration. On February 13, 2000, the sponsor submitted a correspondence that appears to formally accept both the [redacted] shelf-life and the Agency-recommended dissolution specification. We await receipt of a chemistry review in order to be assured that these matters are resolved.

Shelf-life is particular critical for this NDA since the issue of diminishing product quality over time has arisen at several status meetings. Specifically, the chemistry review was concerned that

[redacted]

According to the sponsor's correspondence, dated February 13, 2002, the sponsor has agreed to commercialize Cardura XL only in [redacted] bottles [redacted] With this agreement, Dr. Agarwal informs me that the issue of [redacted] is probably resolved. Again, we await receipt of a chemistry review in order to be assured that these matters are fully resolved.

In addition, I have also been informed that negotiations regarding OPDRA's recommendatiosn regarding revisions to the container label have not been fully resolved (see relevant section regarding OPDRA consult in this memo).

Of note, Dr. Agarwal informed the review team on February 13th that the overall recommendation from the Office of Compliance regarding manufacturing site inspections was "acceptable".

Finally, without at least a draft review for assessment, other issues of clinical relevance may exist without my knowledge of them.

Comment: Based upon my discussions with Drs. Agarwal, Rhee and Srinivasachar, my overall regulatory recommendations are predicated on an understanding that the only remaining chemistry issue is the container label.

5.3 Biometrics

Dr. Gebert's memo was reviewed. 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 standard. Several issues are of note:

1. Dr. Gebert "could not duplicate the sponsor's analyses exactly" (of BPH Studies #1 and #2). However, the differences were negligible and did not affect the conclusions.
2. Dr. Gebert comments that the maximal total IPSS score is 41. That is not correct. The maximal score is 30 points. However, I do not believe that this mistake impacts on the any of the overall Biometrics conclusions.
3. 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.
4. 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 states that this "fails the sponsor's definition of statistical equivalence".

   Comments:
   1. In my opinion, failure to meet achieve statistical equivalence is not an impediment to approval. These products appear clinically comparable when dosed as in BPH Studies #1 and #2.
   2. Doxazosin GITS gave slightly more reduction in Qmax than doxazosin standard in both studies.

5. 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 states that this "just meets the sponsor's definition of statistical equivalence".

   Comment: Again, it is not clear from Dr. Gebert's review whether the active groups were equivalent for flow rate parameters in BPH Study #2. However, Doxazosin GITS gave slightly more reduction in Qmax than doxazosin standard in both studies.

6. Dr. Gebert comments that "formal testing of equivalence is somewhat problematic" for this NDA because the pivotal studies used a titration design to final dose, but there were different starting dosages. He writes that the doxazosin standard group was allowed to stop at 2 mg. Approximately 11.7% of standard patients actually did stop at 2 mg.

   Comment: For this issue, it may be relevant to repeat that the 4 mg GITS formulation provides pharmacokinetics similar to the 2 mg standard formulation.

7. Dr. Gebert ultimately concludes 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.

5.4 Toxicology

Dr. DeFelice's memo states that no new preclinical pharmacology or toxicology studies were submitted to support this NDA. However, he does comment that:

> "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."

I assume, therefore, that this was a negative test of the potential for Cardura GITS to erode the colonic wall. Dr. DeFelice then provided labeling comments to relevant sections of the Cardura label. None of these comments were specific to Cardura XL.

> **Comment**: Dr. DeFilice's labeling revisions have NOT yet been communicated to sponsor and must be resolved when labeling negotiations are appropriate.

5.5 Division of Scientific Investigation (DSI)

DSI conducted routine inspections for BPH Study #2 only. Three sites in Canada were inspected Dr Duval (N=24 randomized) and Dr. Fradet (N=14 randomized), both in Quebec, and Dr. Morales (N=19 randomized) in Ontario. Minor protocol violations and record-keeping inadequacies were noted at all three sites but none of these findings were considered of enough significance to adversely affect the acceptability of the data. Thus, DSI concluded that the data generated by Drs. Duval, Fradet and Morales could be used in support of the NDA.

5.6 Financial Disclosure

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 under NDA 21-269.

5.7 Pediatrics

Since this indication is intended for the treatment of the signs and symptoms of BPH in adult men, a pediatric waiver is appropriate. The sponsor requested a waiver in Section 13 of the NDA. A regulatory letter granting the pediatric waiver was signed by Dr. Shames on February 12, 2002.

5.8 OPDRA Tradename Review

OPDRA 's assessment of the proposed tradename, Cardura XL, was completed on August 15, 2001. In summary, OPDRA had no objection to the use of the proposed tradename. However, OPDRA proposed several changes to the container label. These included the following:

1. The sponsor should more clearly differentiate the label appearance between Cardura XL 4 mg and 8 mg.
2. The sponsor should more clearly differentiate the label appearance of Cardura XL and Cardura standard.
3. The encircled numbers "4" and "8" expressed immediately after the tradename are unclear and could be confusing.
4. The proposed containers of 30 tablets should provide [redacted]

> **Comment**: The sponsor's correspondence dated February 13th indicates that the proposed container utilizes [redacted], so this is issue is likely to be resolved. I am

aware that active container label negotiations are ongoing with sponsor about the remaining three items but these are not yet fully resolved.

5.9 Division of Cardio-Renal Drug Products Clinical Team

[redacted]

"The proposed Cardura GITS formulation is substantially less bioavailable then the already approved Cardura IR formulation without demonstrated net benefit over the already approved formulation. Both the GITS and IR formulations are for once-daily dosing. There is, consequently, no benefit of the GITS formulation in decreasing the number of daily doses."

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 include:

1. There were notably 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 lists these actual events individually, derived only from the pivotal hypertension trials, in Table 5 of his review.
2. There were relatively few frail elderly (at least 75 years of age) and no 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. Dr. Karkowsky remains concerned that no intra-individual, inter-daily measurements of pharmacokinetics were submitted.
5. The Cardura XL label should be separate from the Cardura standard label. [redacted]

[redacted]

Comment: A revised "BPH [redacted] label was received on February 14, 2002. Dr. Karkowsky should be consulted when labeling negotiations are appropriate.

6. Dr. Karkowsky makes mention of the ALLHAT trial; specifically to note that its results should not impact on the regulatory decisions [redacted] In ALLHAT, Cardura standard (at doses up to 8 mg) was compared to chlorthalidone with respect to non-fatal MI

and fatal CHD. The drug groups did not differ for the primary endpoint. However, chlorthalidone was superior to Cardura in the secondary endpoints of time to onset of congestive heart failure and time to CHD event (defined as death, non-fatal MI, hospitalized angina, and revascularization procedure).

While this finding generated significant interest (and was discussed at an Agency Advisory Committee), the reason for this finding is not clear. It may be related to the "truncated" dose of Cardura used in ALLHAT (8 mg). It may be related to the withholding of appropriate diuretic therapy in those patients with CHF in the Cardura group. Regardless, there is no evidence that Cardura is inferior to placebo and the Division of Cardio-Renal Drug Products has never labeled Cardura as "second-line" therapy.

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

1. In Study [redacted] the effect of the IR formulation was slightly greater than the GITS formulation. The actual results are shown in his Table #1.
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 measurements, there were no measurements of the BP effect at any other time during the dose interval.
4. In Study [redacted] the effect of Cardura IR on the primary endpoint (sitting diastolic BP) was again greater than that of Cardura GITS. However, other metrics of BP were not "overwhelmingly different between treatments."
5. Neither study explored the entire dose range of Cardura IR (up to 16 mg).
6. [redacted]
7. 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 employed a dose-titration design based upon attaining pre-defined BP-lowering effects. The effect in the BPH trials was actually "relatively small" and "somewhat inconsistent" between the two BPH trials (see his Table #4).

Comment:

1. It is notable that in the BPH trials, BP was measured only at 24 hours after dosing.
2. The differential BP-lowering effects of the individual 4 mg and 8 mg doses in the BPH trials is not available to me at this time.

7. Regulatory Summary

At this time, I recommend that Cardura XL should not be granted marketing approval for BPH until additional information is submitted. The following items would comprise the **approvable deficiencies:**

1. There is inadequate information to determine the direct effect of a first dose of 4 mg GITS on blood pressure and pulse, versus 1 mg standard, versus placebo around the time of maximum plasma concentration.
2. There is inadequate information to directly compare the incidence of vasodilatory and cardiovascular adverse events between 4 mg GITS and 1 mg standard after one day and after one week of therapy.

Given the nature of these deficiencies, I am recommending an "**approvable**" action.

The **items that would be required to resolve these deficiencies** include

1. Actual BP data at periodic intervals for 24 hours after first dosing with 4 mg GITS, compared with 1 mg standard, and with placebo. Include orthostatic procedural maneuvers.

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

As part of the approvable letter, but not so-called "approvable deficiencies", I would add the following items:

> "The following deficiencies have also been noted during the review of your NDA. While these to do not constitute formal approvable deficiencies, we are also requesting 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.
> 2. Provide all available safety information for the use of Cardura XL in men aged 75 years or older.
> 3. Clarify why 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.
> 4. [redacted]
> 5. Highlight in labeling that patients should not chew the GITS tablet.
> 6. Highlight in labeling the fact that that syncopal events have been reported to occur (albeit rarely) days or weeks after the start of therapy.
> 7. Submit pharmacokinetic data relevant to intra-subject daily variability from Phase 1 Studies DAZ-NY-96-007 and DAZ-NY-96-009.
> 8. Provide revised container labels that more clearly differentiate the tradenames Cardura from Cardura XL.

Finally, I still am not afforded a chemistry review. However, based upon my interaction with these reviewers, I believe that the only outstanding issue is the container label revisions (see Item #7 above).

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/s/

Mark S. Hirsch
2/22/02 09:52:33 AM
MEDICAL OFFICER

Daniel A. Shames
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