NDA 21-269 - Cardura XL®

Medical Officer's Review

Date submitted: April 23, 2001

Review completed: February 12, 2002

Reviewer: Gerald D. Willett MD

Applicant:

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

Chemical name:

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

Dosage forms:

Cardura XL ® (Doxazosin mesylate GITS) 4 mg tablet
Cardura XL ® (Doxazosin mesylate GITS) 8 mg tablet

Route of administration: Oral

Proposed indication:

Indicated for the treatment, [redacted] symptoms associated with benign prostatic hyperplasia (BPH) [redacted]

Related INDs:

[redacted]

Related NDAs:

NDA 19-668 Cardura® (hypertension)
NDA 20-371 Cardura® (benign prostatic hyperplasia)

Abbreviations

ACE = Angiotensin converting enzyme
AE = Adverse event
Alk Phos = Alkaline phosphatase
ALT = Alanine aminotransferase
AMI = Acute myocardial infarction
AST = Aspartate aminotransferase
AUA = American Urological Association
AUC = Area under the plasma concentration-time curve
BP = Blood pressure
BPH = Benign prostatic hyperplasia
CBC = Complete Blood Count
CHF = Congestive heart failure
CI = Confidence interval
$\mathbf{C_{max}}$ = Maximum plasma concentration
DRE = Digital rectal exam
ECG = Electrocardiography
GITS = Gastro-intestinal therapeutic system (Cardura XL®)
IIEF = International index of erectile function
I-PSS = International Prostate Symptom Score (see Appendix for scoring table)
ITT = Intent-to-treat
LS = least squares
MI = myocardial infarction
MUFR = Maximum urinary flow rate
PBO = placebo
Pk = Pharmacokinetics
PPA = Per-protocol analysis
PSA = Prostate specific antigen
SAE = Serious adverse event
SD = Standard deviation
SE = Standard error
SFQ = Sexual function questionnaire
STD = Standard formulation (Cardura®)
$\mathbf{T_{half}}$ = Terminal elimination half-life
$\mathbf{T_{max}}$ = Time of maximum concentration
TURP = Transurethral resection of the prostate
VTE = Venous thromboembolism

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Executive Summary

I. Recommendation on supplement approval

Based on the clinical efficacy and safety data presented by the sponsor, Cardura XL® is approvable from a clinical standpoint for the treatment of [redacted] symptoms associated with benign prostatic hyperplasia (BPH).

Approval is contingent on further safety analysis that demonstrates that the lowest dose of Cardura XL® (4 mg) shows no greater risk for initial dosing adverse events than the lowest dose of Cardura® (1 mg).

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

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

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

B. Efficacy

Efficacy summary comments:

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

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

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

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

C. Safety

Safety summary comments

- Although the number and type of adverse events seen with Cardura XL® is not greater or different than Cardura®, the sponsor has not provided sufficient blood pressure and symptom analysis of initial dosing of 4 mg Cardura XL®. A comparative trial of 4mg Cardura XL®, 1mg Cardura, and placebo evaluating symptoms and blood pressure at multiple time intervals in men following first dose is recommended.

- Data line listings from the BPH pivotal trials (DAZ-N/S/DK-95-001 and DAZ-NY-95-001) shows 2mg doxazosin standard dosing at a time in the protocol when 1mg of standard should have been given. Though this may be a recording error, the study design should have included an additional visit to assess the first week of dosing. If the 2mg dose is correct in some of these cases this could bias the safety comparison of Cardura XL® and Cardura®. The sponsor should clarify the discrepancies.

- The principal safety concern for Cardura XL® and for Cardura® is syncope. The number of syncopal episodes for both drug products were comparable based on the safety data from both the hypertensive trials and the BPH trials. It is important to note that the syncopal episodes for both products can occur at delayed time intervals from the initiation of therapy with the lower doses. Strengthening the "Warnings" and Patient Information sections of the label in regard to these later episodes of syncope is recommended.

- The four month safety update submitted September 6, 2001 did not indicate any additional serious safety concerns. A slightly increased number of urticarial events were reported by the sponsor and urticaria was added to the submitted label

- The commonly reported adverse events occur with comparable frequency in the over and under 65 year age groups. Dizziness and postural hypotension occur with slight

greater frequency in the over 65 age group but this is also true with placebo, suggesting age or other contributing factors.

D. Dosing

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

It is recommended that the sponsor strengthen patient information section of the label to clearly inform patients not to chew Cardura XL®.

E. Special Populations

Cardura XL® is designated for middle to elderly age men by its indication of BPH. Pharmacokinetic studies have indicated increases of 27% in maximum plasma concentrations and 34% in the area under the concentration-time-curve were seen in the elderly (≥65 years old).

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

Clinical Review

I. Introduction and Background

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

Doxazosin mesylate gastro-intestinal therapeutic system (GITS) is a modified-release formulation of doxazosin. The releasing mechanism for this formulation employs a semipermeable membrane that allows for osmotic pressure to release the drug through a small, laser-drilled orifice in the membrane on the drug side of the tablet. The proposed name for this drug is Cardura XL®. Doxazosin (Cardura®) is a selective α_1-blocker, approved for the treatment of hypertension and benign prostatic hyperplasia (BPH). Doxazosin is a quinazoline compound structurally related to prazosin and terazosin.

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

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

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

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

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

Additional assessment in everyday clinical practice for BPH patients includes the digital rectal examination (DRE) to assess prostatic size and screen for evidence of prostatic

cancer, urinalysis to assess other reasons for urinary symptomatology (i.e., urinary tract infection), and serum creatinine to assess renal function.

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

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

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

Both α-adrenergic and cholinergic receptors are present in the prostate. The α-adrenergic receptors have been subtyped into α_1 and α_2 receptors, with α_1 receptors mainly responsible for contractile function. Further typing of α_1 has identified α_{1A} (previously known as α_{1c}) as the primary prostatic adrenergic receptor. Therapeutic adrenergic blocking agents vary from non-selective (phenoxybenzamine) through α_1 selective agents such as doxazosin up to α_{1A} selective agents like tamulosin. Doxazosin (Cardura®) specifically is a long acting selective α_1 blocking agent.

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

The most common adverse events associated with selective α_1 blockers include dizziness, light-headedness and asthenia. For some of these patients bedtime administration appears to lessen the severity of these adverse events. Syncopal episodes are the most severe side effect of doxazosin. The present label for Cardura® includes warnings in regard to these severe side effects.

B. State of Armamentarium for Indication

The treatment of benign prostatic hyperplasia includes the following:

Surgical:

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

Medical:

- Selective short acting α_1-blockers
  - Prazosin (Minipress®, Minizide®) – approved for hypertension, used off-label for BPH
- Selective long acting α_1-blockers
  - Terazosin (Hytrin®, approved in U.S. for BPH)
  - Doxazosin (Cardura®, approved in U.S. for BPH)
- Selective α_{1A} blocker
  - Tamsulosin (Flomax®, approved in U.S. for BPH)
- 5α-reductase inhibitors
  - Finasteride (Proscar®, approved in U.S. for BPH)

II. Clinically Relevant Findings from Other Reviews

Financial Disclosure

Adequate documentation was submitted to comply with 21 CFR 54.

DSI Review

Though some protocol violations and recordkeeping inadequacies were identified, DSI did not find anything that adversely impacted on the acceptability of the study data at the inspection sites.

OPDRA Review

OPDRA has no objection to use of the proposed proprietary name Cardura XL.

Chemistry Review

The review is not yet complete.

Biostatistical Review

Principal findings from the statistician include the following:

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

III. Human Pharmacokinetics and Pharmacodynamics

The Office of Clinical Pharmacology and Biopharmaceutics found their section acceptable provided that four labeling comments are addressed. The labeling issues reflect the following:

1. The sponsor has not performed a true IV-IVC analysis. [redacted] The sponsor has agreed to resubmit the analysis with the raw data.

2. The sponsor's dissolution method is adequate, but in the absence of IV-IVC, the maximum width allowed per guidance is ± 10%. Therefore the 4,8, and 16 hours Q needs to be [redacted] of label claim respectively.

3. Intrasubject variability should be assessed for the 4 and 8mg GITS formulation for three different time points in study DAZ-NY-96-007.

4. Intrasubject variability should be assessed for the 4mg GITS formulation for five different time points in study DAZ-NY-96-009.

Additional points:

After a single dose of doxazosin GITS 4mg, plasma concentrations were below the lower limit of quantification until 3 hours post-dose in most subjects regardless of age and gender. Maximum plasma levels were observed around 8-9 hours post-dose and remained stable up to 24 hours post-dose. For Cardura®, peak plasma levels occur at about 2-3 hours.

The relative bioavailability of Cardura XL® compared with Cardura® was 54% at the 4mg dose and 59% for the 8mg dose.

IV. Description of Clinical Data and Sources

Overall Data/ Clinical Trials

Four clinical pharmacology studies were conducted to examine the pharmacokinetic profile of Cardura XL®.

[redacted]

Two large, controlled clinical studies were conducted to examine the efficacy and safety of Cardura XL® in the BPH patient population.

A placebo-controlled study was conducted in the Nordic Region (Denmark, Norway and Sweden) and a non-placebo controlled study was conducted in Belgium, Canada, Germany, Hungary, Ireland, Italy, Poland, South Africa and the UK. These studies are listed in the following table (table 1).

Table 1. Overview of the pivotal studies for Cardura XL® in benign prostatic hyperplasia.

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

The following table (table 2) combines the two pivotal BPH efficacy studies and lists the number randomized, the ITT population, and the PPA population.

Table 2. Subject Evaluation Groups - BPH Efficacy Studies- DAZ-N/S/DK/95-001 and DAZ-NY-95-001

	Doxazosin GITS	Doxazosin standard	Placebo
Randomized Subjects	666	651	156
ITT Population	651	640	155
PPA Population	646	633	154

Foreign Approvals

Doxazosin mesylate GITS has been approved in 24 foreign countries and launched in 13.

V. Clinical Review Methods

This review is based on the clinical data section submitted by the sponsor for NDA 21-269, information from the electronic document room and DFS, and information from the literature obtained through PUBMED and library sources.

VI. Integrated Review of Efficacy

A. Conclusions

Efficacy for Cardura XL® for benign prostatic hyperplasia was demonstrated by the following summary comments:

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

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

- In the open label extension study DAZ-NY-95-001B, Cardura XL® clinically maintained efficacy for BPH symptomatology and maximum urinary flow rate in subjects with BPH during the 24-week extension.

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

B. Detailed Review of Pivotal Trials

DAZ-N/S/DK-95-001

Title:
A 15-week, double-blind, placebo-controlled trial of the efficacy and safety of doxazosin versus doxazosin mesylate GITS in patients with benign prostatic hyperplasia.

Investigators:

[redacted]

Study Centers:

- Denmark (19)

- Norway (54)
- Sweden (24)
  Total = 97

Compliance:

The sponsor audited 30 of the 97 centers

Study Design:

Phase III, double-blind, double-dummy, randomized, multicenter, placebo-controlled, parallel-group study (randomization = doxazosin mesylate GITS: doxazosin standard: placebo = 2:2:1)

Inclusion Criteria:

- Informed consent
- Males, age 50-80
- Symptomatic benign prostatic hyperplasia defined as:
  Maximum urinary flow rate ≥ 5mls/sec and ≤ 15 mls/sec in a total voided volume ≥ 150 mls and a score of ≥ 12 on the I-PSS

Exclusion Criteria:

- Previous prostate surgery; presence of prostatic stent or microwave thermotherapy; balloon dilation within previous 6 months

- Suspected malignancy findings on a digital rectal examination (DRE)

- Any known causes other than prostatic hyperplasia for urinary symptoms or reduction in flow rate (e.g. neurogenic bladder, bladder neck contracture, urethral stricture, urinary tract infection, bladder malignancy, acute or chronic prostatitis)

- Abnormal erythrocyte findings on a urine dipstick until other reasons than BPH is excluded or treated

- Known acute urinary retention within the past year, major residual urine (>300ml), bladder stones, recurrent urinary tract infection (>3 within the last year), large bladder diverticulum, prostate malignancy.

- Known or suspected prostate malignancy and/or prostate specific antigen (PSA) > 10 ng/ml. PSA levels in the range of 4.1 to 10.0 ng/ml will require documentation that the subject is clinically free of malignancy such as a digital rectal examination, negative biopsy, or negative trans-rectal ultrasound.

- Hepatic or renal dysfunction (defined as hepatic enzymes greater than 1.5 times the upper limit of normal or serum creatinine greater than 150 µmol/l); significant gastrointestinal stricture or disease.

- Uncontrolled or poorly controlled diabetes mellitus

- Known congestive heart failure, angina pectoris, acute myocardial infarction within the past 6 months. Subjects on calcium channel blockers or on ACE inhibitors who do not have a history of angina or congestive heart failure are eligible for inclusion in the study

- A stroke within the past 6 months

- Hypotension (sitting BP less than 90/60); orthostatic hypotension or know fluid depletion

- Documented or clinically suspected serious drug reaction or idiosyncrasy to alpha adrenergic blocking agents, doxazosin, alfuzosin or quinazolines in general.

- Concomitant therapy with agents known to affect vesico-urethral function (anticholinergics, cholinergics or other alpha blockers), other agents such as 5-alpha reductase inhibitors, other anti-androgens, potentially vasoactive medications such as tricyclic anti-depressants or phytotherapy.

- Plans to donate blood during and/or for four weeks after completion of the study

- History of alcohol or drug abuse, psychological or other emotional problems that are likely to invalidate informed consent, or limit the ability of the subject to comply with the protocol requirements

- A need for an introduction, discontinuation or change in dose of diuretics or beta-blockers during or 2 weeks prior to initiation of study treatment period.

- Introduction or discontinuation of anti-androgens or 5-alpha reductase inhibitors for the 6 months prior to initiation of study.

- Participation in any other studies involving investigational or marketed products concomitantly or within one month prior to entry into study.

Medical officer's comments: Although excluding subjects with known congestive heart failure and acute myocardial infarction is reasonable based on the medical condition, it is unclear to this reviewer why all subjects with angina within the preceding six months should be excluded. This exclusion should be reflected in the labeling.

Study Design: The study design is presented in the following table (table 3)

Table 3. Study design for DAZ-N/S/DK-95-001.

Study Phase	Phase I Screening	Phase II Placebo		Run-In Phase III Efficacy		
End of Week	0	1	2	5	9	15*
Visit	1	2	3	4	5	6
Informed Consent	X					
Medical history	X					
Physical exam/body weight	X					
Digital rectal exam	X					
Blood pressure & Heart Rate	X	X	X	X	X	X
Electrocardiogram	X					
Laboratory tests**	X					X
Doxazosin Plasma Level (Norway)	X				X	X
Urine Dipstick	X					X
Prostate Specific Antigen	X					
Distribute Patient Voiding Diary/measuring cup		X	X	X	X	
Collect Patient Voiding Diary			X	X	X	X
Flow rates	X		X	X	X	X
I-PSS Index	X		X	X	X	X
Randomization			X			
Concomitant Drug Treatment	X	X	X	X	X	X
Assess Drug Compliance		X	X	X	X	X
Adverse Event Evaluation		X	X	X	X	X
Investigators Overall Assessment			X	X	X	X
Summary Evaluation						X

Study Drug Administration						
Study Week	1	2	3	4-5	6-9	10-15
Placebo	PBO	PBO	PBO	PBO	PBO	PBO
Doxazosin Standard	PBO	PBO	1 mg	2mg	2mg or 4mg	2mg or 4mg or 8mg
Doxazosin GITS	PBO	PBO	4mg	4mg	4mg	4mg or 8mg

* Or at early discontinuation

** Includes AST, ALT, Alk Phos, Sodium, Potassium, Creatinine, Uric Acid, CBC

Medical officer's comments: The lack of end of study physical and electrocardiograms are deficiencies but do not preclude approval.

The titration for the standard preparation is actually somewhat slower than employed in clinical practice. As mentioned later in the review, this slower approach may account for the difference between the two products in regard to the time it takes to attain the improved urinary flow rates.

Dosing/Duration:

- Doxazosin GITS 4mg or matched placebo, increasing to 8 mg after 7 weeks according to response; single daily oral doses, 13 weeks active drug following 2 week washout and 2 week placebo run-in.

- Doxazosin standard 1mg or matched placebo, then 2 mg after 1 week, increasing to 4 mg after 3 weeks, then 8 mg after 7 weeks according to response; single daily doses, 13 weeks active drug following 2 week washout and 2 week placebo run-in.

Patients should have their dosage titrated to achieve maximum efficacy, or if limiting adverse events have occurred, to the maximally titrated dose. Titration was accomplished based on a pre-defined "response" as follows: An adequate response is defined as having both: 1) an increase in the maximum flow rate of at least 3ml/sec and 2) a reduction of the patient's I-PSS of at least 30% from baseline.

Primary endpoints:

- Change from baseline to the final visit in total I-PSS and maximum urinary flow rate

Secondary endpoints:

- Change from baseline to each visit in the total I-PSS and the maximum urinary flow rate

- Change from baseline to each visit and the final visit in:

    1. the proportion of subjects achieving an adequate response [defined as having an increase in the maximum urinary flow rate ≥3 ml/sec (flow rate response), a reduction of the I-PSS ≥30% from baseline (I-PSS response) and both]
    2. I-PSS individual symptom scores
    3. mean urinary flow rate
    4. investigator's overall impression of efficacy (assessed on a scale of 1 = Excellent to 4 = Poor)

5. quality of life due to urinary symptoms score

Protocol Amendments:

1. Addition of doxazosin plasma levels and incorporation in flow chart, amendment to the reporting of serious adverse events (administrative)
2. Combined the stroke exclusion into the exclusion wording for CHF, angina, and AMI.
3. Changed maximum urinary flow rate in inclusion (from >5 to ≥ 5), changed wording for urinalysis, and revised a statement about medication allocation.

Medical officer's comments: The amendment changes do not effect safety or efficacy of the study.

Subjects enrolled and analyzed (table 4):

Table 4. Subjects enrolled and analyzed in study DAZ-N/S/DK/95-001

	GITS	Standard	Placebo	Total
Randomized	317	322	156	795
Completed	295	284	148	727
PPA	311	315	154	780
ITT	311	318	155	784
Safety	317	322	156	795

Medical officer's comments:

The reasons listed by the sponsor for exclusion of subjects from the per protocol population include:

Missing all on-treatment efficacy assessments
Missing baseline visit
Missing week 2 IPSS and/or maximum urinary flow rate
Missing on-treatment IPSS and/or maximum urinary flow rate assessment
Voiding interrupted
Week 2 IPS score <12
Week 2 maximum urinary flow rate < 5 or > 20ml/sec
Total voided volume <140 ml

The reasons listed by the sponsor for exclusion of subjects from the ITT population include:

Missing week 2 IPSS
Missing week 2 maximum urinary flow rate
Missing on-treatment IPSS and/or maximum urinary flow rate assessment
Voiding interrupted

Discontinuations:

A total of 68 subjects discontinued from the study, 22 subjects (6.9%) in the doxazosin GITS group, 38 subjects (11.8%) in the doxazosin standard group and 8 subjects (5.1%) in the placebo group. The breakout of the discontinuations is described in the following table.

Discontinuations and the reason for discontinuation are listed in the following table (Table 5).

Table 5. Discontinuations from study DAZ-N/S/DK/95-001

	Doxazosin GITS N=317	Doxazosin Standard N=322	Placebo N=156
Insufficient clinical response	0	1	0
Adverse events	14	30	4
Lab abnormality	1	0	0
Protocol violation	1	2	0
Lost to follow –up	1	1	2
Did not meet entrance criteria	1	1	1
Withdrew consent	0	0	1
Other	4	3	0
Total	22	38	8

Medical officer's comments: doxazosin GITS had only about half the discontinuations due to adverse events compared to doxazosin standard.

Demographics/diagnosis duration – ITT:

The following table (table 6) provides the demographics for the study arms.

Table 6. Demographics for study DAZ-N/S/DK/95-001

	Doxazosin GITS	Doxazosin Standard	Placebo
N	311	318	155
Age < 65	139	144	72
Age ≥ 65	172	174	83
Mean age	64.9	65.3	65.4
Age range	50-80	47-80	50-80
White	311	318	153
Black	0	0	0
Asian	0	0	1
Other	0	0	1
Mean weight (kg)	80.8	80.6	81.7
Mean duration from first diagnosis (yrs)	3.76	3.43	3.72

Medical officer's comments: The lack of ethnicity evaluation represents a deficiency

Final Visit Dose by Country and ITT

For study DAZ-N/S/DK/95-001, the sponsor also presented data information by individual country. The following table (table 7) shows the final visit dosing information for the ITT population.

Table 7. Final visit dosing level for the active treatment arms – ITT – study DAZ-N/S/DK/95-001

Final dose (mg/day)	Doxazosin GITS			Doxazosin Standard		
	Denmark	Norway	Sweden	Denmark	Norway	Sweden
2	NA	NA	NA	3 (6%)	19 (11%)	15 (14%)
4	14 (34%)	74 (45%)	39 (38%)	21 (45%)	53 (31%)	26 (26%)
8	27 (66%)	92 (55%)	65 (62%)	23 (49%)	97 (57%)	61 (60%)
Mean (mg/day)	6.63	6.22	6.50	5.83	6.07	6.10

Medical officer's comments: Nearly 60% of the total doxazosin GITS population was taking the higher dosage (8mg) at the end of study compared to a total 57% taking the highest dose (8mg) of doxazosin standard. Only a small percentage of the standard group can stick with the lowest (2mg) in regard to symptom improvement.

Primary Efficacy Endpoint results – I-PSS change

The following table (table 8) demonstrates the I-PSS Change from baseline to final visit by country and ITT.

Table 8. I-PSS change from baseline to final visit by country and ITT- study DAZ-N/S/DK/95-001

Change from baseline to final visit	Doxazosin GITS			Doxazosin Standard			Placebo		
	D	N	S	D	N	S	D	N	S
	-7.17	-7.98	-8.43	-7.83	-8.14	-9.33	-5.68	-5.96	-6.71

D= Denmark
N = Norway
S = Sweden

Medical officer's comments: There may be some subtle country differences in subject perception of I-PSS questions to explain better results in Norway and Sweden. Similar results are seen in the placebo group.

The following table (table 9) presents the critical primary endpoint data for the I-PSS in study DAZ-N/S/DK/95-001. The numbers in brackets are taken from the biostatisticians data file analysis.

Table 9. Total I-PSS Score and Mean Changes from Baseline (± Standard Deviation) in ITT Analysis Population- study DAZ-N/S/DK/95-001. Biostatistical reviewers results when different in brackets

	Doxazosin GITS	Doxazosin Standard	Placebo	p-value
N	310	316	152	
Total I-PSS at baseline	17.74 ± 4.31	17.78 ± 4.48	17.95 ± 4.31	0.783[a]
Total I-PSS at end of study	9.71 ± 5.34	9.31 ±5.30 [9.30 ± 5.31]	11.78 ± 5.49 [11.80 ± 5.49]	
Change from baseline	-8.02 ± 5.35 [-8.03 ± 5.35]	-8.47 ± 5.49 [-8.48 ± 5.48]	-6.17 ± 5.17 [6.14 ± 5.15]	
Change LS mean	-8.01 ± .30[b] [-8.02 ± .30[b]]	-8.45 ± 0.29[b] [-8.46 ± 0.29[b]]	-6.06 ± 0.41[b] [-6.04 ± 0.41[b]]	<0.001
P-value vs Placebo	<0.001	<0.001		

a = Kruskal-Wallis test
b = Standard Error

Medical officer's comments:

In addition to the important finding that doxazosin GITS (Cardura XL®) performs statistically better than placebo and compares clinically to doxazosin standard (Cardura®), the quantitative results shown (-8 range) compare favorably to other approved adrenergic blockers for this indication.

Primary Efficacy Endpoint results – Urinary Flow Change

The following table (table 10) presents the data for maximum urinary flow rate change from baseline to final visit by country and ITT.

Table 10. MUFR change from baseline to final visit by country and ITT- study DAZ-N/S/DK/95-001

Change from baseline to final visit	Doxazosin GITS			Doxazosin Standard			Placebo		
	D	N	S	D	N	S	D	N	S
	2.47	2.85	2.20	2.04	2.31	2.32	2.34	1.21	0.41

D= Denmark
N = Norway
S = Sweden

Medical officer's comments: There is more of balance to this data compared to I-PSS. The Swedish data for MUFR for the placebo group is quite low. Though the Swedish placebo data helped in the statistical analysis versus placebo, the quantitative MUFR results from Cardura XL® are acceptable and comparable to similar approved products.

The following table (table 11) illustrates the primary endpoint information for MUFR.

Table 11. Changes from Baseline in Maximal Urinary Flow Rate (MUFR) at Endpoint (± Standard Deviation) in ITT Analysis Population. Reviewer's results when different are given in brackets .

	Doxazosin GITS	Doxazosin Standard	Placebo	p-value
N	304	315	154	
Baseline MUFR	10.30 ± 2.63	9.98 ± 2.77	9.86 ± 2.63	0.215[a]
MUFR at end of study	12.88 ± 4.54 [12.87 ± 4.55]	12.26 ± 4.41	10.94 ± 3.95 [10.87 ± 3.86]	
Change from baseline	2.58 ± 4.12 2.57 ± 4.13]	2.27 ± 3.74	1.07 ± 3.83 [1.01 ± 3.67]	
Change LS mean	2.63 ± 0.24[b]	2.24 ± 0.23[b]	1.02 ± 0.32[b] [0.96 ± 0.32[b]]	<0.001
P-value vs Placebo	<0.001	<0.001		

a = Kruskal-Wallis test
b = Standard Error

Secondary efficacy endpoints:

Responder rates were similar for both active treatment groups and greater than for the placebo group. The proportion of subjects with a reduction from baseline in I-PSS of at least 30% was 73.5% in the doxazosin GITS group, 74.7% in the doxazosin standard group and 53.3% in the placebo group, at the final visit. The proportion of subjects with an increase in maximum urinary flow rate ≥3 ml/sec was 38.8%, 38.7% and 21.4%, respectively. Clinically, the I-PSS response was very high, while the urinary flow rate response was lower. The combined responder rate was 31.4% in the doxazosin GITS group, 31.9% in the doxazosin standard group and 13.9% in the placebo group.

The following table (table 12) combines the rest of the secondary endpoints in one table.

Table 12. ANCOVA Analysis of LS Mean Change ± SE from Baseline to Final Visit in Secondary Efficacy Parameters and Vital Signs. DAZ-N/S/DK-95-001 (ITT Population)

Parameter	Doxazosin GITS (N=310)	Doxazosin standard (N=316)	Placebo (N=152)	p-Value of treatment effect	p-Value of GITS vs Std
I-PSS Q.1	-1.24±0.06	-1.29±0.06	-1.04±0.09	0.046	0.556
I-PSS Q.2	-1.26±0.06	-1.24±0.06	-1.03±0.09	0.061	0.826
I-PSS Q.3	-1.11±0.06	-1.17±0.06	-0.83±0.09	0.003	0.478
I-PSS Q.4	-1.21±0.07	-1.38±0.07	-0.92±0.10	<0.001	0.065
I-PSS Q.5	-1.59±0.08	-1.63±0.08	-1.00±0.11	<0.001	0.717
I-PSS Q.6	-0.89±0.06	-1.04±0.06	-0.66±0.08	<0.001	0.042
I-PSS Q.7	-0.72±0.05	-0.71±0.05	-0.61±0.07	0.377	0.896
Mean flow rate (ml/sec)+	1.21±0.13	1.05±0.13	0.53±0.18	0.005	0.340
Inv assessment of efficacy	-1.13±0.06	-1.16±0.06	-0.63±0.08	<0.001	0.738
Quality of life (urinary)	-1.34±0.07	-1.38±0.07	-0.87±0.10	<0.001	0.713
Sitting DBP (mmHg)	-2.12±0.45	-2.28±0.44	0.03±0.62	0.004	0.793
Sitting SBP (mmHg)	-4.42±0.77	-2.66±0.77	1.61±1.08	<0.001	0.085
Sitting HR (bpm)	0.75±0.49	0.20±0.47	-0.75±0.72	0.225	0.419

Medical officer's comments: Doxazosin GITS compares favorably to doxazosin standard on all the individual components of the I-PSS questions in addition to the rest of the secondary endpoints.

DAZ-NY-95-001

Title:

A 15-week, prospective, randomized, double-blind trial of the efficacy and safety of doxazosin versus doxazosin mesylate GITS in patients with benign prostatic hyperplasia.

Investigators:

Roger Kirby et al.

Study Centers:

- Belgium (7)
- Canada (11)
- Germany (7)
- Hungary (6)
- Ireland (4)
- Italy (4)
- Poland (8)
- Republic of South Africa (12)
- United Kingdom (10)
  Total = 69

Compliance:

The sponsor audited 20 of the 69 centers

Study Design:

Phase III, double-blind, double-dummy, randomized, placebo-baseline, multicenter, parallel-group study (randomization = doxazosin mesylate GITS: doxazosin standard = 1:1)

Inclusion Criteria:

- Informed consent
- Males, age 50-80
- Symptomatic benign prostatic hyperplasia defined as: maximum urinary flow rate ≥ 5mls/sec and ≤ 15 mls/sec in a total voided volume ≥ 150 mls and a score of ≥ 12 on the I-PSS
- Evidence of prostate gland enlargement as determined by a digital rectal examination

Medical officer's comments: DAZ-NY-95-001 differs in that the inclusion criteria adds "the subject has evidence of prostate gland enlargement on a DRE. DAZ-NY-95-001 also has no placebo control

Exclusion Criteria:

The exclusion criteria are identical to DAZ-N/S/DK-95-001

Study Design – Flow Chart:
The design is identical to DAZ-N/S/DK-95-001 except for placebo

Dosing/Duration:
The dosing and duration are identical to DAZ-N/S/DK-95-001 except for placebo

Primary & Secondary Endpoints:

These are identical to DAZ-N/S/DK-95-001 except for sexual function data (secondary endpoint) that was measured at the final visit.

Protocol Amendments:

Amendments to the protocol included:

- Changed maximum urinary flow rate in inclusion (from >5 to ≥ 5ml/sec)
- Alfuzosin was added to the exclusion criteria
- Study drug administration was amended so that subjects in the doxazosin GITS group could receive 8mg at the Week 9 visit instead of Week 5
- "sexual stimulation" was added to the sexual function questionnaire

Medical officer's comments: The amendment changes do not effect safety or efficacy of the study. The 8mg level acceptance at Week 9 conforms to the DAZ-N/S/DK-95-001 protocol.

Subjects enrolled and analyzed (table 13):

Table 13. Subjects enrolled and analyzed in study DAZ-NY-95-001

	GITS	Standard	Total
Randomized	350	330	680
Completed	311	299	610
PPA	335	318	653
ITT	340	322	662
Safety	349	329	678

Discontinuations:

Discontinuations and the reason for discontinuation are listed in the following table (Table 14).

Table 14. Discontinuations from study DAZ-NY-95-001

	Doxazosin GITS N=317	Doxazosin Standard N=322
Insufficient clinical response	3	0
Adverse events	21	16
Lab abnormality	2	0
Subject died	0	1
Protocol violation	5	4
Lost to follow – up	3	2
Did not meet entrance criteria	2	2
Withdrew consent	2	4
Other	1	2
Total	39	31

Medical officer's comments: In this study the discontinuations for adverse events is the same for both treatment arms.

Demographics/diagnosis duration – ITT

The following table (table 15) provides the demographics for the study arms.

Table 15. Demographics for study DAZ-N/S/DK/95-001

	Doxazosin GITS	Doxazosin Standard
N	340	322
Age < 65	196	190
Age ≥ 65	144	132
Mean age	62.9	62.5
Age range	49-79	49-83
White	330	312
Black	3	4
Asian	7	3
Other	0	3
Mean weight (kg)	80.9	80.5

Primary Efficacy Endpoint results – I-PSS change

The following table (table 16) presents the critical primary endpoint data for the I-PSS in study DAZ-NY-95-001. The numbers in brackets are taken from the biostatisticians data file analysis.

Table 16. Total I-PSS Score and Changes from Baseline (± Standard Deviation) in ITT Analysis Population- study DAZ-NY-95-001. Biostatistical reviewers results when different in brackets

	Doxazosin GITS	Doxazosin Standard	p-value
N	335	320	
Baseline Total I-PSS	18.37 ± 5.00	18.33 ± 4.84	0.804[a]
Total I-PSS at end of study	10.35 ± 5.73 [10.28 ± 5.73]	10.58 ± 5.58 [10.53 ± 5.58]	
Change from baseline	-8.02 ± 5.57 [-8.03 ± 5.35]	-7.75 ± 5.45 [-7.80 ± 5.46]	
Change LS mean	-8.00 ± .30[b] [-8.07 ± .30[b]]	-7.78 ± 0.30[b] [-7.83 ± 0.30[b]]	0.553 [0.534]

a = Using Wilcoxon rank sum test
b = Standard error

Medical officer's comments: These results compare well to study DAZ-N/S/DK/95-001 and again demonstrate the clinically significant quantitative improvement sought for in an adrenergic blocking agent used for BPH.

Primary Efficacy Endpoint results – Urinary Flow Change

The following table (table 17) illustrates the primary endpoint information for MUFR.

Table 17. Changes from Baseline in Maximal Urinary Flow Rate (ml) at Endpoint (± Standard Deviation) in ITT Analysis Population. Study DAZ-NY-95-001. Reviewer's results when different are given in brackets.

	Doxazosin GITS	Doxazosin Standard	p-value
N	337 [336]	319 [318]	
Baseline MUFR	10.46 ± 2.89	10.53 ± 2.64	0.793[a] [0.818]
MUFR at end of study	13.02 ± 4.61	12.95 ± 4.95 [12.95 ± 4.96]	
Change from baseline	2.57 ± 4.27 [2.56 ± 4.27]	2.42 ± 4.61	
Change LS mean	2.74 ± 0.24[b] [2.73 ± 0.26[b]]	2.61 ± 0.27[b]	0.705 [0.718]

a = Using Wilcoxon rank sum test
b = Standard Error

Medical officer's comments: Again, the quantitative improvement in MUFR is acceptable.

Secondary efficacy endpoints:

Responder rates were similar for both groups. The proportion of subjects with a reduction from baseline in I-PSS of at least 30% was 69.0% in the doxazosin GITS group and 67.5% in the doxazosin standard group. The proportion of subjects with an increase in maximum urinary flow rate of ≥3 ml/sec was 40.4% and 36.1%, respectively. The combined responder rate was 32.8% and 27.8% in the GITS and standard groups, respectively.

Additional secondary endpoint results are listed in the following table (table 18)

Table 18. ANCOVA Analysis of LS Mean Change ± SE from Baseline to Final Visit in Secondary Efficacy Parameters and Vital Signs. DAZ-NY-95-001 (ITT Population)

Parameter	Doxazosin GITS (N=335)	Doxazosin standard (N=320)	p-Value of treatment effect
I-PSS Q.1	-1.12±0.07	-1.08±0.07	0.647
I-PSS Q.2	-1.18±0.06	-1.24±0.07	0.518
I-PSS Q.3	-1.21±0.07	-1.13±0.07	0.395
I-PSS Q.4	-1.09±0.07	-1.00±0.07	0.294
I-PSS Q.5	-1.49±0.07	-1.46±0.07	0.814
I-PSS Q.6	-1.08±0.06	-1.03±0.06	0.499
I-PSS Q.7	-0.81±0.06	-0.81±0.06	0.958
Mean flow rate (ml/sec)+	1.60±0.15	1.33±0.15	0.213
Inv assessment of efficacy	-0.96±0.05	-0.96±0.05	0.967
Quality of life (urinary)	-1.36±0.07	-1.20±0.07	0.086
Sitting DBP (mmHg)	-3.23±0.48	-2.18±0.49	0.095
Sitting SBP (mmHg)	-4.23±0.74	-4.49±0.76	0.790
Sitting HR (bpm)	-0.43±0.49	0.34±0.50	0.226

Medical officer's comments: Comparison between the two treatment groups for the individual I-PSS questions indicates comparability.

In addition in study DAZ-NY-95-001, a sexual function questionnaire (SFQ) was completed by each subject at baseline and the final visit. The SFQ used was the same as the International Index of Erectile Function (IIEF). For BPH subjects with sexual dysfunction at baseline there was a statistically significant improvement in all SFQ parameters analyzed following doxazosin GITS and all SFQ parameters analyzed, except Question 2 (erections hard enough for penetration) following doxazosin standard. In addition, there was no statistically significant difference between treatments for any SFQ parameter analyzed.

C. Integration of both studies

BPH Efficacy

The efficacy data (I-PSS and urinary flow rate) from the two BPH efficacy studies were integrated. The sponsor provided the following reasons for integration:

- The efficacy measurements were made at the same times in both studies
- The baseline total I-PSS and maximum urinary flow rate were similar for all treatments in both studies (approximately 18 and 10 ml/sec, respectively).

The two primary efficacy parameters were the change from baseline to the final visit for total I-PSS and maximum urinary flow rate. The reduction in total I-PSS was similar for both active treatments over the study period and was greater than placebo.

The following table (19) integrates the two pivotal BPH studies for change in the I-PSS.

Table 19. Total I-PSS during Phase III – ITT Subjects (DAZ-N/S/DK/95-001 and DAZ-NY-95-001)

	Doxazosin GITS	Doxazosin Standard	Placebo
N	645	636	152
Total I-PSS at baseline	18.07 ± 4.69	18.06 ± 4.67	17.95 ± 4.31
Total I-PSS at end of study	10.04 ± 5.55	9.95 ± 5.48	11.78 ± 5.49
Change from baseline	-8.02 ± 5.46	-8.11 ± 5.48	-6.17 ± 5.17
Change LS mean	7.85 ± 0.23	-7.95 ± 0.23	-5.73 ± 0.46

The following table (table 20) presents the number of subjects who had a reduction in total I-PSS of ≥3, ≥5 and ≥9 at the final visit. These categories correspond to a slight, moderate and marked improvement in symptoms, respectively.

Table 20. Total I-PSS Stratified by Magnitude of Score Reduction at Final Visit
BPH Efficacy Studies (ITT Population)

Decrease in total I-PSS:	Doxazosin GITS (N=645)	Doxazosin standard (N=636)	Placebo (N=152)
≥3	552 (85.6%)	539 (84.7%)	117 (77.0%)
≥5	482 (74.7%)	475 (74.7%)	92 (60.5%)
≥9	290 (45.0%)	296 (46.5%)	43 (28.3%)

The increase in maximum urinary flow rate at the final visit was similar for both active treatments, with a greater increase seen earlier following doxazosin GITS than doxazosin standard. The increase for both treatments was greater than for placebo. The following table (table 21) integrates the results of both pivotal trials for change in MUFR.

Table 21. Maximum Urinary Flow Rate during Phase III – ITT Subjects (DAZ-N/S/DK/95-001 and DAZ-NY-95-001)

MUFR (ml/sec)	Doxazosin GITS	Doxazosin Standard	Placebo
N	641	634	154
Baseline	10.38 ± 2.77	10.26 ± 2.72	9.86 ± 2.63
Final	12.96 ± 4.58	12.61 ± 4.70	10.94 ± 3.95
Change from baseline	2.57 ± 4.19	2.35 ± 4.20	1.07 ± 3.83
Change LS mean	2.78 ± 0.19	2.51 ± 0.19	1.22 ± 0.38

In the sponsor's expert report there was a presentation of data to suggest an earlier onset of efficacy following Cardura XL® compared with doxazosin standard. At Week 5, subjects had been receiving 4 mg/day of Cardura XL for 3 weeks or 1 mg/day doxazosin standard for 1 week, followed by 2 mg/day doxazosin standard for 2 weeks. At this visit there was a statistically significantly greater improvement in maximum urinary flow rate following Cardura XL than doxazosin standard. This was also the case for total I-PSS.

Medical officer's comments: As mentioned earlier the titration protocol was more prolonged for the standard treatment arm compared to usual clinical practice. This

may explain the difference week 5. The information appears exploratory [redacted]

D. Extension study (DAZ-NY-95-001B)

This was an optional, 24-week, open-label, dose-titration extension to the 15-week study DAZ-NY-95-001 with all subjects commencing on Cardura XL® (4mg) once daily. The entry visit was to be within two weeks of completing the 15 week study with visit 2 scheduled two weeks later. At this point Cardura XL® could be up-titrated to 8mg

Table 22. Total I-PSS Score during extension – ITT Subjects

	Doxazosin GITS
N	289 (256 completed)
Baseline Total I-PSS	18.78 ± 5.24
Total I-PSS at final extension visit	9.51 ± 6.29
Change from baseline	-9.27 ± 6.59
P-value vs Placebo	<0.001

Table 23. Maximum Urinary Flow Rate During Extension – ITT Subjects

	Doxazosin GITS
N	285 (256 completed)
Baseline MUFR	10.50 ± 2.79
Final extension visit MUFR	13.20 ± 4.62
Change from baseline	2.70 ± 4.27
P-value vs Placebo	<0.001

Medical officer's comments: Despite voluntary enrollment, drop-out, and lack of control data, there is some evidence of durability of response in those who enrolled in this study.

VII. Integrated Review of Safety

A. Conclusions

- Although the number and type of adverse events seen with Cardura XL® is not greater or different than Cardura®, the sponsor has not provided sufficient blood pressure and symptom analysis of initial dosing of 4 mg Cardura XL®. Initial day dosing blood pressure analysis is available on just 21 males in study DAZ-NY-96-009. Though no dramatic blood pressure changes appear at the time of peak drug effect, six first day adverse events were recorded. A comparative trial of 4mg Cardura

XL®, 1mg Cardura, and placebo evaluating symptoms and blood pressure at multiple time intervals in men following first dose is recommended.

- Data line listings from the BPH pivotal trials (DAZ-N/S/DK-95-001 and DAZ-NY-95-001) shows 2mg doxazosin standard dosing at a time in the protocol when 1mg of standard should have been given. Though this may be a recording error, the study design should have included an additional visit to assess the first week of dosing. If the 2mg dose is correct in some of these cases this could bias the safety comparison of Cardura XL® and Cardura®. The sponsor should clarify these discrepancies.

- The principal safety concern for Cardura XL® and for Cardura® is syncope. The number of syncopal episodes for both drug products were comparable based on the safety data from both the hypertensive trials and the BPH trials. It is important to note that the syncopal episodes for both products can occur at delayed time intervals from the initiation of therapy with the lower doses. Strengthening the "Warnings" section of the label in regard to these later episodes of syncope is recommended.

- The four-month safety update submitted September 6, 2001 did not indicate any additional serious safety concerns. A small number of urticarial events have prompted the sponsor to include that side effect in the label

- The commonly reported adverse events occur with comparable frequency in the over and under 65 year age groups. Dizziness and postural hypotension occur with slight greater frequency in the over 65 age group but this is also true with placebo, suggesting age or other contributing factors.

B. Patient Exposure

The standard formulation of doxazosin has been marketed for approximately 10 years with over two billion patient-days experience. The safety database for the GITS release system consists of the following numbers of subjects (table 24). The number of subject-months of exposure exceeds 2800.

Table 24. Subject exposure to Cardura XL® (safety)

Clinical Pharmacology Studies	123 maximum treatment period was 21 days
Primary Hypertension Efficacy Studies (12 week)	318
Hypertension extension study	280 14 completed < 24 weeks 128 completed 24-36 weeks 138 completed ≥ 36 weeks
Hypertension supporting studies (10-14 weeks)	177
BPH Efficacy studies (13 weeks)	666
BPH extension study (24 week)	289 256 completed 24 weeks
Total safety numbers	1854

Medical officer's comments: Approximately 1100 completed three months, 380 completed 6 months, and 138 completed 9 months of use of doxazosin GITS.

C. Methods and Specific Findings

Methods used to evaluate safety

The safety analysis in the BPH trials included the following:

- Screening assessment for evidence of prostate cancer
- Safety labs at screening and end of study
- Screening electrocardiogram
- Screening history and physical
- Blood pressure and heart rate evaluation at each visit
- Evaluation of adverse events at each visit

Findings related to safety

Deaths

Table 25. Deaths reported in the NDA submission

Studies	Number of Deaths	Clinical description
Clin Pharm Studies	0	
Hypertension Studies	1	following sepsis, stroke and atrial fibrillation
BPH Studies	1	reported following severe cerebral infarction

As listed above there was one death reported during the BPH efficacy studies. In Study DAZ-NY-95-001, a subject in the doxazosin standard group died due to a non treatment-related serious adverse event. Subject 7980267, a 69 year old white male, had a severe cerebral infarction on Day 92, whilst taking a daily dose of 2 mg. This was not considered to be related to treatment.

Serious Adverse Events

Table 26. SAEs recorded in clinical pharmacology and BPH trials

Clinical pharmacology studies	0
BPH Studies	
DAZ-N/S/DK-95-001	GITS =7 Std =15 Placebo = 4
DAZ-NY-95-001	GITS = 10 Std = 4
DAZ-NY-95-001B	GITS = 8

Medical officer's comments: Although no SAEs were reported in the clinical pharmacology studies, one report of postural hypotension and 2 reports of syncope were recorded for DAZ-NY-96-010 (bioavailability, pk, and safety study). There was also one reported case of syncope in DAZ-NY-96-009 (pk and safety study)

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Table 27. SAEs in the Hypertension Studies

Study	SAEs
[redacted]	9 SAE total 3- GITS = bleeding duodenal ulcer, MI, abdominal pain 5- STD = anemia, GI reflux, cerebral infarct, VTE, syncope 1- Placebo = diabetes
	5 SAE total 5-STD = vertigo, heart failure, colon cancer, transcervical fracture supraventricular tachycardia
	1 SAE total 4mg GITS = myocardial infarction
	No SAE
	No SAE
	8 SAE total= extrasystoles, hypertension progression, myocardial infarction, non-cardiac chest pain, atrial fibrillation, cholelithiasis, stroke, sepsis-stroke- atrial fibrillation

The following table (table 28) lists the number of cases of possible adrenergic blocking side effects in the large hypertensive trials.

Table 28. Adrenergic blocking related side effects in Cardura XL® hypertensive 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
	GITS = 0 STD = 2	GITS = 3 STD = 4	GITS = 3 STD = 0	GITS = 0 STD = 0

The following table (table 29) lists the SAEs in the BPH studies.

Table 29. SAE in the BPH studies:

Study	SAEs
DAZ-N/S/DK-95-001	26 SAE total 7- GITS = colon cancer, progression of BPH, stomach cancer, epistaxis, atrial fibrillation & heart failure, MI, inguinal hernia 15- STD = dyspnea, hematemesis, rectal abscess, DVT, diarrhea, pneumonia, urinary retention, subendocardial MI, heart operation, MI, **chest pain**, bladder cancer, andioedema, pneumonia, femur fracture, 4- Placebo = chest pain, cerebral hemorrhage, bronchitis, apoplexy
DAZ-NY-95-001	14 SAE total 10-GITS = lung cancer, empyema of gall bladder, prostate cancer, **hypotension** & slurred speech, **syncope**, CHF, hypotonia, t-cell lymphoma, cardiac failure, MI 4-STD = degenerative spinal cord disease, suspected MI, cerebral infarction, heart palpitations
DAZ-NY-95-001B extension	8 SAE total GITS = influenza, rheumatoid disease, progression of BPH, herniotomy, varicose veins, pneumonia, progression of BPH, spinal stenosis surgery

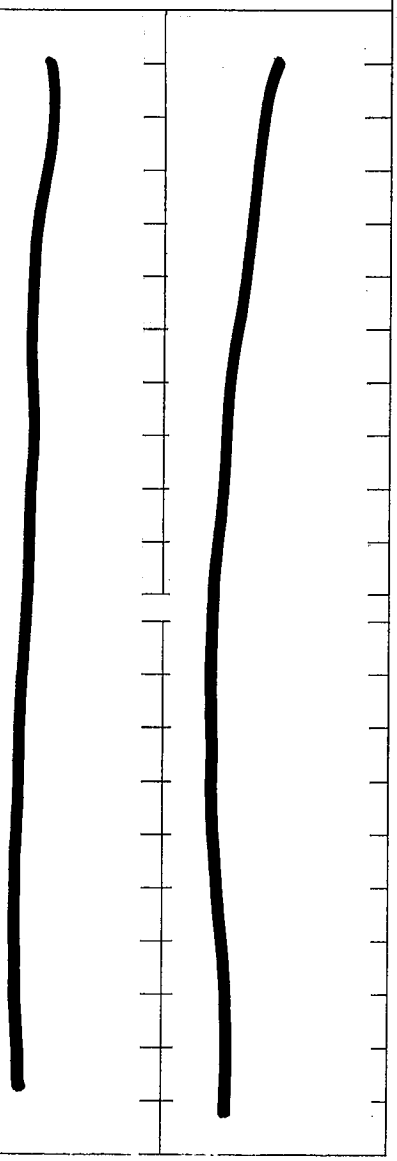
Two events were considered to be treatment-related following doxazosin GITS. The report of syncope for one subject; and the reports of hypotension, lethargy, slurred speech, unsteady gait, headaches and dizziness for one subject were considered to be related to the study drug.

One event was considered to be treatment-related following doxazosin standard. The report of chest pain for one subject was considered to be related to the study drug.

Study DAZ-NY-96-009 analyzed 4mg doxazosin GITS in elderly and young males and females. The following table (Table 30) shows an analysis of adverse events and first day dosing blood pressure (sitting) in the male subjects.

Table 30 Adverse events and first day dosing blood pressures from study DAZ-NY-96-009.

Subject #	Adverse Event	Dosing Day	Pre-dose Sitting BP 1st and 2nd readings	12 hour post dose sitting BP 1st and 2nd readings
Young males				
1				
2				
3				
4				
5				
6	Palpitation	7		
7				
8				
9				
10	Syncope (138/66) occurred at approx. 30 hours	1		
110	Dizziness, headache	7		
Elderly males				
21	Headache	1, 7		
22	Asthenia	1		
24	Headache	1		
25	Headache	1		
28				
29				
31				
32				
33	Abdomen enlarged	1		
38				



Medical officer's comments: The above table does not shows signs of excessive blood pressure decreases in these male subjects, but the numbers are small. Five of the

subjects overall and four of the elderly males showed adverse events on day one. Additional safety monitoring on day one is recommended. An additional study (DAZ-NY-96-007) also analyzed frequent blood pressure determinations and included both the 4mg GITS and 1mg standard but did not assess the blood pressures frequently on the first dose day.

The following table (table 31) lists the number of cases of possible adrenergic blocking side effects in the large BPH trials.

Table 31. Adrenergic blocking related side effects in Cardura XL® BPH trials

Study	Postural hypotension	Dizziness	Vertigo	Palpitation	Syncope
DAZ-NY-95-001 and DAZ-N/S/DK-95-001	GITS = 8 STD = 14 Plac = 1	GITS = 35 STD = 59 Plac = 3	GITS = 10 STD = 27 Plac = 1	GITS = 5 STD = 10 Plac = 0	GITS = 4 STD = 2 Plac = 0
DAZ-NY-95-001 (open label extension)	GITS = 2	GITS = 19	GITS = 1	GITS = 0	GITS = 0

Medical officer's comments: The numbers in the above table do not suggest that the GITS product demonstrates more adrenergic side effects than the approved product, however there is a discrepancy for 2mg standard dosing as noted later in the review.

Special assessment for the timing of syncope is shown in the following table (table 32)

Table 32. DAZ-N/S/DK-95-001 and DAZ-NY-95-001 syncope reports by day of occurrence

Side effect	Treatment and occurrence by day of treatment
Syncope	GITS = 3, 19, 40, 53 STD = 28, 60

Medical officer's comments: The previous table illustrates the fact that syncopal episodes are occurring distant from initial dosing. The syncope could be a result of other factors or could be related to missing doses or increasing doses. Both Cardura XL® and Cardura® show delayed syncopal events.

Discontinuation Due to Adverse Events

In study DAZ-N/S/DK-95-001, 11 GITS subjects and 20 STD subjects were discontinued due to treatment-related, treatment-emergent adverse events. The most commonly occurring treatment-emergent adverse events leading to discontinuation and considered to be treatment-related were dizziness, headache, and vertigo.

In study DAZ-NY-95-001, 11 GITS subjects and 11 STD subjects were discontinued due to treatment-related, treatment-emergent adverse events. The most commonly occurring

treatment-emergent adverse events leading to discontinuation and considered to be treatment-related were dizziness and hypotension.

There was a higher proportion of subjects discontinued due to adverse events following doxazosin standard (7.2%) than doxazosin GITS (5.7%) or placebo (2.6%). The full break down of the adverse event discontinuations is listed in the subsequent table (table33).

Table 33. Adverse Events Reported as Leading to Discontinuation For More Than One Subject - BPH Efficacy Studies

COSTART TERM	Doxazosin GITS	Doxazosin Standard	Placebo
Total number of subjects	666	651	156
No. subjects discontinued due to adverse events #$+	38 (5.7%)	47 (7.2%)	4 (2.6%)
Dizziness	7	8	
Asthenia	3	6	
Headache	3	3	1
Hypotension	3	3	
Vertigo	1	5	
Somnolence	3	2	
Dyspnoea	4		
Postural hypotension	3	1	
Abdominal pain	2	2	
Angina pectoris	1	2	
Chest pain	1	2	
Migraine	1	2	
Nausea	1	2	
Rash		3	
Peripheral edema	2		
Stomach ulcer	2		
Cerebral ischaemia	1	1	
Diarrhea	1	1	
Dyspepsia	1	1	
Epistaxis	1	1	
Myocardial infarct	1	1	
Rhinitis	1	1	
Syncope	1	1	
Impotence		2	
Palpitation		2	

\# Three subjects in the doxazosin GITS group discontinued due to an adverse event reported as a laboratory abnormality

$ One subject in the doxazosin standard group discontinued due to an adverse event reported as subject died

\+ One subject in the doxazosin standard group took active study medication in Phase II and discontinued due to an adverse event reported during Phase II

Subjects could be discontinued for >1 adverse event

Includes non-treatment emergent adverse events

Incidence of Commonly Reported Adverse Events

The incidence of subjects reporting adverse events was similar for doxazosin GITS (41.4%) and placebo (39.1%) and highest for doxazosin standard (53.6%). Table 34 illustrates commonly reported adverse events.

Commonly reported adverse events in BPH patients included dizziness, headache, asthenia and respiratory tract infection. These were all reported at a higher frequency following either doxazosin treatment than placebo.

There was a higher incidence of dizziness, vertigo and postural hypotension following doxazosin standard than doxazosin GITS. There were six reports of syncope, four following doxazosin GITS, two following doxazosin standard and none following placebo.

There was a lower incidence of adverse events in the digestive system following doxazosin GITS than doxazosin standard and a lower incidence of adverse events in the elderly population compared with the non-elderly, with a similar pattern of adverse events between the two age groups. There was a similar incidence of adverse events reported on Day 1 following all three treatments. There were three subjects discontinued due to laboratory abnormalities, none of which was considered to be treatment-related.

Table 34. 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%)

Medical officer's comments:

Data line listings from the BPH pivotal trials (DAZ-N/S/DK-95-001 and DAZ-NY-95-001) shows 2mg doxazosin standard dosing at a time in the protocol when 1mg of standard should have been given. Though this may be a recording error, the study design should have included an additional visit to assess the first week of dosing. If the 2mg dose is correct in some of these cases this could bias the safety comparison of Cardura XL® and Cardura®

Five case report forms were evaluated to assess the above discrepancy. The adverse events (by date) appeared during the time that subjects were taking a bottle with seven tablets. By protocol it would be expected that this bottle contained 1mg doxazosin standard however it is difficult to ascertain for certain what proportion of the 2mg doxazosin standard line listings should be 1mg.

Doxazosin GITS shows a lower percentage in the categories of dizziness, asthenia, nausea, vertigo, and postural hypotension compared to Cardura®. Whether this relates to the formulation release or possible use of higher Cardura® doses is unclear. As noted in other parts of the review the rare, but more severe side effect of syncope occurred with equal frequency and at delayed time points with both formulation types. Assessment of adverse events occurring in the first week show a similarity between Cardura XL® and Cardura®, but again there is a possibility that 2mg Cardura® use may be biasing the results.

As mentioned earlier in the review, a critical analysis of first day and first week dosing comparison of 4mg Cardura XL® versus 1mg Cardura in regard to blood pressure and adverse events is recommended additionally to be more confident of safety.

Incidence of Commonly Reported Adverse Events by Age

Within each of the treatment groups, there was a higher incidence of adverse events for subjects who were <65 years compared with those ≥65 years, as presented in the following table. The pattern of adverse events in both age groups was similar.

Table 35. Incidence of commonly reported adverse events by age at screening- BPH efficacy studies

	Doxazosin GITS		Doxazosin standard		Placebo	
	<65 years (N=341)	≥65 years (N=325)	<65 years (N=339)	≥65 years (N=312)	<65 years (N=72)	≥65 years (N=84)
TOTAL	148 (43.4%)	128 (39.4%)	188 (55.5%)	161 (51.6%)	31 (43.1%)	30 (35.7%)
Dizziness	15 (4.4%)	20 (6.2%)	22 (6.5%)	37 (11.9%)	0 (0.0%)	3 (3.6%)
Headache	29 (8.5%)	11 (3.4%)	20 (5.9%)	13 (4.2%)	5 (6.9%)	2 (2.4%)
Asthenia	11 (3.2%)	15 (4.6%)	27 (8.0%)	18 (5.8%)	1 (1.4%)	1 (1.2%)
Respiratory tract infection	17 (5.0%)	15 (4.6%)	18 (5.3%)	11 (3.5%)	3 (4.2%)	0 (0.0%)
Flu syndrome	8 (2.3%)	8 (2.5%)	17 (5.0%)	5 (1.6%)	2 (2.8%)	5 (6.0%)
Back pain	17 (5.0%)	2 (0.6%)	7 (2.1%)	4 (1.3%)	2 (2.8%)	2 (2.4%)
Vertigo	6 (1.8%)	4 (1.2%)	8 (2.4%)	19 (6.1%)	1 (1.4%)	0 (0.0%)
Bronchitis	3 (0.9%)	4 (1.2%)	3 (0.9%)	5 (1.6%)	3 (4.2%)	1 (1.2%)
Abdominal pain	8 (2.3%)	4 (1.2%)	8 (2.4%)	7 (2.2%)	1 (1.4%)	0 (0.0%)
Nausea	6 (1.8%)	2 (0.6%)	9 (2.7%)	6 (1.9%)	1 (1.4%)	0 (0.0%)
Postural hypotension	3 (0.9%)	5 (1.5%)	5 (1.5%)	9 (2.9%)	0 (0.0%)	1 (1.2%)

Medical officer's comments: Analysis of the individual components in the previous graph indicate that when looking at both forms of doxazosin, that dizziness and postural hypotension are slightly greater in

the ≥65 age group. This was also true in the placebo group. There is no clear signal however in this data to suggest special labeling for the over 65 age group.

D. Four Month Safety Update

Additional safety information was submitted by the sponsor on 9-6-01, that included deaths and serious adverse events from January 1,2000 through December 31, 2000 for patients participating in doxazosin GITS **hypertension** clinical trials. Some of these studies were still blinded on December 31, 2000.

A total of 13 patients died; 6 were receiving doxazosin GITS and 7 were receiving doxazosin standard. Of those receiving doxazosin GITS, two died of chronic renal failure, 1 died from leukemia, 1 died of a cerebrovascular accident and 2 committed suicide. Of the 7 patients receiving doxazosin standard tablets 2 died from cancer (ovarian and pulmonary) and one each died from post-operative sepsis, sudden death following cardiac catheterization, death at home, traffic accident and one was murdered.

Medical officer's comments: The death at home occurred one month after discontinuing doxazosin. The cause was unknown but thought to be related to heart failure or heat stroke. The traffic accident was not considered to be drug related

A total of 44 patients in these hypertensive trials experienced serious events that did not result in death. Of these only one case was thought to be related to doxazosin. This was a 60 year old male with a history of gout and multiple back surgeries who developed tachycardia.

There were no deaths reported during the time period January 1, 2000 through December 31, 2000 in patient participating in doxazosin GITS clinical trials for **benign prostatic hyperplasia**. There were 17 patients who experienced serious adverse events other than death. One case with tachycardia was felt to be drug related.

The safety update also included a report from the sponsor that identified some cases of urticaria associated with doxazosin. The sponsor is recommending that urticaria be added to the doxazosin and doxazosin GITS labeling.

VIII. Dosing Regimen and Administration Issues

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

It is recommended that the sponsor strengthen patient information section of the label to inform patients not to chew Cardura XL®.

IX. Use in Special Populations

Cardura XL® is designated for middle to elderly age men by its indication of BPH. Pharmacokinetic studies have indicated increases of 27% in maximum plasma concentrations and 34% in the area under the concentration-time-curve were seen in the elderly (≥65 years old).

The use of Cardura XL® was evaluated in 12 hepatically impaired (stable alcoholic cirrhosis). The clearance of doxazosin decreased by 30% in the impaired subjects compared with normal subjects. There was no significant difference in T_{max}, C_{max}, and T_{half} between the two populations.

Medical officer's comments: There is no clinical experience with severe hepatic impairment. The sponsor's expert report states that Cardura XL® use in these patients is not recommended and this is reflected in the labeling.

X. Conclusions and Recommendations

Overall risk-benefit analysis

Cardura XL® is comparable to the approved Cardura® in regard to efficacy for BPH. There is a benefit in regard to a more simplified dosage titration regimen of two levels compared to four levels in Cardura®. Though the overall safety analysis appears to indicate that Cardura XL® does not have more or different adverse events compared to Cardura®, the sponsor has not studied adequate numbers of subjects in a way that focuses on thorough blood pressure evaluation and symptoms with first day dosing. This analysis should be compared to the 1mg Cardura® dose. The numbers of syncopal episodes appears to be similar for both Cardura XL® and Cardura®.

Remaining unresolved issues

There are three unresolved issues:

- The analysis of blood pressure effect of 4mg GITS compared to 1mg standard and placebo (during the first 24 hours following first dose).
- The analysis of clinical safety for first dosing of 4mg Cardura XL® with particular emphasis on the first dose and first week as compared to 1mg standard.
- Resolving the discrepancy of 2mg versus 1mg dosing of Cardura® in the adverse events data listings of the two pivotal BPH trials.

Labeling issues

As of February 12, 2002 a new label for Cardura XL® for the BPH indication has been submitted.

Appendix

AUA/I-PSS Scoring table

AUA/I-PSS Scoring						
Symptom	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
1. Incomplete emptying	0	1	2	3	4	5
2. Frequency (urinate again within 2 hours)	0	1	2	3	4	5
3. Intermittency	0	1	2	3	4	5
4. Urgency	0	1	2	3	4	5
5. Weak stream	0	1	2	3	4	5
6. Straining	0	1	2	3	4	5
	None	1 time	2 times	3 times	4 times	5 or more time
7. Nocturia	0	1	2	3	4	5
Symptom score is total of the seven categories						

Quality of life due to urinary symptoms score =

	Delighted	Pleased	Mostly satisfied	Mixed	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about it?	0	1	2	3	4	5	6

Sexual Function Questionnaire Questions

Sexual Intecourse = vaginal penetration
Sexual Activity = includes intercourse, caressing, foreplay, and masturbation
Sexual Stimulation = loveplay with partner, looking at erotic picture, etc.

1. Over the past 4 weeks, how often were you able to get an erection during sexual activity (defined as intercourse, caressing, foreplay, and masturbation)?

2. Over the past 4 weeks, when you had erections with sexual stimulation (includes situations with partner, erotic pictures etc.), how often were your erections hard enough for penetration?

3. Over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate your partner?

4. Over the past 4 weeks, during sexual intercourse how often were you able to maintain your erection after you had penetrated your partner?

5. Over the past 4 weeks, during sexual intercourse how difficult was it to maintain your erection to completion of intercourse?

6. Over the past 4 weeks how many times have you attempted sexual intercourse?

7. Over the past 4 weeks when you attempted sexual intercourse how often was it satisfactory for you?

8. Over the past 4 weeks, how much have you enjoyed sexual intercourse?

9. Over the past 4 weeks when you had sexual stimulation or intercourse how often did you ejaculate?

10. Over the past 4 weeks when you had sexual stimulation or intercourse how often did you have the feeling of orgasm with or without ejaculation?

11. Over the past 4 weeks, how often have you felt sexual desire?

12. Over the past 4 weeks, how would you rate your level of sexual desire?

13. Over the past 4 weeks, how satisfied have you been with your overall sex life?

14. Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?

15. Over the past 4 weeks, how would you rate your confidence that you could get and keep an erection?

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/s/

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2/22/02 12:46:45 PM
MEDICAL OFFICER

Mark S. Hirsch
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I concur.