SUMMARY

- Cardura XL is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). Cardura XL is not approved by the Food and Drug Administration (FDA) for the treatment of hypertension.

- Cardura is indicated for the treatment of both the urinary outflow obstruction and obstructive and irritative symptoms associated with BPH. Cardura is also indicated for the treatment of hypertension.

- The pharmacokinetics of doxazosin extended release (XL) are different from those of doxazosin immediate release (IR) because doxazosin XL provides a controlled release of doxazosin over a 24-hour period. A randomized, open-label, 3-way crossover study showed that food had a minimal effect on the pharmacokinetics of both doxazosin formulations. In a randomized, open-label, 2-way crossover study, reduced peak-to-trough blood level fluctuations occurred with doxazosin XL compared with doxazosin IR.

- In a combined analysis of 2 randomized, double-blind, parallel-group studies, doxazosin XL was significantly more effective than placebo and as effective as doxazosin IR in reducing the clinical symptoms of benign prostatic hyperplasia (BPH). In a retrospective analysis of a subgroup of BPH patients who also had erectile dysfunction (ED), patients treated with either doxazosin XL or doxazosin IR had statistically and clinically significant improvements in sexual function.

- In 2 prospective, randomized, double-blind, active-controlled, multicenter studies, doxazosin XL 4 mg and doxazosin IR 4 mg were similarly effective in reducing blood pressure (BP) in patients with mild to moderate hypertension.

- In an integrated analysis of 2 pivotal randomized, double-blind, active-controlled, multicenter studies, doxazosin XL and doxazosin IR provided equally effective BP reduction; doxazosin XL appeared to eliminate the need for dose titration in most patients.

INTRODUCTION

Cardura XL utilizes the gastrointestinal therapeutic system (GITS), which is designed to provide a controlled rate of delivery of doxazosin into the gastrointestinal (GI) lumen, which is independent of pH or GI motility. The function of Cardura XL depends upon the existence of an osmotic gradient between the contents of the bilayer core and fluid in the GI tract. Drug delivery is essentially constant as long as the osmotic gradient remains constant, and then gradually falls to zero.[1] For the purposes of this letter, doxazosin GITS is equivalent to Cardura XL and to doxazosin XL.

Dosage and Administration of Cardura and Cardura XL for the Treatment of BPH

The initial dosage of Cardura is 1 mg, given once daily in the a.m. or p.m. Depending on the individual patient's urodynamics and BPH symptomatology, dosage may then be increased to

2 mg and thereafter to 4 mg and 8 mg once daily, the maximum recommended dose for BPH. The recommended titration interval is 1 to 2 weeks. Blood pressure should be evaluated routinely in these patients.[2]

The initial dose of Cardura XL, 4 mg given once daily, should be administered with breakfast. Depending on the patient's symptomatic response and tolerability, the dose may be increased to 8 mg, the maximum recommended dose. The recommended titration interval is 3 to 4 weeks. If Cardura XL administration is discontinued for several days, therapy should be restarted using the 4 mg once daily dose. Tablets should be swallowed whole, and must not be chewed, divided, cut or crushed.[1]

If switching from Cardura to Cardura XL, therapy should be initiated with the lowest dose (4 mg once daily). Prior to starting therapy with Cardura XL, the final evening dose of Cardura should not be taken.[1]

Dosage and Administration of Cardura for the Treatment of Hypertension

The initial dosage of Cardura is 1 mg given once daily. Depending on the individual patient's standing BP response (based on measurements taken at 2-6 hours postdose and 24 hours postdose), dosage may then be increased to 2 mg and thereafter if necessary to 4 mg, 8 mg, and 16 mg to achieve the desired reduction in BP. Increases in dose beyond 4 mg increase the likelihood of excessive postural effects including syncope, postural dizziness/vertigo and postural hypotension. At a titrated dose of 16 mg once daily, the frequency of postural effects is about 12% compared to 3% for placebo.[2]

Literature Search

As of November 2007, a computerized search of the medical literature has identified a number of articles that compare doxazosin IR with doxazosin XL. A review of some of these articles follows.

PHARMACOKINETIC DATA

The pharmacokinetics of doxazosin XL are different from those of doxazosin IR. Cardura XL provides a controlled release of doxazosin over a 24-hour period. The relative bioavailability of doxazosin XL compared with doxazosin IR was 54% for the 4 mg dose and 59% for the 8 mg dose.[1]

Chung et al conducted a prospective, randomized, open-label, 3-way crossover study that compared the pharmacokinetic profiles of single doses of doxazosin GITS and doxazosin IR under fasting and fed conditions in healthy male subjects. The effects of food on pharmacokinetic activity were also evaluated. The pharmacokinetics of doxazosin GITS were assessed while subjects were in both fed (dose received within 15 minutes of finishing a high-fat breakfast) and fasted (subject received the dose after a 10-hour fast and then continued to fast for 4 hours postdose) states. Doxazosin IR pharmacokinetics were only assessed in the fasted state. Twenty-four subjects (mean±SD age=27±6 years; age range=18-40 years) were randomized to

one of the following treatment regimens: doxazosin GITS 8 mg fasted, doxazosin IR 2 mg fasted, or doxazosin GITS 8 mg fed. Crossover between treatment regimens was separated by a 7-day washout period. Blood samples were collected at various time points up to 96 hours postdose and were assessed to determine the maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the concentration versus time curve (AUC), and half-life ($t_{½}$).[3]

Pharmacokinetic parameters for doxazosin GITS 8 mg and doxazosin IR 2 mg are summarized in Table 1.[3]

Table 1. Mean±SD Pharmacokinetic Parameters of Doxazosin GITS and Doxazosin IR in Fed and Fasted States

Parameter	Doxazosin GITS 8 mg Fasted	Doxazosin GITS 8 mg Fed	Doxazosin IR 2 mg Fasted
C_{max}, ng/mL	18.3±5.9	24.0±7.1 *	13.7±2.9
T_{max}, h	14±4	11±2 *	2±0.8
AUC, ng•h/mL	569±187	670±234 *	195±45
$t_{½}$, h	15.0±2.5	16.1±2.7 *	14.0±3.6
* $p<0.05$ based on analysis of variance.			

The differences in C_{max} and AUC between doxazosin GITS 8 mg in the fed state and the fasting state were statistically, but not clinically, significant ($p<0.05$). The authors concluded that food had minimal effects on the pharmacokinetics of doxazosin and that the improved absorption profile of doxazosin GITS might minimize the risk for unintended hypotensive effects.[3]

Chung et al also conducted a prospective, randomized, open-label, 2-way crossover study that compared the steady-state pharmacokinetic profiles of multiple doses of doxazosin GITS and doxazosin IR in healthy men. Thirty-five subjects (mean±SD age=32±9 years; age range=18-60 years) were randomized to a treatment arm with either doxazosin GITS (placebo for 7 days and then doxazosin GITS 4 mg *qd* for 7 days, which was then increased to 8 mg *qd* for 7 days) or doxazosin IR (doxazosin IR 1 mg *qd* for 2 days, 2 mg *qd* for 5 days, 4 mg *qd* for 7 days, and then 8 mg *qd* for 7 days). Crossover between treatment arms was separated by a 7-day washout period. Blood samples were collected at various time points up to 96 hours postdose and were assessed to determine the pharmacokinetic profile of each formulation, as shown in Table 2.[3]

Table 2. Mean±SD Pharmacokinetic Parameters of Doxazosin GITS and Doxazosin IR at Steady State (N=31)

Parameter	Doxazosin GITS 4 mg	Doxazosin IR 4 mg	Doxazosin GITS 8 mg	Doxazosin IR 8 mg
C_{max}, ng/mL	11.3±5.6	29.3±8.4 *	28.0±12.1	66.8±17.6 *
T_{max}, h	8.2±3.7	3.7±1.5 *	9.1±4.7	3.9±1.2 *
AUC, ng•h/mL	201±86	379±131 *	504±171	878±273 *
C_{min}, ng/mL	6.4±3.2	7.4±3.7	17.8±9.3	19.0±8.2
$t_{½}$, h	NA	NA	18.6±3.7	20.5±6.1
Relative bioavailability, %	54.1±16.3	100	58.6±12.0	100
Peak-to-trough FI	0.60±0.43	1.47±0.40 *	0.52±0.47	1.37±0.37 *

C_{min}=minimum plasma concentration; FI=fluctuation index; NA=not analyzable.
* $p<0.05$ for IR versus GITS based on analysis of variance.

The authors concluded that the reduced peak-to-trough blood level fluctuations of doxazosin GITS compared with doxazosin IR will likely result in more uniform control of BP and symptoms of BPH, as well as enhanced tolerability.[3]

CLINICAL DATA

Benign Prostatic Hyperplasia

Two controlled clinical studies were conducted with doxazosin XL in patients with BPH, followed by an open-label extension study. Study 1 was a randomized, double-blind, parallel-group, placebo- and active-controlled study that compared the safety and efficacy of doxazosin XL (4 or 8 mg/day) with those of doxazosin IR (1, 2, 4, or 8 mg/day) and placebo over 13 weeks in 795 patients with BPH, of whom 317 patients were randomized to doxazosin XL. Study 2 was a randomized, double-blind, parallel-group, active-controlled study that compared the safety and efficacy of doxazosin XL (4 or 8 mg/day) with those of doxazosin IR (1, 2, 4, or 8 mg/day) over 13 weeks in 680 patients with BPH, of whom 350 patients were randomized to doxazosin XL.[1]

In both studies, men aged 50 to 80 years with symptomatic BPH were enrolled. Symptomatic BPH was defined as a total score of at least 12 points on the 35-point International Prostate Symptom Score (IPSS) and a maximum urinary flow rate of ≤15 mL/sec but ≥5 mL/sec (total voided volume ≥150 mL). In these 2 studies, conducted in a total of 1475 patients, the mean age was 64 years (age range=47-83 years). Patients were Caucasian (96%), Black (1.5%), Asian (1.5%), and of other ethnicity (1%).[1]

In both studies, doxazosin XL dosing was initiated after a 2-week placebo run-in period at 4 mg/day and increased to 8 mg/day after 7 weeks of treatment if an adequate response was not

seen. Adequate response was defined as having both an increase in maximum urinary flow rate of ≥3 mL/sec and a decrease in total IPSS of ≥30% from baseline. Doxazosin IR was titrated from an initial dose of 1 mg daily to 2 mg daily after 1 week with the option to increase to 4 mg daily after 3 weeks and then to a maximum of 8 mg daily after 7 weeks if an adequate response was not seen. The final daily dose of doxazosin XL was 4 mg in 43% of patients and 8 mg in 57% of patients. The final daily dose of doxazosin IR was 1 mg in 1%, 2 mg in 12%, 4 mg in 30%, and 8 mg in 57% of patients.[1]

There were 2 primary efficacy variables in each of these 2 controlled clinical studies: the IPSS and the peak urinary flow rate (Qmax). The IPSS consists of 7 questions that assess the severity of both irritative (frequency, urgency, and nocturia) and obstructive (incomplete emptying, stopping and starting, weak stream, and pushing or straining) symptoms, with possible total scores ranging from 0 to 35. The Qmax was measured in both studies just prior to the next dose. The results for total symptom score are given in Table 3 and maximum urinary flow rates are given in Table 4.[1]

Table 3. Total IPSS for Patients with BPH *

	Mean±SD Baseline	Mean±SE Change †
Study 1		
Placebo (N=151)	17.9±4.3	-6.1±0.41
Doxazosin XL (N=310)	17.7±4.3	-8.0±0.30 ‡
Doxazosin IR (N=311)	17.8±4.5	-8.4±0.29 ‡
Study 2		
Doxazosin XL (N=330)	18.4±5.0	-8.1±0.30
Doxazosin IR (N=313)	18.4±4.8	-7.9±0.31

* Derived from the IPSS questionnaire (range=0-35).
† Mean change from baseline to Week 13.
‡ $p<0.001$ versus placebo.

Table 4. Maximum Flow Rates (mL/sec) in Patients with BPH

	Mean±SD Baseline	Mean±SE Change *
Study 1		
Placebo (N=151)	9.8±2.6	0.8±0.32
Doxazosin XL (N=300)	10.3±2.6	2.6±0.24 †
Doxazosin IR (N=303)	10.1±2.7	2.2±0.23 †
Study 2		
Doxazosin XL (N=322)	10.5±2.6	2.7±0.27
Doxazosin IR (N=314)	10.6±2.6	2.7±0.27

* Mean change from baseline to Week 13.
† $p<0.001$ versus placebo.

In these 2 studies, 6% of patients who received doxazosin XL withdrew from the study because of adverse events compared to 7% who received doxazosin IR and 3% who received placebo. The most commonly reported adverse events leading to discontinuation in the doxazosin XL group were dizziness, dyspnea, asthenia, headache, hypotension, postural hypotension, and somnolence.[1]

The incidence rates summarized in Table 5 are based on combined data from the 2 controlled studies (Studies 1 and 2). Adverse events with an incidence in the doxazosin XL group of at least 1% and reported more frequently than with placebo are summarized.[1]

Table 5. Treatment-Emergent Adverse Events Occurring in ≥1% of BPH Patients Treated with Doxazosin XL and More Frequently Than with Placebo (%)

Adverse Event	Doxazosin XL (N=666)	Doxazosin IR (N=651)	Placebo (N=156)
Abdominal pain	1.8	2.3	0.6
Asthenia	3.9	6.9	1.3
Back pain	2.9	1.7	2.6
Headache	6.0	5.1	4.5
Hypotension	1.7	1.8	0.0
Postural hypotension	1.2	2.2	0.6
Dyspepsia	1.4	1.2	0.0
Nausea	1.2	2.3	0.6
Myalgia	1.4	0.5	0.0
Dizziness	5.3	9.1	1.9
Somnolence	1.5	1.2	0.0
Vertigo	1.5	4.1	0.6
Dyspnea	1.2	1.2	0.0
Respiratory tract infection	4.8	4.5	1.9
Urinary tract infection	1.4	0.8	0.6

Kirby et al[4] conducted a combined analysis of the 2 randomized, double-blind, parallel-group studies described above as Studies 1 and 2[1] to more fully characterize the benefits of doxazosin GITS for the treatment of BPH. This summary will discuss the efficacy results for the per protocol−analysis (PPA) population only (N=1433).[4]

There was a significantly greater reduction in the mean total IPSS in patients treated with doxazosin GITS and doxazosin IR (approximately 45% for each group) compared with placebo-treated patients (34%; $p<0.001$). Statistically significant increases in Q_{max} from baseline to the final visit were observed following treatment with doxazosin GITS and doxazosin IR ($p<0.001$). These changes were also significantly greater than placebo ($p<0.001$). The IPSS and Q_{max} results observed in the combined analysis were similar to those seen in the individual studies (Table 6).[4]

Table 6. Change from Baseline to the Final Visit for Total IPSS and Q_{max} in the PPA Population

	Doxazosin GITS	Doxazosin IR	Placebo
IPSS			
No. of patients	N=640	N=624	N=151
Least squares mean (SE) change	-7.9 (0.2) *†	-8.0 (0.2) *†	-5.8 (0.5) *
Q_{max}, mL/s			
No. of patients	N=622	N=617	N=151
Least squares mean (SE) change	2.8 (0.2) *†	2.6 (0.2) *†	1.1 (0.4) *

* p<0.001 versus baseline.
† p<0.001 versus placebo.

The overall incidence of adverse events was similar in patients treated with doxazosin GITS (41.4%) and placebo (39.1%), whereas a higher incidence of adverse events was observed with doxazosin IR (53.6%; p<0.001 versus doxazosin GITS). These safety results were similar to those seen in the individual studies. The authors concluded that doxazosin GITS was significantly more effective than placebo and as effective as doxazosin IR in reducing the clinical symptoms of BPH and improving Q_{max}.[4]

Concomitant Benign Prostatic Hyperplasia and Erectile Dysfunction

Cardura and Cardura XL are not approved by the FDA for the treatment of ED. Pfizer Inc does not suggest or recommend the use of Cardura or Cardura XL for this condition.

Kirby et al[5] conducted a retrospective analysis of the previously described Study 2[1] to assess the effects of doxazosin GITS and doxazosin IR on the sexual health of patients with concomitant BPH and ED. Two hundred thirty-seven of the 680 patients enrolled in Study 2 had baseline ED as assessed by using the erectile function, intercourse satisfaction, orgasmic function, sexual desire, and overall sexual satisfaction domains of the International Index of Erectile Function (IIEF) questionnaire. After 13 weeks of treatment, there were statistically and clinically significant improvements from baseline in all 5 IIEF domains ($p \leq 0.0019$ for both groups). The authors concluded that, considering the high incidence of comorbid ED in patients with BPH and the beneficial effects of doxazosin on sexual dysfunction, doxazosin GITS was an appropriate treatment for most patients with BPH.[5]

Hypertension

Cardura XL is not approved by the Food and Drug Administration for the treatment of hypertension. Pfizer Inc does not suggest or recommend the use of Cardura XL for this condition.

Os conducted a prospective, randomized, double-blind, parallel-group, multicenter study that evaluated the efficacy and safety of doxazosin GITS and doxazosin IR for the treatment of patients with mild to moderate hypertension (sitting systolic BP [SBP] of <180 mm Hg and sitting diastolic BP [DBP] of 95-110 mm Hg). Patients (N=310; age range=18-80 years) were randomized to doxazosin GITS 4 mg, doxazosin IR 4 mg, or doxazosin IR 2 mg for 9 weeks following a 2-week placebo run-in period. The daily dose of doxazosin GITS was fixed throughout the study. All patients randomized to doxazosin IR 2 mg received a starting daily dose of 1 mg, which was increased to 2 mg at the end of Week 1. For patients randomized to doxazosin IR 4 mg, the dose was increased from 1 to 2 mg at the end of Week 1 and from 2 to 4 mg at the end of Week 3. The primary efficacy outcome was the mean change from baseline to postbaseline visits in sitting DBP. Secondary efficacy outcomes included mean changes from baseline to postbaseline visits in sitting SBP and sitting heart rate (HR); mean changes from baseline in standing DBP, standing SBP, and standing HR; and the proportion of patients with sitting DBP of <90 mm Hg or sitting SBP of <140 mm Hg. BP was measured at baseline, at Weeks 1, 3, 5, 9, and at study endpoint. Adverse events were recorded at each postbaseline visit.[6]

The intent-to-treat (ITT) population consisted of 304 patients (doxazosin GITS 4 mg, N=101; doxazosin IR 4 mg, N=100; doxazosin IR 2 mg, N=103). The mean changes from baseline in sitting DBP for the doxazosin GITS 4 mg and doxazosin IR 4 mg groups are shown in Table 7.[6]

Table 7. Mean ±SE Difference in Adjusted Mean Changes from Baseline in Sitting DBP Between Doxazosin GITS 4 mg and Doxazosin IR 4 mg

Time Point	Mean±SE Difference, mm Hg	Number of Patients		95% CI
		Doxazosin GITS 4 mg	Doxazosin IR 4 mg	
Week 1	-1.0±0.94	101	99	-2.88, 0.85
Week 3	-0.9±0.94	99	99	-2.80, 0.93
Week 5	-0.2±1.00	97	96	-1.81, 2.13
Week 9	-0.7±1.11	96	94	-2.90, 1.49
Endpoint	-0.8±1.09	101	100	-2.92,1.39

Treatment with doxazosin GITS 4 mg or doxazosin IR 2 mg resulted in statistically significant decreases from baseline in sitting DBP and SBP and standing SBP and DBP at all time points (p=0.001 for both groups). Results for change from baseline in standing SBP for patients who received doxazosin IR 4 mg were not reported. There were no significant changes in standing or sitting HR within or between treatment groups at any time point. A similar proportion of patients among the 3 treatment groups responded to treatment and had a sitting DBP of <90 mm Hg or sitting SBP of <140 mm Hg.[6]

Five patients discontinued treatment because of treatment-related adverse events (doxazosin GITS 4 mg, N=1; doxazosin IR 4 mg, N=3; doxazosin IR 2 mg, N=1). There were no clinically significant differences between treatment groups in the incidence of adverse events. The most frequently reported adverse event was headache in all 3 groups. The author noted that both doxazosin GITS and doxazosin IR were well tolerated; however, the GITS formulation

allowed a therapeutic dose to be delivered from the study inception, thereby achieving a quicker response. The author concluded that doxazosin GITS 4 mg was therapeutically equivalent to doxazosin IR 4 mg for the reduction of BP in patients with mild to moderate hypertension.[6]

Calvo et al[7] conducted a prospective, randomized, double-blind, active-controlled, multicenter study to evaluate the efficacy and safety of doxazosin GITS and doxazosin IR in patients with mild to moderate hypertension (mean daytime SBP of >135 mm Hg or DBP of >85 mm Hg). Patients were randomized to doxazosin GITS 4 mg (N=114), doxazosin IR 4 mg (N=110), or doxazosin IR 2 mg (N=111) for 9 weeks following a 2-week placebo run-in period. The daily dose of doxazosin GITS was fixed throughout the study, whereas the IR dose was increased as described in the previous study.[6] Efficacy measurements included changes from baseline in sitting SBP, DBP, and mean BP at baseline and at Weeks 1, 3, 5, and 9. Changes from baseline to Week 9 in ambulatory BP and in lipid parameters were also assessed. Adverse events were recorded at each visit.[7]

A total of 335 patients were randomized to treatment. The ITT population consisted of 331 patients (mean age=51 years); 4 patients (doxazosin GITS 4 mg, N=2 and doxazosin IR 2 mg, N=2) without postbaseline values were excluded from the efficacy analysis. At Week 1, patients treated with doxazosin GITS had statistically significant reductions in sitting DPB, sitting SBP, and mean BP compared to patients treated with doxazosin IR ($p \leq 0.04$). By the final visit, there was no statistically significant difference in mean change from baseline in sitting SBP, DBP, or mean BP between the doxazosin GITS 4 mg and doxazosin IR 4 mg groups; however, there was a statistically significant difference between the doxazosin GITS 4 mg and doxazosin IR 2 mg groups ($p \leq 0.006$ for all measures). Both formulations of doxazosin were associated with reductions from baseline in ambulatory BP in the daytime ($p \leq 0.0001$ for each treatment group) and during a 24-hour period ($p \leq 0.01$), but only doxazosin GITS significantly reduced nighttime ambulatory BP from baseline ($p \leq 0.0001$). No statistically significant effect on serum lipids was observed with doxazosin therapy.[7]

Both formulations of doxazosin were well tolerated. Seven patients (6%) each in the doxazosin GITS and doxazosin IR 2 mg groups withdrew from the study because of adverse events compared with 4 patients (4%) in the doxazosin IR 4 mg group. The most commonly reported adverse events overall were headache and dizziness. The authors concluded that doxazosin GITS 4 mg and doxazosin IR 4 mg were similarly effective in reducing the clinic and ambulatory BP of patients with mild to moderate hypertension without adversely affecting serum lipid profiles. The authors also noted that the earlier and significantly greater BP reduction observed with the GITS formulation indicated that it might be a better treatment choice than the IR formulation in this patient population.[7]

Os and Stokke conducted an integrated analysis of 2 randomized, double-blind, parallel-group, multicenter studies of doxazosin GITS and doxazosin IR in patients with mild to moderate hypertension.[8] One study (Study A) evaluated the safety and efficacy of doxazosin GITS, doxazosin IR, and placebo in patients with mild hypertension (SBP of ≤180 mm Hg and DBP of 95-105 mm Hg).[8,9] The other study (Study B) compared the safety and efficacy of doxazosin GITS with doxazosin IR in patients with mild to moderate hypertension (SBP of ≤220 mm Hg and DBP of 95-115 mm Hg).[8]

In both studies, patients (age range=18-80 years) received daily doses of doxazosin GITS 4 mg after a 2-week placebo run-in period. The dose of doxazosin GITS was started at 4 mg and then increased to 8 mg/day at Week 5 as needed in order to achieve an adequate response (defined as a sitting DBP of ≤90 mm Hg or a decrease of ≥10 mm Hg in sitting DBP). Patients randomized to doxazosin IR received an initial daily dose of 1 mg, which was increased to 2 mg/day after Week 1, to 4 mg/day at Week 3, and then to 8 mg/day at Week 5 as needed in order to achieve an adequate response.[8,9] The integrated analysis had 2 primary efficacy endpoints: the relative percentage of patients in the PPA population who responded adequately to treatment and the mean change from baseline in BP in the ITT population. Secondary endpoints included the relative percentage of responders at the final visit and the change in hypertensive severity category in the ITT population. BP measurements were obtained at baseline and 24 hours postdose at Weeks 1, 3, 5, and 12. Adverse events were recorded throughout the 12 weeks.[8]

In the combined analysis, the ITT population included 705 patients (mean age=56.5 years; age range=24-80 years) and the PPA population included 683 patients. All patients were white. The majority of patients treated with doxazosin GITS in the PPA population had a final daily dose of 4 mg (N=199, 64.4%); 110 (36.6%) patients had a final daily dose of 8 mg. Of the 304 patients who received doxazosin IR, 1.6%, 35.9%, 27.0%, and 35.5% had final daily doses of 1, 2, 4, and 8 mg, respectively. The percentages of patients in the PPA population who had an adequate response are listed in Table 8.[8]

Table 8. Percentages of Patients in the PPA Population Who Achieved Adequate BP Response at Last Visit

Study	Doxazosin GITS	Doxazosin IR	Placebo
Integrated analysis of Studies 1 and 2; n/N (%)	198/309 (64.1) *	207/304 (68.1)	25/70 (35.7)
Study 1; n/N (%)	92/156 (59.0)	86/152 (56.6)	25/70 (35.7)
Study 2; n/N (%)	106/153 (69.3)	121/152 (79.6)	Not evaluated
* Estimated odds ratio versus doxazosin IR was 0.83 (95% CI: 0.59-1.17); p<0.001. Estimated odds ratio versus placebo was 2.98 (95% CI: 1.71-5.20); p<0.001.			

In the ITT population, treatment with doxazosin GITS and doxazosin IR significantly reduced BP (both standing and sitting) from baseline compared with placebo (p<0.001); these results were consistent with those obtained in each individual study. The numbers of ITT patients treated with doxazosin GITS, doxazosin IR, and placebo who were responders at the final visit were 204 (64.2%), 214 (68.4%), and 28 (37.8%), respectively. No significant changes in HR were observed in any of the treatment groups. In the ITT population, similar improvements in hypertensive severity category were observed with doxazosin GITS and doxazosin IR (64.2% and 68.7% patients with improvement, respectively).[8]

Both formulations of doxazosin were well tolerated. There was a higher incidence of treatment discontinuations due to adverse events with doxazosin IR (9.3%) than with doxazosin GITS (5.3%) or placebo (9.2%), and only 1 serious treatment-related adverse event was reported in the

doxazosin IR group. Headache was the most frequently reported adverse event in all 3 groups. The authors concluded that doxazosin GITS and doxazosin IR provided equally effective BP reduction. The authors also noted that doxazosin GITS appeared to eliminate the need for titration in most patients.[8]

Refs.

1. Cardura® XL (doxazosin mesylate extended release) Package Insert.
2. Cardura® (doxazosin mesylate) Package Insert.
3. Chung M, Vashi V, Puente J, et al. Clinical pharmacokinetics of doxazosin in a controlled-release gastrointestinal therapeutic system (GITS) formulation. *Br J Clin Pharmacol* 1999;48:678-687.
4. Kirby RS, Andersen M, Gratzke P, et al. A combined analysis of double-blind trials of the efficacy and tolerability of doxazosin-gastrointestinal therapeutic system, doxazosin standard and placebo in patients with benign prostatic hyperplasia. *BJU Int* 2001;87:192-200.
5. Kirby RS, O'Leary MP, Carson C. Efficacy of extended-release doxazosin and doxazosin standard in patients with concomitant benign prostatic hyperplasia and sexual dysfunction. *BJU Int* 2005;95:103-109.
6. Os I. Comparison of doxazosin GITS and standard doxazosin in the treatment of high blood pressure. *Int J Clin Pharmacol Ther* 2006;44:99-106.
7. Calvo C, Gil-Extremera B, Gomez-Fernández P, et al. Doxazosin GITS versus standard doxazosin in mild to moderate hypertension. *Int J Cardiol* 2005;101:97-104.
8. Os I, Stokke HP. Effects of doxazosin in the gastrointestinal therapeutic system formulation versus doxazosin standard and placebo in mild-to-moderate hypertension. *J Cardiovasc Pharmacol* 1999;33:791-797.
9. Os I, Stokke HP. Doxazosin GITS compared with doxazosin standard and placebo in patients with mild hypertension. *Blood Press* 1999;8:184-191.