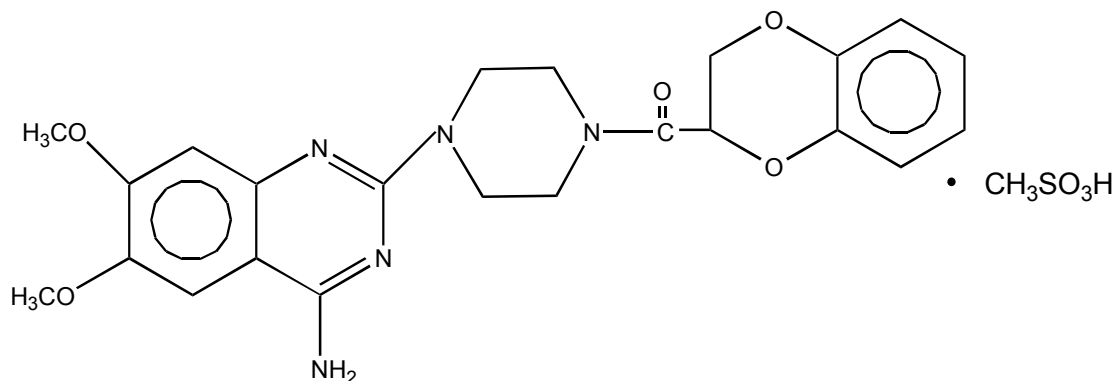


CARDURA[®] XL

(doxazosin mesylate extended release tablets)

DESCRIPTION

CARDURA[®] XL (doxazosin mesylate extended release tablets) contains doxazosin mesylate which is a quinazoline compound with the chemical name 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(1,4-benzodioxan-2-ylcarbonyl) piperazine methanesulfonate. The empirical formula for doxazosin mesylate is $C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$ and the molecular weight is 547.6. It has the following structure:



CARDURA XL is an extended release tablet for oral use and is designed to deliver 4 or 8 mg of doxazosin as the free base. Each 4 and 8 mg tablet contains 5.1 and 10.2 mg doxazosin mesylate (includes a 5% overage) to provide 4 and 8 mg doxazosin as a free base, respectively. The inactive ingredients for CARDURA XL are: polyethylene oxide, sodium chloride, hypromellose, red ferric oxide, titanium dioxide, magnesium stearate, cellulose acetate, Macrogol[®], pharmaceutical glaze, and black iron oxide.

CARDURA XL System Components and Performance

CARDURA XL is similar in appearance to a conventional tablet. It consists, however, of an osmotically active drug core surrounded by a semipermeable membrane. The core itself is divided into two layers: an “active” layer containing the drug, and a “push” layer containing pharmacologically inert (but osmotically active) components. The membrane surrounding the tablet is permeable to water but not to drug or osmotic excipients. As water from the gastrointestinal tract enters the tablet, pressure increases in the osmotic layer and “pushes” against the drug layer, resulting in the release of drug through a small, laser-drilled orifice in the membrane on the drug side of the tablet.

CARDURA XL utilizes GITS (Gastrointestinal Therapeutic System) which is designed to provide a controlled rate of delivery of doxazosin into the gastrointestinal lumen which is independent of pH or gastrointestinal (GI) motility. The function of CARDURA XL depends upon the existence of an osmotic gradient between the contents of the bi-layer 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. The

biologically inert components of the tablet remain intact during GI transit and are eliminated in the feces as an insoluble shell.

CLINICAL PHARMACOLOGY

Mechanism of Action

The symptoms associated with benign prostatic hyperplasia (BPH), such as urinary frequency, nocturia, weak stream, hesitancy, and incomplete emptying are related to two components, anatomical (static) and functional (dynamic). The static component is related to an increase in prostate size caused, in part, by a proliferation of smooth muscle cells in the prostatic stroma. However, the severity of BPH symptoms and the degree of urethral obstruction do not correlate well with the size of the prostate. The dynamic component of BPH is associated with an increase in smooth muscle tone in the prostate and bladder neck. The degree of tone in this area is mediated by the α_1 adrenoceptor, which is present in high density in the prostatic stroma, prostatic capsule, and bladder neck. Blockade of the α_1 receptor decreases urethral resistance and may relieve the BPH symptoms and improve urine flow. Doxazosin mesylate is a selective inhibitor of the α_1 -subtype of alpha adrenergic receptors. In human prostate, doxazosin mesylate antagonizes phenylephrine (α_1 agonist)-induced contractions, *in vitro*, and binds with high affinity to the α_{1A} adrenoceptor.

Pharmacokinetics

The pharmacokinetics of CARDURA XL is different from that of doxazosin immediate-release (IR). CARDURA XL provides a controlled release of doxazosin over a 24-hour period.

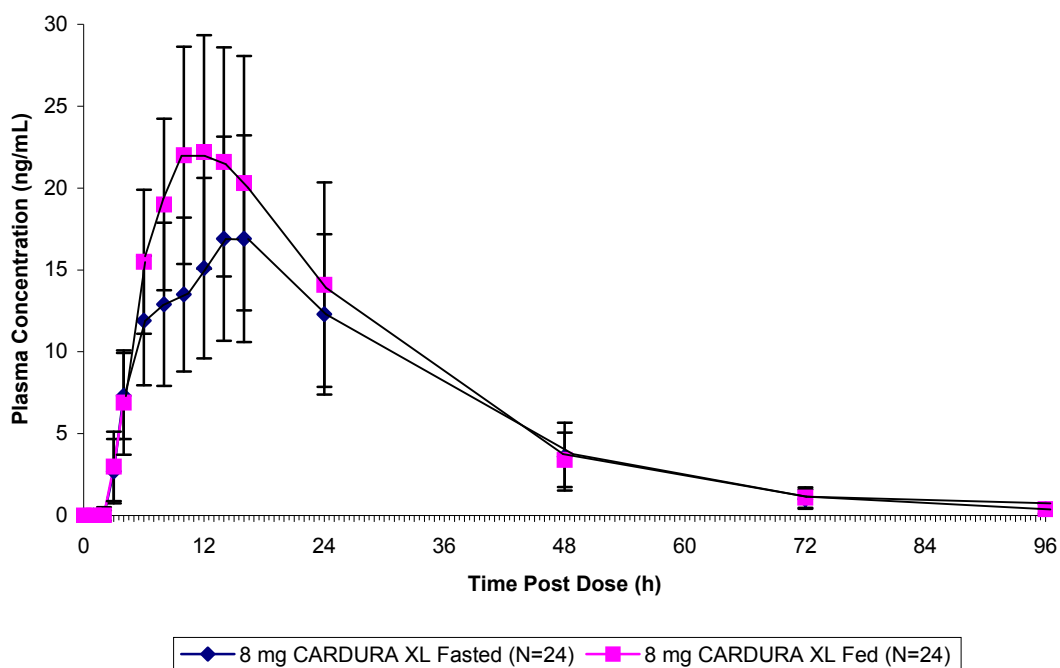
Absorption: Pharmacokinetic parameters describing absorption following 4 and 8 mg CARDURA XL daily doses are reported in Table 1 below. The relative bioavailability of CARDURA XL compared with doxazosin IR was 54% at the 4 mg dose and 59% for the 8 mg dose.

Parameter	CARDURA XL (4 mg)	CARDURA XL (8 mg)
C_{\max} (ng/mL)	10.1 \pm 5.6	25.8 \pm 12.1
$AUC_{(0-\infty)}$	183 \pm 85.5	472 \pm 170.8
T_{\max} (h)	8 \pm 3.7	9 \pm 4.7

Effect of Food

As illustrated in Figure 1, the maximum plasma concentration (C_{\max}) and the area under the plasma concentration versus time curve (AUC) were approximately 32% and 18% higher, respectively, after CARDURA XL was administered in the fed state compared with the fasted state. In order to provide the most consistent exposure, CARDURA XL should be administered with breakfast. (See **DOSAGE AND ADMINISTRATION.**)

Figure 1: Mean (+SD) Plasma Concentration of Doxazosin Following Single Oral Doses of 8 mg CARDURA XL (Fed and Fasted)



Effect of GI Retention Time

Markedly reduced GI retention times (e.g., short bowel syndrome) may influence the pharmacokinetics of CARDURA XL and possibly result in lower plasma concentrations. Conversely, markedly prolonged GI retention times (e.g. chronic constipation) can increase systemic exposure to doxazosin and potentially result in increased adverse reactions. (See **PRECAUTIONS; General.**)

Distribution

At the plasma concentrations achieved by therapeutic doses, approximately 98% of the circulating drug is bound to plasma proteins.

Metabolism

Doxazosin is extensively metabolized in the liver. *In vitro* studies suggest that the primary pathway for elimination is via CYP3A4; however, CYP2D6 and CYP2C19 metabolic pathways also exist to a lesser extent. No *in vivo* drug interaction studies have been performed with CARDURA XL. Although several active metabolites of doxazosin have been identified, the pharmacokinetics of these metabolites has not been characterized. (See **PRECAUTIONS; Drug Interactions.**)

Excretion

In a study of two subjects administered radiolabeled doxazosin IR 2 mg orally and 1 mg intravenously on two separate occasions, approximately 63% of the dose was eliminated in the feces and 9% of the dose was found in the urine. On average, only 4.8% of the dose was excreted as unchanged drug in the feces and only a trace of the

total radioactivity in the urine was attributed to unchanged drug. The apparent elimination half-life of CARDURA XL is 15–19 hours.

Pharmacokinetics in Special Populations

Age: The effects of age on the pharmacokinetics of CARDURA XL were examined. At steady state, 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) compared to the young. (See **PRECAUTIONS; Geriatric Use.**)

Hepatic Impairment: Administration of a single 2 mg dose of doxazosin IR to patients with mild hepatic impairment (Child-Pugh Class A) showed a 40% increase in exposure to doxazosin compared to patients without hepatic impairment. No studies have been performed to assess the effect of hepatic impairment on the pharmacokinetics of CARDURA XL. CARDURA XL should be administered with caution to patients with evidence of mild or moderately impaired hepatic function or to patients receiving drugs known to influence hepatic metabolism. Use in patients with severe hepatic impairment is not recommended.

Drug-Drug Interactions

No *in vivo* drug-drug interaction studies have been performed to assess the effect of concomitant medications on the pharmacokinetics of CARDURA XL or to assess the effect of CARDURA XL on the pharmacokinetics of other drugs. In one placebo-controlled trial in normal volunteers, the administration of a single 1 mg dose of doxazosin IR on day 1 of a fourday regimen of cimetidine (400 mg twice daily) resulted in a 10% increase in the mean AUC of doxazosin, 6% increase in mean C_{max} of doxazosin, and no significant change in mean half-life of doxazosin. Based upon the differences in dose and formulation, the applicability of these results to CARDURA XL is unknown. Otherwise, the interaction potential with other inhibitors or substrates of cytochrome P450 enzymes has not been determined. Pharmacodynamic interactions between CARDURA XL and anti-hypertensive medications or other vasodilating agents have also not been determined. Finally, drugs which reduce gastrointestinal motility leading to markedly prolonged GI retention times (e.g., anticholinergic agents) may increase systemic exposure to doxazosin.

Clinical Studies

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

In both studies, men aged 50-80 years with symptomatic benign prostatic hyperplasia (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 no less than 5 mL/sec (total voided volume ≥ 150 mL). In these two studies, conducted in a total of 1475 patients, the mean age was 64 years (range 47–83 years). Patients were Caucasian (96%), Black (1.5%), Asian (1.5%), and of Other ethnicity (1%).

In both studies, CARDURA XL dosing was initiated after a 2 week placebo run-in period at 4 mg per day increasing to 8 mg per day after 7 weeks of treatment if adequate response (defined as having both an increase in maximum urinary flow rate of at least 3 mL/sec and a decrease in total IPSS of at least 30% from baseline) was not seen. 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 CARDURA 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.

There were two primary efficacy variables in each of these two controlled clinical studies: the International Prostate Symptom Score (IPSS) and the peak urinary flow rate (Q_{max}). The IPSS consists of seven questions that assess the severity of both irritative (frequency, urgency, 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 Q_{max} was measured in both studies just prior to the next dose. The results for total symptom score are given in Table 2, and for maximum urinary flow rate in Table 3.

TABLE 2			
TOTAL INTERNATIONAL PROSTATE SYMPTOM SCORE (IPSS) ^a			
	N	MEAN BASELINE (±SD)	MEAN CHANGE (±SE) ^b
STUDY 1			
Placebo	151	17.9 ± 4.3	-6.1 ± 0.41
CARDURA XL	310	17.7 ± 4.3	-8.0 ± 0.30*
Doxazosin IR	311	17.8 ± 4.5	-8.4 ± 0.29*
STUDY 2			
CARDURA XL	330	18.4 ± 5.0	-8.1 ± 0.30
Doxazosin IR	313	18.4 ± 4.8	-7.9 ± 0.31

^a Derived from IPSS questionnaire (range 0-35)

^b Mean change from baseline to Week 13

* Statistically significant difference (p <0.001) vs. placebo

TABLE 3			
MAXIMUM FLOW RATE (mL/sec)			
	N	MEAN BASELINE (±SD)	MEAN CHANGE (±SE) ^b
STUDY 1			
Placebo	151	9.8 ± 2.6	0.8 ± 0.32
CARDURA XL	300	10.3 ± 2.6	2.6 ± 0.24*
Doxazosin IR	303	10.1 ± 2.7	2.2 ± 0.23*
STUDY 2			
CARDURA XL	322	10.5 ± 2.6	2.7 ± 0.27
Doxazosin IR	314	10.6 ± 2.6	2.7 ± 0.27

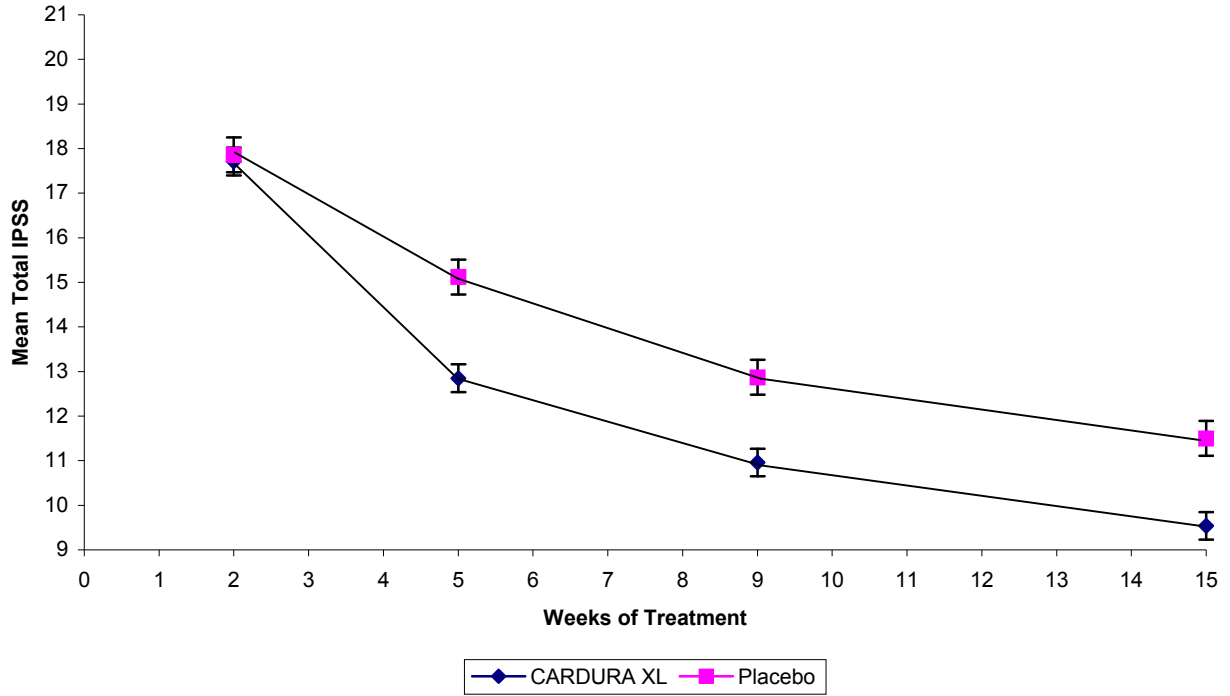
^a Derived from IPSS questionnaire (range 0-35)

^b Mean change from baseline to Week 13

* Statistically significant difference (p <0.001) vs. placebo

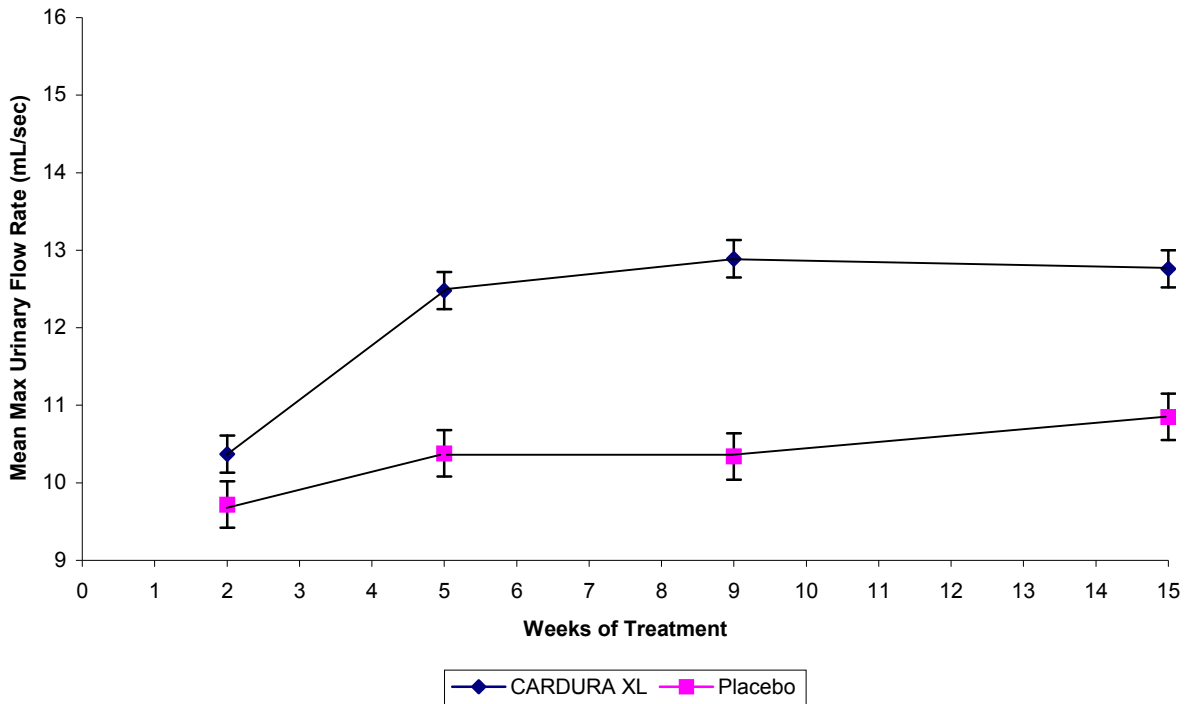
Mean changes in IPSS scores for CARDURA XL and placebo in Study 1 are summarized in Figure 2.

FIGURE 2: Mean Change (\pm SE) in Total IPSS Score by Visit in Study 1



Mean changes in maximum urinary flow rate (Q_{max}) for both CARDURA XL and placebo in Study 1 are summarized in Figure 3.

FIGURE 3: Mean Change (\pm SE) in Maximum Urinary Flow Rate (mL/sec) by Visit in Study 1



INDICATIONS AND USAGE

CARDURA XL is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH).

CARDURA XL is not indicated for the treatment of hypertension.

CONTRAINDICATIONS

CARDURA XL is contraindicated in patients with a known sensitivity to doxazosin, other quinazolines (e.g., prazosin, terazosin), or any of the inert ingredients.

WARNINGS

Postural hypotension with or without symptoms (e.g., dizziness) may develop within a few hours following administration of CARDURA XL (doxazosin mesylate extended release tablets). However, infrequently, symptomatic postural hypotension has also been reported later than a few hours after dosing. As with other alpha-blockers, there is a potential for syncope, especially after the initial dose or after an increase in dosage strength. Patients should be warned of the possible occurrence of such events and should avoid situations where injury could result should syncope occur. Care should be taken when CARDURA XL is administered to patients with symptomatic hypotension or patients who have had a hypotensive response to other medications.

PRECAUTIONS

General

Prostate Cancer: Carcinoma of the prostate causes many of the same symptoms associated with BPH and the two disorders frequently co-exist. Carcinoma of the prostate should therefore be ruled out prior to commencing therapy with CARDURA XL.

Cataract Surgery: Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in some patients on or previously treated with alpha₁ blockers. This variant of small pupil syndrome is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigation currents, progressive intraoperative miosis despite preoperative dilation with standard mydriatic drugs, and potential prolapse of the iris toward the phacoemulsification incisions. The patient's surgeon should be prepared for possible modifications to their surgical technique, such as the utilization of iris hooks, iris dilator rings, or viscoelastic substances. There does not appear to be a benefit of stopping alpha₁ blocker therapy prior to cataract surgery.

Gastrointestinal Disorders: As with any other non-deformable material, caution should be used when administering CARDURA XL to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of another drug in this non-deformable extended release formulation. Markedly increased GI retention times, as may occur in patients with chronic constipation, can increase systemic exposure to doxazosin and thereby potentially increase adverse reactions.

Patients with Hepatic Impairment: CARDURA XL should be administered with caution to patients with evidence of mild or moderate hepatic dysfunction (see **CLINICAL PHARMACOLOGY; Pharmacokinetics in Special Populations**). Since there is no clinical experience in patients with severe hepatic dysfunction, use in these patients is not recommended.

Drug Interactions: No *in vivo* drug interaction studies were conducted with CARDURA XL (see **CLINICAL PHARMACOLOGY; Drug-Drug Interactions**). *In vitro* studies suggest that doxazosin is a substrate of CYP3A4. Caution should be exercised when concomitantly administering a potent 3A4 inhibitor, such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, or voriconazole with CARDURA XL. Pharmacodynamic interactions between CARDURA XL and anti-hypertensive medications or other vasodilating agents have also not been determined.

Concomitant administration of CARDURA XL with a phosphodiesterase-5 (PDE-5) inhibitor can result in additive blood pressure lowering effects and symptomatic hypotension (see **DOSAGE AND ADMINISTRATION**).

Patients with Coronary Insufficiency: Patients with congestive heart failure, angina pectoris, or acute myocardial infarction within the last 6 months were excluded from the Phase 3 studies. If symptoms of angina pectoris should newly appear or worsen, CARDURA XL should be discontinued.

Information for Patients

Patients should be told about the possible occurrence of symptoms related to postural hypotension, such as dizziness or syncope, when beginning therapy or when increasing dosage strength of CARDURA XL. Patients should be cautioned about driving, operating machinery, or performing hazardous tasks during this period, until the drug's effect has been determined.

Patients should be informed that CARDURA XL extended release tablets should be swallowed whole. Patients should not chew, divide, cut, or crush tablets. Patients should not be concerned if they occasionally notice in their stool something that looks like a tablet. In the CARDURA XL extended release tablet, the medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. When this process is completed, the empty tablet is eliminated from the body.

CARDURA XL should be taken each day with breakfast.

Drug/Laboratory Test Interactions: Doxazosin mesylate does not affect the plasma concentration of prostate specific antigen in patients treated for up to 3 years.

No clinically significant abnormalities in white blood cell (WBC) counts were reported in patients treated with CARDURA XL in controlled clinical BPH trials. In previous studies of doxazosin IR in BPH patients, the incidence of clinically significant decreases in WBC counts was 0.4% in patients treated with doxazosin IR and 0% in patients treated with placebo. There was no statistically significant difference between these two groups.

Cardiac Toxicity in Animals: Studies in Sprague-Dawley rats after 6, 12, and 18 months, and in CD-1 mice after 18 months of dietary administration, showed an increased incidence of myocardial necrosis or fibrosis at doxazosin base exposure of 26-fold above the human exposure (AUC) at the maximum human recommended dose (MHRD) of 8 mg CARDURA XL. No cardiotoxicity was observed in dogs or Wistar rats after 12 months of oral dosing at doxazosin base exposures of 65- and 85-fold, respectively, above the human exposure (C_{max}) at the MHRD of 8 mg CARDURA XL. There is no evidence that similar lesions occur in humans.

Carcinogenesis and Mutagenesis: Doxazosin mesylate was not carcinogenic to rats or mice when administered daily for 2 years at doses up to 40 mg/kg/day or 120 mg/kg/day, respectively. Systemic drug exposures, as measured by AUC, were approximately 34-fold in rats and 16-fold in mice above the exposures at the MHRD of 8 mg CARDURA XL.

Doxazosin base was not mutagenic in the *in vitro* bacterial Ames assays, the chromosomal aberration assay in human lymphocytes, or the mouse lymphoma assay. Doxazosin was not clastogenic in the *in vivo* mouse micronucleus assay. Doxazosin mesylate has not been evaluated for genotoxicity.

Fertility in Males: Studies in rats after oral administration of doxazosin base showed reduced fertility in males, which was reversible after two weeks of treatment termination at doxazosin base exposure of 13-fold above the human exposure (AUC) at the MHRD of 8 mg CARDURA XL. There have been no reports of any effects of doxazosin on male fertility in humans.

Pregnancy: Teratogenic Effects, Pregnancy Category C. CARDURA XL is not indicated for use in women.

There was no evidence of teratogenicity or embryotoxicity in rat or rabbit fetuses that received up to 20 mg/kg/day or 41 mg/kg/day doxazosin base, respectively, administered during major organ development. Plasma exposure at these doses is approximately 32- and 13-fold, respectively, above the AUC values for doxazosin base in humans given the MHRD of 8 mg CARDURA XL. Embryoletality was observed in rabbits at a dose of 100 mg/kg/day of doxazosin mesylate when administered during major organ development. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, CARDURA XL should be used during pregnancy only if clearly needed.

Doxazosin base was found to cross the placenta following oral administration to pregnant rats, resulting in fetal exposure.

Nonteratogenic Effects. In pre- and postnatal development studies in rats, postnatal development was delayed as evidenced by body weight gain suppression and a slight delay in the appearance of

developmental anatomical landmarks and reflexes at a doxazosin base exposure of 26-fold above the human exposure (AUC) at the MHRD of 8 mg CARDURA XL.

Nursing Mothers: CARDURA XL is not indicated for use in women.

Doxazosin base was secreted into the milk in lactating rats at concentrations approximately 20-fold above the exposure found in the maternal plasma following an oral dose of 1 mg/kg. It is not known if doxazosin is excreted in human breast milk. Use of CARDURA XL in nursing mothers is not recommended.

Pediatric Use: The safety and effectiveness of CARDURA XL in pediatric patients have not been established.

Geriatric Use: Of the 666 patients with BPH who received CARDURA XL in the two controlled clinical efficacy and safety studies, 325 patients (49%) were 65 years of age or older. One hundred thirty-six patients treated with CARDURA XL (20%) were >70 years of age.

In these two studies, the cumulative incidence of hypotension appeared to be age related. The reason for an increased incidence of hypotension in patients older than 70 years of age may be related to a modest increase in systemic exposure to doxazosin (see **CLINICAL PHARMACOLOGY; Pharmacokinetics in Special Populations**), to an increased propensity to orthostasis in the elderly, or to an enhanced sensitivity to vasodilatory agents in the elderly. The incidence of hypotension reported as an adverse event was higher in patients 70 years of age and older (4/136; 2.9%) as compared to patients < 70 years of age (7/530; 1.3%).

ADVERSE REACTIONS

The incidence of adverse events was derived from two controlled efficacy and safety trials involving 1473 BPH patients. In Study 1, CARDURA XL (n=317) was compared to doxazosin IR tablets (n=322) and to placebo (n=156). In Study 2, CARDURA XL (n=350) was compared just to doxazosin IR tablets (n=330). In both these studies, CARDURA XL was initiated at a dose of 4 mg, which could be increased by the investigator to 8 mg after seven weeks if an adequate response was not seen (see **CLINICAL PHARMACOLOGY; Clinical Studies**). Similarly, doxazosin IR was begun at a dose of 1 mg, which was increased in all patients to 2 mg after 1 week, followed by the option to increase to 4 mg after 4 weeks, and 8 mg after 7 weeks.

In these two studies, 6% of patients receiving CARDURA XL withdrew from the study due to adverse events, compared to 7% receiving doxazosin IR, and 3% receiving placebo. The most commonly reported adverse events leading to discontinuation in the CARDURA XL group were: dizziness, dyspnea, asthenia, headache, hypotension, postural hypotension, and somnolence.

The incidence rates presented below (Table 4) are based on combined data from the two controlled studies (Studies 1 and 2). Adverse events with an incidence in the CARDURA XL group of at least 1% and reported more frequently than with placebo are summarized in Table 4.

TABLE 4			
Treatment-Emergent Adverse Events Occurring in $\geq 1\%$ of BPH Patients Treated with CARDURA XL and Reported More Frequently Than with Placebo in the Two Controlled Clinical Studies			
Body System	CARDURA XL (N = 666)	Doxazosin IR (N = 651)	Placebo (N = 156)
BODY AS A WHOLE			
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%
CARDIOVASCULAR			
Hypotension	1.7%	1.8%	0.0%
Postural Hypotension	1.2%	2.2%	0.6%
DIGESTIVE			
Dyspepsia	1.4%	1.2%	0.0%
Nausea	1.2%	2.3%	0.6%
MUSCULOSKELETAL			
Myalgia	1.4%	0.5%	0.0%
NERVOUS			
Dizziness	5.3%	9.1%	1.9%
Somnolence	1.5%	1.2%	0.0%
Vertigo	1.5%	4.1%	0.6%
RESPIRATORY			
Dyspnea	1.2%	1.2%	0.0%
Respiratory Tract Infection	4.8%	4.5%	1.9%
UROGENITAL			
Urinary Tract Infection	1.4%	0.8%	0.6%

Additional adverse events reported with CARDURA XL at an incidence of less than 1% and those of clinical interest include: *Cardiovascular System*: angina pectoris, syncope, tachycardia, chest pain, palpitations; *Digestive System*: diarrhea; *Musculoskeletal System*: arthralgia; *Nervous System*: libido decreased; *Urogenital System*: impotence, dysuria. Of these, the following events were reported more frequently with CARDURA XL than with placebo: syncope, tachycardia, palpitations, and dysuria.

In general, the adverse events reported in the open-label safety extension, in approximately 295 BPH patients treated for up to 37 weeks, were similar in type and frequency to the events described above in the 13-week controlled trials.

In post-marketing experience, the following additional adverse reactions have been reported with doxazosin IR: *Autonomic Nervous System*: priapism; *Cardiovascular System*: cerebrovascular accidents, dizziness postural, myocardial infarction; *Central and Peripheral Nervous System*: hypoesthesia, paresthesia; *Endocrine System*: gynecomastia; *Gastrointestinal System*: vomiting; *General Body System*: fatigue, hot flushes, malaise; *Heart Rate/Rhythm*: bradycardia, cardiac arrhythmias; *Hematopoietic*: leukopenia, purpura, thrombocytopenia; *Liver/Biliary System*: abnormal liver function tests, hepatitis, hepatitis cholestatic, jaundice; *Musculoskeletal System*: muscle cramps, muscle weakness; *Psychiatric*: agitation, anorexia, nervousness; *Respiratory System*: bronchospasm aggravated; *Skin Disorders*: alopecia, urticaria; *Special Senses*: blurred vision, Intraoperative Floppy Iris Syndrome (see **PRECAUTIONS, Cataract Surgery**); *Urinary System*: hematuria, micturition disorder, micturition frequency, nocturia, polyuria.

There have been rare reports of gastrointestinal irritation and gastrointestinal bleeding with use of another drug in this non-deformable sustained release formulation, although causal relationship to the drug is uncertain.

OVERDOSAGE

There is no experience with CARDURA XL overdosage. Overdosage experience with the doxazosin IR is limited. Two adolescents who each intentionally ingested 40 mg doxazosin IR with diclofenac or paracetamol were treated with gastric lavage with activated charcoal and made full recoveries. A two-year-old child who accidentally ingested 4 mg doxazosin IR was treated with gastric lavage and remained normotensive during the five-hour emergency room observation period. A six-month-old child accidentally received a crushed 1 mg tablet of doxazosin IR and was reported to have been drowsy. A 32-year-old female with chronic renal failure, epilepsy, and depression intentionally ingested 60 mg doxazosin IR (blood level 0.9 µg/mL; normal values in hypertensives=0.02 µg/mL); death was attributed to a grand mal seizure resulting from hypotension. A 39-year-old female who ingested 70 mg doxazosin IR, alcohol, and Dalmane® (flurazepam) developed hypotension which responded to fluid therapy.

The most likely manifestation of overdosage would be hypotension, for which the usual treatment would be intravenous infusion of fluid, keeping the patient in the supine position, and in certain circumstances, the administration of vasopressors. As doxazosin is highly protein bound, dialysis would not be indicated.

DOSAGE AND ADMINISTRATION

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 3–4 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.

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.

Concomitant administration of CARDURA XL with a PDE-5 inhibitor can result in additive blood pressure lowering effects and symptomatic hypotension; therefore, PDE-5 inhibitor therapy should be initiated at the lowest dose in patients taking CARDURA XL.

HOW SUPPLIED

CARDURA® XL (doxazosin mesylate extended release tablets) is available as 4 mg (white, imprinted with CXL 4) and 8 mg (white, imprinted with CXL 8) tablets.

Bottle of 30: 4 mg (NDC 0049-2710-30)

Bottle of 30: 8 mg (NDC 0049-2720-30)

Recommended Storage: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Rx only



Distributed by

Roerig

Division of Pfizer Inc, NY, NY 10017

LAB-0326-2.0
Revised July 2009