PRODUCT MONOGRAPH

Pr CARDURA-1®

CARDURA-2®

CARDURA-4®

(doxazosin mesylate)

Tablets 1, 2 and 4 mg

Antihypertensive Agent

Symptomatic Treatment of Benign Prostatic Hyperplasia (BPH)

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THERAPEUTIC CLASSIFICATION

Antihypertensive Agent
Symptomatic Treatment of Benign Prostatic Hyperplasia (BPH)

ACTIONS AND CLINICAL PHARMACOLOGY

The mechanism of action of CARDURA (doxazosin mesylate) is selective blockade of $alpha_1$ subtype of post-synaptic, post-junctional alpha-adrenergic receptors.

Pharmacodynamics

Hypertension

Administration of CARDURA results in a reduction in systemic vascular resistance. In patients with hypertension there is little change in cardiac output. Maximum reductions in blood pressure usually occur 2-6 hours after dosing and are associated with a small increase in standing heart rate. CARDURA has a greater effect on blood pressure and heart rate in the standing position. Tolerance has not been observed in long-term therapy.

Systolic and diastolic blood pressure is lowered in both the supine and standing positions. In clinical trials, blood pressure responses were measured at the end of the dosing interval (24 hours), with the usual supine response 6-11 mm Hg systolic and 5-9 mm Hg diastolic. The response in the standing position tended to be larger by 3-5 mm Hg. Peak blood pressure effects (1-6 hours) were larger by about 50-75% (i.e., trough values were about 55-70% of peak effect), with the larger peak-trough differences seen in systolic pressures. There was no apparent difference in the blood pressure response of Caucasians and Blacks or of patients ≥65 years old and <65 years old.

During controlled clinical studies, predominantly normocholesterolemic patients receiving CARDURA had small but statistically significant reductions in total serum cholesterol (2.7%) and low-density lipoprotein (LDL) cholesterol (4.3%), and increase in the high-density lipoprotein (HDL)/total cholesterol ratio (4.3%) relative to placebo. No significant changes were observed in HDL fraction and triglycerides compared to placebo.

Benign Prostatic Hyperplasia (BPH)

Benign Prostatic Hyperplasia (BPH) is a common cause of urinary outflow obstruction in aging males. Severe BPH may lead to urinary retention and renal damage. A static and a dynamic component contribute to the symptoms and reduced urinary flow rate associated with BPH. 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 α_1-adrenoceptors which are present in high density in the prostatic stroma, prostatic capsule and bladder neck. Blockage of the α_1-receptor decreases urethral resistance and may relieve the obstruction and BPH symptoms. In 30-70% of patients with symptomatic BPH, placebo has also shown a remarkable and sometimes dramatic effect in controlled short-term studies.

The symptoms may subside or fade away without treatment in approximately 20% of patients.

Doxazosin antagonizes phenylephrine-induced contractions, *in vitro*, in the human prostate. Doxazosin is bound with high affinity to the α_{1A}-adrenoceptor subtype, thought to be the predominant functional type in the prostate.

The effect of CARDURA in BPH is thought to result from selective blockade of the α_{1A}-adrenoceptors located in the prostatic muscular stroma, capsule and bladder neck. This action results in relief of the urinary outlet obstruction and symptomatology associated with BPH.

In controlled clinical trials in >900 patients, the efficacy of CARDURA was evaluated. In two studies CARDURA 4-8 mg once daily significantly improved maximum urinary flow rate (MFR) by 2.3-3.3 mL/sec (placebo 0.1-0.7 mL/sec).

Significant improvements were usually noticed within 2 weeks of commencing CARDURA treatment and a significantly larger proportion of patients (32-42%) responded with MFR improvements $\geq$ 3 mL/sec (placebo 13-17%). Average flow rate also improved with CARDURA treatment, (1.3-2.1 mL/sec vs placebo 0.2-0.3 mL/sec). CARDURA also resulted in a significant relief of the obstructive and irritative symptoms associated with BPH.

Using invasive urodynamics in a controlled clinical trial in 43 BPH patients, CARDURA 2 mg improved MFR 3.4 mL/sec, and reduced urethral resistance 7.5-13.5 cmH_2O (placebo, MFR -0.6 mL/sec and resistance of 3.3 cmH_2O).

In a 29-week controlled BPH trial in 100 patients, CARDURA was significantly more effective than placebo in improving urinary flow rates and reducing BPH symptoms; the effect was sustained over the entire treatment period. No tolerance to the effect of CARDURA on urodynamics or BPH symptomatology was observed in patients treated for ≤4 years in open-label studies.

Both hypertensive and normotensive BPH patients treated with CARDURA demonstrate statistically significant improvements in urodynamics and symptomatology compared to placebo.

Pharmacokinetics

After oral administration of therapeutic doses of CARDURA absorption occurs with peak blood levels at about 2 hours. Bioavailability is approximately 65%. Food has little or no effect on the bioavailability.

Approximately 98% of the circulating drug is bound to plasma proteins. Plasma elimination is biphasic with a terminal elimination half-life of about 22 hours. There is an accumulation of plasma doxazosin levels following steady state dosing, consistent with the terminal elimination half-life.

In a study of elderly hypertensive patients, the pharmacokinetic parameters of doxazosin at steady state were similar to those observed in a previous study of young and elderly healthy subjects who received a single oral dose of CARDURA.

In a crossover study in 24 normotensive subjects, the pharmacokinetics and safety of doxazosin were shown to be similar with morning and evening dosing regimens. CARDURA may, therefore, be administered as a single daily morning or evening dose (see DOSAGE and ADMINISTRATION).

CARDURA is primarily metabolized, mainly by O-demethylation of the quinazoline nucleus or hydroxylation of the benzodioxan moiety. Doxazosin is extensively metabolized in the liver. In vitro studies suggest that the primary pathway for elimination is via CYP 3A4; however, CYP 2D6 and CYP 2C9 metabolic pathways are also involved for elimination, but to a lesser extent (see PRECAUTIONS, Drug Interactions). Excretion is mainly via the feces with 9% of the dose excreted in urine as doxazosin (<0.5%) or metabolites. Less than 5% is excreted as the unchanged drug, mainly in the feces.

The disposition of CARDURA in patients with renal insufficiency is similar to that in patients with normal renal function. Only limited data are available in patients with liver impairment and on the effects of drugs known to influence hepatic metabolism (e.g., cimetidine) (see PRECAUTIONS - Use in Patients with Impaired Liver Function).

INDICATIONS AND CLINICAL USE

Hypertension

CARDURA (doxazosin mesylate) is indicated in the treatment of mild to moderate essential hypertension. It is employed in a general treatment program in association with a thiazide diuretic and/or other antihypertensive agents, as needed, for proper patient response.

CARDURA may be tried as a sole therapy in those patients for whom treatment with other agents caused adverse effects or is inappropriate.

Benign Prostatic Hyperplasia (BPH)

CARDURA is also indicated for the treatment of symptoms of benign prostatic hyperplasia (BPH). The onset of effect is rapid, with improvement in peak flow and symptoms observed within 1-2 weeks. The effect on these variables was maintained over the entire study duration (≤4 years). CARDURA may be used in BPH patients who are either hypertensive or normotensive. While the reduction in blood pressure in normotensive patients with BPH is clinically insignificant, patients with hypertension and BPH have both conditions effectively treated with doxazosin monotherapy (see DOSAGE and ADMINISTRATION for dosage regimens).

A number of clinical conditions can mimic symptomatic BPH (i.e., stricture of urethra, stricture of bladder neck, urinary bladder stones, neurogenic bladder dysfunction secondary to diabetes, Parkinsonism, etc.). These conditions should therefore be ruled out before doxazosin therapy is initiated.

CONTRAINDICATIONS

CARDURA is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see PHARMACEUTICAL INFORMATION, **Composition** section of the product monograph.
- Patients with a known sensitivity to other quinazolines (e.g. prazosin, terazosin).
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption because lactose is a non-medicinal ingredient in CARDURA.

WARNINGS

Syncope and "First Dose" Effect

CARDURA (doxazosin mesylate) can cause marked hypotension, especially postural hypotension and syncope in association with the first dose or first few doses of therapy. A

similar effect can occur if therapy is reinstated following interruption for more than a few doses. Postural effects are most likely to occur between 2-6 hours after dose.

In controlled studies of CARDURA, the incidence of syncopal episodes was 0.7%. An initial dose of 1 mg/day resulted in a 4% incidence of postural side effects with no cases of syncope. In controlled clinical trials for BPH in normotensive patients, there was a 0.2% occurrence of syncope with CARDURA. In controlled trials in patients with both BPH and hypertension receiving CARDURA, the incidence of syncope was 0.8%.

The likelihood of syncopal episodes or excessive hypotension can be minimized by limiting the initial dose of CARDURA to 1 mg, by increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION).

Patients should be advised of the possibility of syncopal and orthostatic symptoms, and to avoid driving or hazardous tasks for 24 hours: after the initial dose of CARDURA, after the dose is increased, and after interruption of therapy when treatment is resumed. They should be cautioned to avoid situations where injury could result should syncope occur.

If syncope occurs, the patient should be placed in the supine position. If this measure is inadequate, volume expansion with intravenous fluids or vasopressor therapy may be used. A transient hypotensive response is not a contraindication to further doses of CARDURA.

Orthostatic Hypotension

While syncope is the most severe orthostatic effect of CARDURA, other symptoms of lowered blood pressure such as dizziness, lightheadedness or vertigo can occur. These were common in clinical trials in hypertension, occurring in ≤23% of all patients treated and causing discontinuation of therapy in about 2%. In placebo-controlled titration trials, there was an increased frequency of orthostatic effects in patients given ≥8 mg (10%) compared to patients given 1-4 mg (5%) or placebo (3%).

In placebo-controlled trials in BPH, the incidence of orthostatic hypotension with CARDURA was ≤1%. With maintenance doses of ≤8 mg/day in normotensive patients with BPH, the average decreases in both sitting and standing blood pressure were small: 5/2 mm Hg with CARDURA and 1/1 mm Hg with placebo.

Patients with occupations in which such events represent potential problems should be treated with particular caution.

Concomitant administration of doxazosin with a PDE-5 inhibitor such as sildenafil, tadalafil or vardenafil, should be used with caution as it may lead to symptomatic hypotension.

Patients should be advised of the need to lie down when symptoms of lowered blood pressure occur, and to be careful when arising from a lying position. If dizziness, lightheadedness or palpitations are bothersome, they should be reported to the physician so that dose adjustment can be considered. Patients should also be told that drowsiness or somnolence can occur with CARDURA, requiring caution in people who must drive or operate heavy machinery.

If hypotension occurs, place the patient in the recumbent position and institute supportive measures as necessary.

Priapism

Rarely (probably less frequently than once in every several thousand patients), α_1-antagonists such as doxazosin have been associated with priapism. Because this condition can lead to permanent impotence if not promptly treated, patients should be advised about the seriousness of the condition.

Hematological Events

Analysis of hematologic data from patients receiving CARDURA in controlled clinical trials showed that the mean white blood cell (WBC) (n=474) and mean neutrophil counts (n=419) were decreased by 2.4% and 1.0% respectively, compared to placebo. A search through a data base of 2,400 patients revealed 4 cases in which drug-related neutropenia could not be ruled out. Two had a single low value on the last day of treatment. Two had stable, non-progressive neutrophil counts in the 1000/mm^3 range over periods of 20 and 40 weeks. No patients became symptomatic as a result of the low WBC or neutrophil counts.

In BPH patients treated with doxazosin, the incidence of clinically significant WBC abnormalities was 0.4%.

In post-marketing experience, rare cases of hematopoietic events such as leukopenia and thrombocytopenia have been reported.

Hepatic Events

In post-marketing experience, rare cases of abnormal liver function tests, cholestasis, jaundice and hepatitis have been reported.

Peripheral Edema

Fluid retention resulting in weight gain may occur during CARDURA therapy. In placebo-controlled monotherapy trials, patients receiving CARDURA gained a mean of 0.6 kg compared to a mean loss of 0.1 kg for placebo-treated patients. The overall incidence of body weight gain reported as a side effect in controlled clinical trials was 0.8%.

PRECAUTIONS

General

CARDURA (doxazosin mesylate) therapy does not modify the natural history of benign prostatic hyperplasia (BPH). It does not retard or stop the progression of BPH, nor does it improve urine flow sufficiently to significantly reduce the residual urine volume. However, significant reduction of the mean residual volume have been shown in patients with baseline residual volumes of >50 mL. The patient may continue to be at risk of developing urinary retention and other BPH complications during doxazosin therapy.

Long-Term Safety and Efficacy

The long-term safety and efficacy (i.e., >4 years) has not yet been established for the use of doxazosin in the treatment of benign prostatic hyperplasia.

Prostatic Cancer

Carcinoma of the prostate and BPH cause many of the same symptoms. These two diseases frequently coexist. Therefore, patients thought to have BPH should be examined prior to starting CARDURA therapy to rule out the presence of carcinoma of the prostate.
CARDURA should not be used in patients with PSA >10 ng/mL unless cancer of the prostate has been ruled out.

Ophthalmologic

The Intraoperative Floppy Iris Syndrome (IFIS, a variant of small pupil syndrome) has been observed during cataract surgery in some patients on or previously treated with alpha$_1$ blockers. As IFIS may lead to increased procedural complications during the operation, current or past use of alpha blockers should be made known to the ophthalmologic surgeon in advance of surgery.

Use in Patients with Impaired Liver Function

As with any drug wholly metabolized by the liver, doxazosin should be administered with caution to patients with evidence of impaired hepatic function or to patients receiving drugs known to influence hepatic metabolism.

Use in Patients with Impaired Renal Function

The use of CARDURA in patients with impaired renal function requires careful monitoring. Clinical studies indicate that the disposition of CARDURA in patients with renal insufficiency is similar to that in patients with normal renal function, however accumulation of the drug with chronic dosing may occur. Less than 10% of the dose of doxazosin is excreted in the urine as unchanged drug and metabolites.

Concomitant Conditions

Doxazosin should not be prescribed to patients with symptomatic BPH who have the following concomitant conditions:

- Chronic fibrous or granulomatous prostatitis,
- Chronic urinary retention,
- Gross hematuria,
- High residual urine (>200 mL),
- History of pelvic irradiation,
- History of prior prostatic surgery,
- Hydronephrosis,
- Peak urine flow of ≤5 mL/sec,
- Presence of calculi in urinary bladder,
- Presence of carcinoma of the prostate,

- Presence of large median lobe of prostate,
- Presence of neurogenic bladder dysfunction (diabetes mellitus, Parkinsonism, uninhibited neurogenic bladder, etc.),
- Presence of prostatic calculi,
- Recent history of epididymitis,
- Urethral stricture.

Doxazosin should also not be prescribed to patients having experienced within the past 6 months:
- A myocardial infarction,
- Transient ischemic attacks, or
- Cerebrovascular accident.

Use in Pregnancy

There are no studies in pregnant women. CARDURA is not recommended in pregnant women unless the potential benefit outweighs the potential risk to mother and fetus.

CARDURA crosses the placental barrier.

Animal data: Studies in pregnant rabbits and rats at daily oral doses of ≤40 and ≤20 mg/kg, respectively, have revealed no evidence of teratogenic effect. A dosage regimen of 82 mg/kg/day in the rabbit was associated with reduced fetal survival, an increase in embryomortality as well as increases in fetal and placental weights.

In peri- and post-natal studies in rats, postnatal development at maternal doses of 40 or 50 mg/kg/day of doxazosin was delayed as evidenced by slower body weight gain and a slightly later appearance of anatomical features and reflexes.

Use in Nursing Mothers

Animal data: Studies in lactating rats given a single oral dose of 1 mg/kg of [2-^{14}C]-doxazosin indicate that doxazosin accumulates in rat breast milk with a maximum of concentration about 20 times greater than the maternal plasma concentration.

A single case report demonstrated transfer of doxazosin into human breast milk. Caution should be exercised when CARDURA is administered to a nursing mother and in general, nursing should be interrupted.

Use in Children

The use of CARDURA is not recommended in children since safety and efficacy have not been established.

Use in Elderly

CARDURA should be used cautiously in elderly patients because of the possibility of postural hypotension. There was an age-related trend towards an increased incidence of postural hypotension and postural dizziness in elderly hypertensive patients treated with this drug.

Cardiac Toxicity in Animals

An increased incidence of myocardial necrosis or fibrosis was displayed by Sprague-Dawley rats after 6 months of dietary administration at concentrations calculated to provide 80 mg doxazosin/kg/day, and after 12 months of dietary administration at concentrations calculated to provide 40 mg doxazosin/kg/day.

Myocardial fibrosis was observed in both rats and mice treated in the same manner with 40 mg doxazosin/kg/day for 18 months. No cardiotoxicity was observed at lower doses (≤10 or ≤20 mg/kg/day, depending on the study) in either species.

These lesions were not observed after 12 months of oral dosing in dogs and Wistar rats at maximum doses of 20 and 100 mg/kg/day, respectively. There is no evidence that similar lesions occur in humans.

Drug Interactions

Doxazosin is highly (98%) bound to plasma protein. *In vitro* data in human plasma indicates that doxazosin mesylate has no effect on protein binding of digoxin, warfarin, phenytoin or indomethacin.

CARDURA has been administered to patients receiving thiazide diuretics, beta-adrenergic blocking agents and non-steroidal anti-inflammatory drugs. No unexpected interactions were reported. An additive hypotensive effect was observed when CARDURA was co-administered with thiazide diuretics and beta-adrenergic blocking agents. There is limited experience with CARDURA in combination with ACE inhibitors or calcium channel blockers.

Digoxin

Serum digoxin concentrations were not affected by treatment with doxazosin.

Cimetidine

In a randomized, open-label, placebo-controlled, cross-over study in 22 healthy male subjects, the single co-administration of 1 mg doxazosin with 400 mg b.i.d. cimetidine resulted in a 10% increase in mean AUC of doxazosin (p=0.006), and a slight but not statistically significant increase in mean Cmax and mean half-life of doxazosin. The effect of further administration of cimetidine has not been studied.

PDE-5 Inhibitors

Symptomatic hypotension has been reported during the concomitant use of PDE-5 inhibitors (e.g. sildenafil, tadalafil, vardenafil) and CARDURA (see WARNINGS).

CYP3A4 Inhibitors

In vitro studies suggest that doxazosin is a substrate of CYP 3A4. Caution should be exercised when concomitantly administering doxazosin with a strong CYP 3A4 inhibitor, such as clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir,

saquinavir, telithromycin or voriconazole (see ACTIONS AND CLINICAL PHARMACOLOGY, **Pharmacokinetics**).

ADVERSE REACTIONS

Hypertension

CARDURA (doxazosin mesylate) has been administered to approximately 4,000 patients in clinical trials of whom 1,679 patients were included in controlled trials. The most serious adverse event (AE) occurring in the controlled clinical trials was syncope occurring in 0.7% of patients and resulting in a discontinuation rate of 0.2%.

The most frequent AEs in controlled clinical trials were: headache (16.5%), fatigue/malaise (14.8%), dizziness (14.6%), postural dizziness (8.7%) and edema (6.6%). Discontinuation of CARDURA due to AEs was required in 7% of patients.

AEs which occurred with an incidence of ≥ 1% in the controlled clinical trials in patients with mild to moderate essential hypertension were as shown in the following table.

Table 1 – Incidence of Adverse Events ≥ 1% in the controlled clinical trials in patients with mild to moderate essential hypertension

Body System/Adverse Event	**CARDURA n = 1679 (%)**
All Adverse Events	49.0%
Nervous System Disorders	
Headache	16.5
Dizziness	14.6
Postural Dizziness	8.7
Somnolence	4.9
Paresthesia	1.7
Hypoesthesia	1.6
General Disorders and Administration Site Conditions	
Fatigue	14.8
Edema	6.6
Asthenia	2.7
Pain (general body)	1.3

Body System/Adverse Event	CARDURA n = 1679 (%)
Gastrointestinal Disorders	
Nausea	3.9
Dry Mouth	3.4
Diarrhea	2.9
Dyspepsia	2.1
Abdominal Pain	1.6
Flatulence	1.4
Constipation	1.3
Respiratory, Thoracic and Mediastinal Disorders	
Dyspnea	3.9
Rhinitis	3.0
Blood and Lymphatic Disorders	
Decrease in Platelets	3.9
Decrease in White Blood Cells	2.4
Decrease in Hematocrit	1.6
Decrease in Hemoglobin	1.4
Decrease in Neutrophil Count	1.0
Cardiac Disorders	
Palpitation	3.6
Chest Pain	2.7
Tachycardia	1.6
Reproductive System and Breast Disorder	
Sexual Dysfunction	3.5
Ear and Labyrinth Disorders	
Vertigo	3.0
Eye Disorders	
Vision/Accommodation Abnormalities	2.4
Conjunctivitis/Eye Pain	1.2
Psychiatric Disorders	
Anxiety/Nervousness	2.3
Insomnia	2.2
Depression/Apathy	1.6
Skin and Subcutaneous Tissue Disorders	
Rash	1.7
Increased Sweating	1.4

Body System/Adverse Event	CARDURA n = 1679 (%)
Musculoskeletal and Connective Tissue Disorders	
Muscle Cramps	1.7
Myalgia	1.3
Renal and Urinary Disorders	
Micturition Frequency	1.2
Polyuria	1.0

Less Common Clinical Trial Adverse Drug Reactions (<1%)
The following other AEs occurred in hypertensive patients with an incidence of <1% in controlled clinical trials (n=1679):

Blood and Lymphatic Disorders: lymphadenopathy

Cardiac Disorders: angina pectoris, arrhythmia

Ear and Labyrinth Disorders: tinnitus

Eye Disorders: abnormal lacrimation, photophobia

Gastrointestinal Disorders: fecal incontinence, vomiting

General Disorders and Administration Site Conditions: face edema, fever/rigors, general edema, thirst

Infections and infestations: infection

Metabolism and Nutrition Disorders: anorexia, gout, hypokalemia, increased appetite, weight increase

Musculoskeletal and Connective Tissue Disorders: arthralgia, back pain, muscle weakness, twitching

Nervous System Disorders: amnesia, ataxia, depersonalization, hypertonia, migraine, movement disorders, paresis, syncope, tremor

Psychiatric Disorders: abnormal thinking, agitation, emotional lability, paroniria

Renal and Urinary Disorders: urinary disorder, urinary incontinence

Reproductive System and Breast Disorder: breast pain

Respiratory, Thoracic and Mediastinal Disorders: bronchospasm/bronchitis, coughing, epistaxis, pharyngitis, sinusitis

Skin and Subcutaneous Tissue Disorders: alopecia, dry skin, eczema, pallor, pruritus, purpura

Special Senses: taste perversion

Vascular Disorders: flushing, hot flushes, hypotension, peripheral ischemia, postural hypotension

Benign Prostatic Hyperplasia

CARDURA (doxazosin mesylate) has been administered once daily to 665 both hypertensive and normotensive patients with BPH in controlled clinical trials. The most serious AE occurring in the controlled trials was syncope (0.5%).

The most frequent AEs in controlled trials were dizziness (15.6%), headache (9.8%) and fatigue (8%).

Discontinuation rate of CARDURA due to AEs was 9%.

AEs which occurred with an incidence of ≥ 1% in the controlled clinical trials in normotensive or hypertensive patients with BPH were as shown in the following table.

Table 2 – Incidence of Adverse Events of ≥ 1% in the controlled clinical trials in normotensive or hypertensive patients with BPH

ADVERSE EVENT	**INCIDENCE**	
	Short Term* (n=665)	**Long Term** (n=450)**
All Adverse Events	45.0%	66.0%
Nervous System Disorders		
Dizziness	15.6%	20.7%
Headache	9.8%	12.2%
Somnolence	3.0%	4.9%
Hypertonia	<1%	1.1%
Paresthesia	<1%	1.1%
Tremor	-	1.1%
General Disorders and Administration Site Conditions		
Fatigue	8.0%	11.6%
Edema	2.7%	4.9%
Pain	2.0%	5.1%
Asthenia	<1%	1.1%

ADVERSE EVENT	INCIDENCE	
	Short Term* (n=665)	**Long Term** (n=450)**
All Adverse Events	45.0%	66.0%
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea	2.6%	<1%
Respiratory Disorder	1.1%	2.5%
Gastrointestinal Disorders		
Diarrhea	2.3%	3.8%
Abdominal Pain	2.3%	1.8%
Dyspepsia	1.8%	2.4%
Nausea	1.5%	3.1%
Dry Mouth	1.4 %	<1%
Constipation	<1%	1.3%
Musculoskeletal and Connective Tissue Disorders		
Back Pain	1.8%	2.9%
Leg Cramps	<1%	1.6%
Arthralgia	<1%	1.3%
Vascular Disorders		
Hypotension	1.7%	2.5%
Eye Disorders		
Abnormal Vision	1.4%	2.2%
Cardiac Disorders		
Palpitation	1.2%	1.8%
Chest Pain	1.2%	3.8%
Arrhythmia	-	1.1%
Myocardial Infarction	<1%	1.3%
Psychiatric Disorders		
Insomnia	1.2%	1.3%
Anxiety	1.1%	<1%
Depression	<1%	3.1%
Decreased Libido	<1%	2.7%
Infections and infestations		
Urinary Tract Infection	1.2%	1.1%
Reproductive System and Breast Disorder		
Impotence	1.1%	4.9%
Prostatic Disorder	<1%	1.8%
Ejaculation Failure	<1%	1.1%

ADVERSE EVENT	INCIDENCE	
	Short Term* (n=665)	**Long Term** (n=450)**
All Adverse Events	45.0%	66.0%
Skin and Subcutaneous Tissue Disorders		
Increased Sweating	1.1%	<1%
Dermatitis	-	1.3%
Rash	<1%	1.3%
Renal and Urinary Disorders		
Urinary Retention	<1%	1.6%
Hematuria	<1%	1.8%
Ear and Labyrinth Disorders		
Tinnitus	<1%	1.3%

* Placebo-controlled clinical trials; treated with doxazosin from 1-203 days.
** Open label extension of 3 placebo controlled clinical trials; treated for up to 50 months.

Less Common Clinical Trial Adverse Drug Reactions (<1%)
Short-term controlled clinical trials:
The following other AEs occurred in normotensive or hypertensive patients with BPH with an incidence of <1% in short-term controlled clinical trials (n=665):

Blood and Lymphatic Disorders: lymphadenopathy

Cardiac Disorders: angina, bradycardia, myocardial infarction, tachycardia

Ear and Labyrinth Disorders: earache, tinnitus

Eye Disorders: cataract, conjunctivitis, eye pain, visual field defect

Gastrointestinal Disorders: constipation, flatulence, gingivitis, melena, vomiting

General Disorders and Administration Site Conditions: allergy, asthenia, fever, influenza like symptoms, malaise, rigors, sudden death

Infections and infestations: fungal infection, sepsis, upper respiratory tract infection, viral infection

Metabolism and Nutrition Disorders: gout, hyperglycemia, increased appetite, weight increase

Musculoskeletal and Connective Tissue Disorders: arthralgia, arthritis, hernia, leg cramps, myalgia, tendon disorder

Neoplasms Benign, Malignant and Unspecified: carcinoma

Nervous System Disorders: amnesia, ataxia, depersonalization, hypertonia, hypoesthesia, paresthesia, speech disorder, syncope

Psychiatric Disorders: abnormal thinking, confusion, decreased libido, depression, emotional lability, impaired concentration, nervousness, paroniria

Renal and Urinary Disorders: abnormal urine, cystitis, dysuria, hematuria, micturition disorder, renal pain, urinary incontinence, urinary retention

Reproductive System and Breast Disorder: ejaculation failure, epididymitis, genital pruritus, prostatic disorder

Respiratory, Thoracic and Mediastinal Disorders: bronchitis, bronchospasm, coughing, epistaxis, pneumonia, rhinitis, sinusitis

Skin and Subcutaneous Tissue Disorders: aggravated psoriasis, dry skin, eczema, erythematous rash, maculopapular rash, pallor, pruritus, rash, urticaria

Special Senses: taste perversion

Vascular Disorders: flushing, hot flushes, postural hypotension, subarachnoid haemorrhage

Long-term controlled clinical trials:
The following other AEs occurred in normotensive or hypertensive patients with BPH with an incidence of <1% in long-term controlled clinical trials (n=450):

Cardiac Disorders: abnormal ECG, angina pectoris, atrial fibrillation, cardiac failure, extra systoles, myocardial ischemia, tachycardia

Ear and Labyrinth Disorders: deafness, earache, otitis media

Eye Disorders: conjunctivitis, diplopia, eye abnormality, eye pain, myopia, visual field defect

Gastrointestinal Disorders: diverticulitis, dry mouth, enlarged abdomen, esophagitis, flatulence, gastric ulcer, melena, rectal haemorrhage, tenesmus, tongue disorder, tooth disorder, tooth hypoplasia, vomiting

General Disorders and Administration Site Conditions: allergic reaction/allergy, fever, malaise, rigor

Hepatobiliary Disorders: cholelithiasis

Infections and Infestations: fungal infection, herpes simplex, herpes zoster

Metabolism and Nutrition Disorders: dehydration, hyperglycemia, hyperuricemia, increased appetite, SGOT increase, SGPT increase, weight increase

Musculoskeletal and Connective Tissue Disorders: arthritis, myalgia, polymyalgia rheumatica

Neoplasms Benign, Malignant and Unspecified: breast neoplasm, carcinoma, pulmonary carcinoma

Nervous System Disorders: amnesia, convulsions, depersonalization, encephalopathy, hypokinesia, migraine, syncope

Psychiatric Disorders: abnormal thinking, anxiety, impaired concentration, nervousness

Renal and Urinary Disorders: abnormal urine, cystitis, dysuria, oliguria, polyuria, urinary incontinence

Reproductive System and Breast Disorder: abnormal semen, epididymitis, perineal pain, sexual dysfunction

Respiratory, Thoracic and Mediastinal Disorders: bronchitis, epistaxis, pharyngitis, rhinitis

Skin and Subcutaneous Tissue Disorders: increased sweating, maculopapular rash, nail disorder, photosensitivity reaction, pruritus, purpura, seborrhea, skin disorder, skin hypertrophy, urticaria

Vascular Disorders: aggravated hypertension, aneurysm, cerebrovascular disorder/accident, flushing, hypertension, intermittent claudication

Data from long-term (≤50 months), open BPH studies (n=450) indicate higher rates of dizziness in younger hypertensive (27%) and normotensive (22%) patients, impotence in younger hypertensive (8%) patients, and discontinuation rates in patients due to AEs (16.7%) compared to data from short-term placebo-controlled BPH studies (n=665).

Uncontrolled Trials and Post-Marketing Experience

The following additional AEs have also been reported in patients with essential hypertension and in normotensive or hypertensive patients with BPH: cholestasis, ejaculation disorders such as retrograde ejaculation, gynecomastia, hepatitis, Intraoperative Floppy Iris Syndrome (see PRECAUTIONS, Ophthalmologic), jaundice, parosmia, priapism, and renal calculus.

Laboratory Abnormalities

No clinically relevant adverse effects were noted on serum potassium, serum glucose, uric acid, blood urea nitrogen (BUN) or creatinine. Decreases in white blood cells, neutrophils, platelets (see WARNINGS), hemoglobin and hematocrit have been reported. Abnormal liver function tests have occurred.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No data are available regarding overdosage with CARDURA (doxazosin mesylate) in humans.

Should administration of CARDURA lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be

accomplished by keeping the patient in the supine position. If this measure is inadequate, shock should first be treated with volume expanders. If necessary, vasopressors should be used. Renal function should be monitored and supported as needed. As CARDURA is highly protein bound, dialysis may not be of benefit.

DOSAGE AND ADMINISTRATION

Dosage must be individualized. Doxazosin may be administered either in the morning or in the evening.

The absorption of CARDURA (doxazosin mesylate) is not affected by food.

When CARDURA is being added to existing antihypertensive therapy, the patient should be carefully monitored for the occurrence of hypotension (see WARNINGS – Syncope and "First Dose" Effect). If a diuretic or other antihypertensive agent is being added to a CARDURA regimen, reducing the dose of CARDURA and retitration, with careful monitoring, may be necessary.

If CARDURA administration is discontinued for several days, or longer, therapy should be reinstituted using the initial dosing regimen.

Hypertension - 1-16 mg Once Daily

The initial dose of CARDURA in patients with hypertension is 1 mg given once daily and this dose should not be exceeded. This starting dose is intended to minimize postural hypotensive effects. The maximum reduction in blood pressure normally occurs between 2-6 hours after a dose.

The dose may be slowly increased to achieve the desired blood pressure response. The usual dose range is 1-8 mg once daily. The maximum recommended daily dose is 16 mg once daily.

Increases in dose >4 mg increased 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.

Benign Prostatic Hyperplasia - 1-8 mg Once Daily

The initial dosage of CARDURA is 1 mg given once daily (see WARNINGS – Syncope and "First Dose" Effect). 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. The recommended titration interval is 1-2 weeks. Blood pressure should be evaluated routinely in these patients.

Doxazosin should be discontinued if the drug has been increased to the maximum tolerated dose and improvement in urinary flowmetry is <25%, or if doxazosin side effects are more bothersome than BPH symptoms, or if the patient develops a urinary complication secondary to BPH while on doxazosin therapy.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

PHARMACEUTICAL INFORMATION

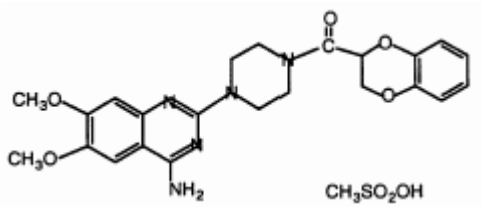
Chemistry

Trade name: CARDURA*

Proper name: Doxazosin mesylate

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

Structural Formula:



Molecular Formula: $C_{23}H_{25}N_5O_5 \cdot CH_4O_3S$

Molecular Weight: 547.6

Description: Doxazosin mesylate is a white to off-white crystalline solid of uniform appearance. It is freely soluble in dimethylsulphoxide, soluble in dimethylformamide, slightly soluble in methanol, ethanol, and water (0.8% w/v at 25°C), and very slightly soluble in acetone and methylene chloride. The pKa of the doxazosin moiety is 6.93 at 25°C and the melting point of doxazosin mesylate is 273.7°C.

Composition

CARDURA is formulated as tablets containing doxazosin mesylate equivalent to 1, 2 and 4 mg of doxazosin.

Non-Medicinal Ingredients: colouring agents (Yellow Lake Blend for the 2 mg and FD&C Yellow #6 Aluminum Lake for the 4 mg), lactose, magnesium stearate, microcrystalline cellulose, sodium lauryl sulphate, and sodium starch glycolate.

Stability and Storage Recommendations

CARDURA (doxazosin mesylate) Tablets 1, 2 and 4 mg: store at room temperature, 15-30°C.

AVAILABILITY OF DOSAGE FORMS

Availability

CARDURA is available as capsular scored-tablets containing doxazosin mesylate equivalent to 1, 2 or 4 mg of doxazosin.

1mg: capsular shaped, white to off white tablet with upper engraved “Cardura” and lower bisected and engraved “1mg”

2mg: capsular shaped yellow tablet with upper engraved "Cardura", lower bisected and engraved "2mg"

4mg: capsular shaped yellow to orange (pale orange) tablet with upper engraved "Cardura", lower bisected and engraved "4mg

CARDURA is supplied in opaque plastic (high density polyethylene) bottles of 100 tablets

PHARMACOLOGY

Animal Pharmacology - *In Vivo*

In anaesthetized cats, doxazosin caused adrenaline reversal and was more effective in antagonizing pressor responses to phenylephrine (ED_{50}=0.06 mg/kg, i.v.) than to noradrenaline, (ED_{50} <10 mg/kg, i.v.) indicating selective effect on post-junctional alpha1- as opposed to $alpha_2$-adrenoceptors. This was confirmed by the lack of effect of doxazosin on the $alpha_2$-mediated pressor responses induced by alpha-methylnor-adrenaline. The lack of effect of doxazosin on pre-junctional $alpha_2$-adrenoceptors was confirmed in anaesthetized dogs.

Animal Pharmacology - *In Vitro*

In the perfused isolated rabbit ear artery and in the rabbit pulmonary artery rings, doxazosin had a selective effect on post-synaptic alpha1-adrenoceptors. The superfused rabbit pulmonary artery preparation was used to show that doxazosin is highly selective (pre-synaptic activity $EC_{20}=2 \times 10^{-5}$M vs post-synaptic activity $EC_{20}=2.4 \times 10^{-8}$M); for the post- as opposed to the pre-junctional alpha receptors in this tissue.

Miscellaneous Actions

At high doses, doxazosin increased both alcohol and pentobarbitone sleeping time in mice and may possess mild CNS sedative activity *per se*, increased basal gastric acid secretion and gastrointestinal motility in rats, and had antidiuretic activity in normotensive rats and dogs.

Human Pharmacology

Hypertension

A comparison of the blood pressure lowering effect of CARDURA (doxazosin mesylate) in patients ≥65 years old (n=204), and those <65 years old (n=1,344) show similar falls in blood pressure. The changes in standing systolic/diastolic pressures were -15/-12 mm Hg for patients ≥65 years old and -13/-11 mm Hg for the patients <65 years old.

Pharmacokinetic studies at steady state in hypertensive patients given doxazosin doses of 2-16 mg once daily showed linear kinetics and dose proportionality. In two studies, following the administration of 2 mg orally once daily, the mean accumulation ratios (steady state AUC vs first dose AUC) were 1.2 and 1.7.

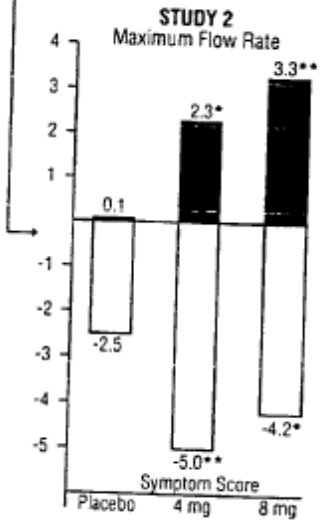
Benign Prostatic Hyperplasia (BPH)

In three placebo-controlled studies of 14-16 weeks' duration obstructive symptoms (hesitation, intermittency, dribbling, weak urinary stream, incomplete emptying of the bladder) and irritative symptoms (nocturia, daytime frequency, urgency, burning) of BPH were evaluated at each visit by patient-assessed symptom questionnaires. The bothersomeness of symptoms was measured with a modified Boyarsky questionnaire. Symptom severity/frequency was assessed using a modified Boyarsky questionnaire or an AUA-based questionnaire. Uroflowmetric evaluations were performed at times of peak (2-6 hours post-dose) and/or trough (24 hours post-dose) plasma concentrations of CARDURA.

The results from the three placebo-controlled studies (N=609) showing significant efficacy with 4 mg and 8 mg doxazosin are summarized in Table 3. In all three studies, CARDURA resulted in statistically significant relief of obstructive and irritative symptoms compared to placebo. Statistically significant improvements of 2.3-3.3 mL/sec in maximum flow rate were seen with CARDURA in Studies 1 and 2, compared to 0.1-0.7 mL/sec with placebo.

Table 3 Summary of effectiveness data in placebo controlled trials

	SYMPTOM SCORE[a]			MAXIMUM FLOW RATE (mL/sec)		
	N	MEAN BASELINE	MEAN[b] CHANGE	N	MEAN BASELINE	MEAN[c] CHANGE
STUDY 1 (Titration to maximum dose of 8 mg)[e]						
Placebo	47	15.6	-2.3	41	9.7	+0.7
CARDURA	49	14.5	-4.9**	41	9.8	+2.9**
STUDY 2 (Titration to fixed dose–14 weeks)[d]						
Placebo	37	20.7	-2.5	30	10.6	+0.1
CARDURA 4 mg	38	21.2	-5.0**	32	9.8	+2.3*
CARDURA 8 mg	42	19.9	-4.2*	36	10.5	+3.3**
STUDY 3 (Titration to fixed dose–12 weeks)						
Placebo	47	14.9	-4.7	44	9.9	+2.1
CARDURA 4 mg	46	16.6	-6.1*	46	9.6	+2.6

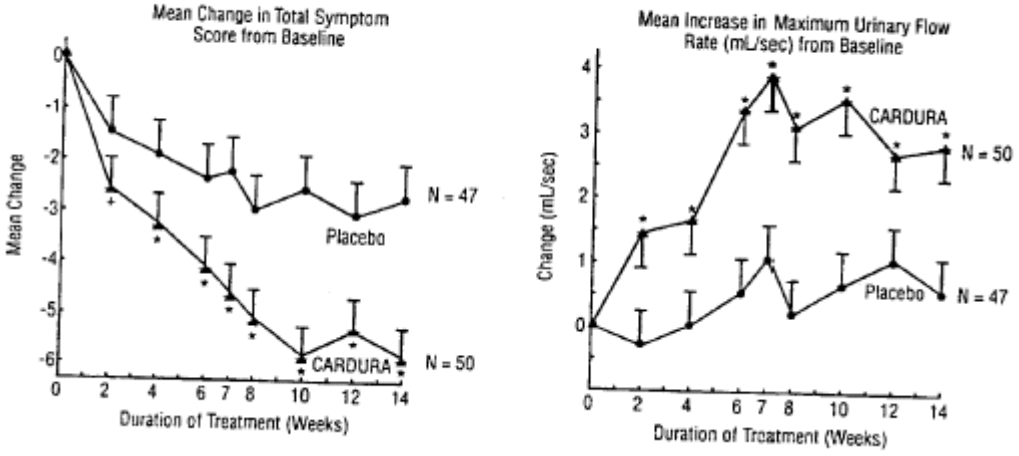


[a] AUA questionnaire (range 0-30) in studies 1 and 3. Modified Boyarsky Questionnaire (range 7-39) in study 2.
[b] Change is to endpoint.
[c] Change is to fixed-dose efficacy phase, 22-26 hours post-dose for studies 1 and 3 and 2-6 hours post-dose for study 2.
[d] Study in hypertensives with BPH
[e] 36 patients received a dose of 8 mg CARDURA®
* (**) $p < 0.05$ (0.01) compared to placebo mean change.

In one fixed dose study (Study 2), CARDURA therapy (4-8 mg, once daily) resulted in a significant and sustained improvement in maximum urinary flow rate of 2.3-3.3 mL/sec (Table 3) compared to placebo (0.1 mL/sec). In this study, the only study in which weekly evaluations were made, significant improvement with CARDURA vs placebo was seen after 1 week. The proportion of patients who responded with a maximum flow rate improvement of ≥3 mL/sec was significantly larger with CARDURA (34-42%) than placebo (13-17%). A significantly greater improvement was also seen in average flow rate with CARDURA (1.5 mL/sec) than with placebo (0.2 mL/sec).

The onset and time course of symptom relief and increased urinary flow from study 1 are illustrated in Figure 1.

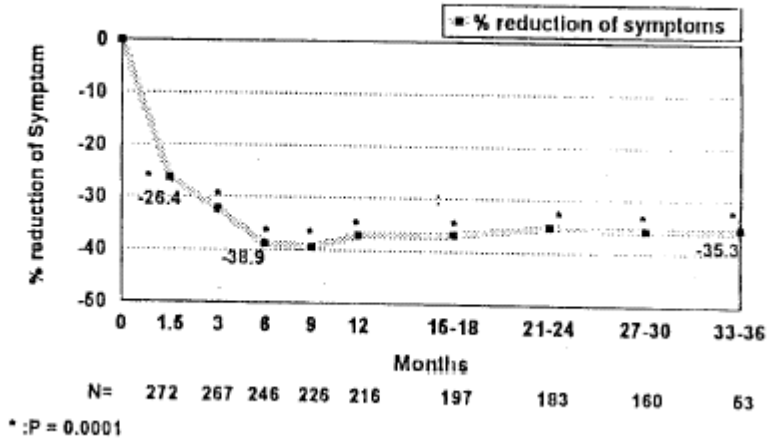
Figure 1



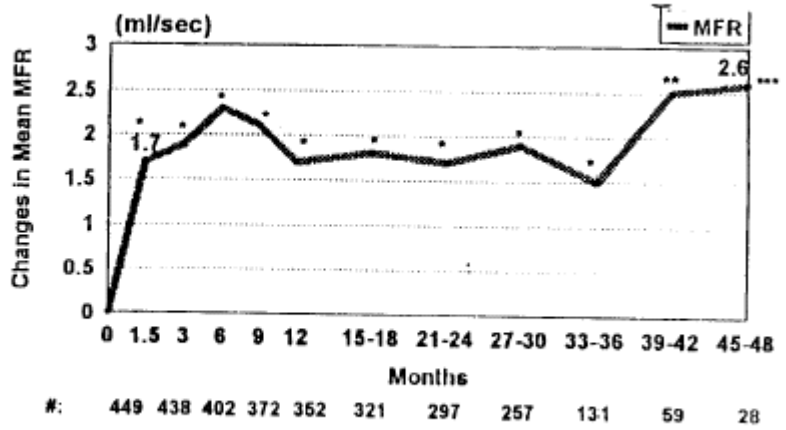
In BPH patients (n=450) treated for ≤4 years in open-label studies, CARDURA therapy resulted in significant improvement above baseline in urinary flow rates and BPH symptoms. The significant effects of CARDURA were maintained over the entire treatment period, as shown in Figure 2.

Figure 2

Mean change in total symptom score from baseline, in normotensive patients.



Mean increase in maximum flow rate (mL/sec) from baseline.



*: P = 0.0001, **: P = 0.001, ***: P= <0.05

Although blockade of α1-adrenoceptors also lowers blood pressure in hypertensive patients with increased peripheral vascular resistance, CARDURA treatment of normotensive men with BPH did not result in a clinically significant blood pressure lowering effect (Table 4). The proportion of normotensive patients with a sitting systolic blood pressure <90 mm Hg and/or diastolic blood pressure <60 mm Hg at any time during treatment with CARDURA 1-8 mg once daily was 6.7% and not statistically significantly different from that with placebo (5%).

Table 4 **Mean Changes in Blood Pressure from Baseline to the Mean of the Final Efficacy Phase in Normotensive (Diastolic BP < 90 mm Hg) in All Double-Blind, Placebo-Controlled U.S. Studies.**

	Group	n	Baseline	Mean Change
Systolic BP	CARDURA	183	128.8	-4.9*
Sitting (mmHg)	Placebo	85	128.4	-1.4
Diastolic BP	CARDURA	183	79.6	-2.4*
Sitting (mmHg)	Placebo	85	79.2	-1.2

* $p \leq 0.05$ compared to placebo

TOXICOLOGY

Acute Toxicology

SPECIES	SEX	ROUTE	LD_{50} (Confidence Limits) mg/base/kg
Mice	M F	p.o. p.o.	> 1,000 > 1,000
Rats	M F	p.o. p.o.	> 1,200 > 1,200

After oral administration of the drug, the animals displayed vulval opening (females), ptosis and prostration, with the signs lasting ≤2 days depending on dose level. The 3 deaths which occurred were between days 2 and 5.

Toxicology					
Subacute and Chronic Toxicity					
SPECIES	**ROUTE**	**DOSE mg/kg/day**	**ANIMAL PER DOSE LEVEL**	**DURATION**	**FINDINGS**
rat	Oral (gavage)	0 5 10 20	10 or 20 M + 10 or 20 F	14 weeks followed by 4 weeks drug withdrawal	Dose-related ptosis, listlessness, subcutaneous vasodilation, vaginal dilatation & descended testes; reductions in plasma potassium & glucose levels in males at the end of the study which disappeared after withdrawal of treatment. Necropsy or histopathological examination revealed no drug related abnormalities.
Rat (Japanese study)	Oral (gavage)	0 20 60 150 300 600	20 M 20 F	1 month	At all dose levels: dose related decrease in spontaneous movement, depression, ptosis, prostration, descent of testes & opening of vagina. At 150, 300 & 600 mg/kg/day dose-related growth inhibition was noted. At 600 mg/kg/day - decrease in food consumption & urinary incontinence was seen. An increase in hemoglobin, hematocrit, erythrocytes & neutrophils & a decrease in lymphocytes were also reported. Mortality occurred in 16/20 males & in 13/20 female rats within one month. Elevation in the SGOT & SGPT levels was seen at 600 & 300 mg/kg/day & at 150 mg/kg/day (males). The elevations of the SGOT & SGPT generally corresponded to the severity of the hepatic lesions. An increase in total bilirubin was noted at 300 & 600 mg/kg/day & at 150 mg/kg/day (males). Histological examination showed drug related changes at dose levels of 150 mg/kg & higher; dose related hepatic cell degeneration & necrosis in males; myocardial necrosis/fibrosis at 300 & 600 mg/kg, & organ changes similar to those seen in wasting conditions due to malnutrition.
dog	oral	0 1 4 16	3M + 3F	13 weeks	At all doses: lowered blood pressure. Necropsy or histopathological examination revealed no drug related abnormalities.

Toxicology					
Subacute and Chronic Toxicity					
SPECIES	**ROUTE**	**DOSE mg/kg/day**	**ANIMAL PER DOSE LEVEL**	**DURATION**	**FINDINGS**
rat	Oral (diet)	0 5 20 80	20M + 20F	6 months	Ptosis, vasodilatation, sedation, opening of the vagina & descended testes; at 80 mg/kg in females there was a reduction in the growth & food intake. Drug-related changes included decreases of plasma glucose & potassium & either an increase (at 5 mg/kg) or decrease (at 80 mg/kg) of total proteins, at months 3 & 6. Also at 5 & 20 mg/kg hemoconcentration & at 80 mg/kg hemodilution were observed. At 80 mg/kg, in males there was an increase in the incidence of myocardial necrosis (16/20 treated vs 7/20 control rats).
rat	oral	0 5 20 50 100	30M + 30F	12 months (interim sacrifice at 3 months & post-treatment sacrifice at 3 months)	At 20, 50 & 100 mg/kg in males there was impairment of body weight gain. At 20 & 50 mg/kg a decrease in urinary volume was noted. Post-mortem showed an increase in heart weights of males at 100 mg/kg & of spleen weight of males at the 50 & 100 mg/kg dose levels & in all female groups. Hepatic single cell degeneration & necrosis was observed at 50 & 100 mg/kg after 3 months & at 100 mg/kg after 12 months.
Rat (age 12 months old at start of study)	oral	0 10 20 40	24 M	12 months	At 40 mg/kg there was an adverse effect on body weight &, in the 2nd half of the study, an increase in mortality. There was also an increase of myocardial fibrosis (22/23 rats at 40 mg/kg vs 15/24 in control rats). At 20 mg/kg & 40 mg/kg testicular atrophy was seen. The non-cardiotoxic dose level was 20 mg/kg.

Toxicology					
Subacute and Chronic Toxicity					
SPECIES	**ROUTE**	**DOSE mg/kg/day**	**ANIMAL PER DOSE LEVEL**	**DURATION**	**FINDINGS**
dog	oral	0 1 5 20	4M + 4F	12 months	Dose related ptosis, sedation, asthenia, vasodilatation, dacryorrhea, salivation & relaxation of the nictitating membrane. Swollen vulvae of most of the treated females were seen. At 20 mg/kg decrease in body weight, lowered blood pressure & raised heart rate were shown to occur. At the end of the study at 5 & 20 mg/kg most dogs showed a persistent pupillary constriction which diminished within days of cessation of treatment. All treated dogs showed a bilateral prominence of the nictitating membrane. At 20 mg/kg, a swelling of the optic disc was seen at 6 months (2/8) & 12 months (5/8). There was also an increase in plasma cholesterol at the end of the study. There was no evidence of drug-related effect on organ weights, macroscopic or microscopic findings.
Special Study (Ophthalmology Study)					
dog	oral	between 25 & 50 mg/kg (according to tolerance)	2M + 2F	28 days	The expected pupillary constriction & relaxation of the nictitating membrane was observed; there were no changes in the optic disc. Ocular reflexes were normal. The effects regressed over 2-3 weeks post-treatment.

Mutagenicity				
STUDY	**TEST ORGANISM**	**DOSE**	**ROUTE**	**MAJOR FINDING**
Ames Test (modified) Quantitative Plate Assay & Metabolic Activation Assay with hepatic microsomes	Salmonella Typhimurium: strains TA 1535, TA 1538, TA 98 & TA 100	2.0 - 0.002 mg/plate for TA 98 & TA 100 1.0 - 0.01 mg/plate for TA 1535 & TA 1538	*in vitro*	No evidence of mutation frequency.
Ellenberger & Mohn: Forward Mutation (galactose locus) Assay	Escherichia coli 341/113	10 to 0.1 mg/mL of culture medium	*in vitro*	No evidence for mutagenicity observed.
Slater et al: Assays utilizing DNA Repair deficient E. coli	Pol A (E. coli p3478) Pol A+ (E. coli W3110)	5 and 10 mg/disc	*in vitro*	No evidence of DNA damaging activity. However, this result is somewhat impaired by the absence of any cytotoxic activity on either the Pol A+ or Pol A strain.
Quantitative Plate Assay of Mouse Urine	Salmonella Typhimurium: TA 1535, TA 98, TA 100 TA 1537 & TA 1538	1.0 to 0.05 mg/kg	*in vitro* i.p.	No mutagenic activity was seen.
In-Vivo Cytogenetics	mouse-bone marrow	1 mg/kg (single dose) 0.5 mg/kg/day (for 5 days)	*in vivo* i.p. s.c.	No indication of chromosome breakage or mutagenicity observed.
In-Vitro cytogenetics	human lymphocytes	10 µg/mL of culture medium	*in vitro*	No evidence of induced-chromosome damage observed.

Mutagenicity studies revealed no drug or metabolite related effects at either chromosomal or subchromosomal levels.

Carcinogenicity

Chronic dietary administration (≤24 months) of doxazosin mesylate at maximally tolerated concentrations (highest dose 40 mg/kg/day) revealed no evidence of carcinogenicity in rats.

Doxazosin was also administered for ≤18 months in the diet of mice, at doses ≤40 mg/kg/day, with no evidence of carcinogenicity observed. This mouse study however, was compromised by the failure to use a maximally tolerated dose of doxazosin. A subsequent 24-month dietary study of doxazosin mesylate, at maximally tolerated concentrations (highest dose 120 mg/kg/day), showed no carcinogenic effect in mice. The highest doses evaluated in the rat and mouse studies are associated with AUCs (a measure of systemic exposure) that are 8x and 4x, respectively, the human AUC at a dose of 16 mg/day.

Reproduction and Teratology					
SPECIES	**ROUTE**	**DOSE mg/kg/day**	**ANIMAL PER GROUP**	**DURATION**	**FINDINGS**
General Fertility					
rat (Charles River CD)	oral	0 5 10 20	10 or 20M + 40F	Males 60-70 days prior to mating. Females 14 days prior to mating and throughout gestation.	Male fertility At 10 & 20 mg/kg an effect on male fertility was observed: reduction in both the copulation frequency (~17%) & in the proportion of these copulations resulting in pregnancy (~23%). There was no evidence of teratogenicity, no effect on parturition, fetal growth or development, nor on postnatal development of reproductive performance of the offspring.
Male Fertility Study (reversibility)					
rat (Charles River CD)	oral	0 20	25M	Males (25 group) dosed for 13, 27 or 62 days. Each allowed to mate with untreated female, at least 2 times, for up to 7 days and nights. Females sacrificed on day 14 post-copulation.	No effect on copulation frequency. For the duration of treatment (males): reduction in the proportion of copulations resulting in pregnancy (i.e., fewer, 70-78%, females became pregnant vs controls, 92-100%). This effect was reversible within 2 weeks of drug withdrawal.
Teratology					
rabbit (New Zealand White)	oral	0 10 20 40	19F	Days 7 to 18 of gestation	No effects were observed.

Reproduction and Teratology					
SPECIES	**ROUTE**	**DOSE mg/kg/day**	**ANIMAL PER GROUP**	**DURATION**	**FINDINGS**
Peri- and Post-Natal Study					
rats (Charles River CD)	oral	0 2.5 10 40	20F	Day 15 of gestation until parturition and throughout lactation.	Dams: Ptosis, vasodilation and vaginal opening. At 10 & 40 mg/kg, increased weight gain during gestation. At 40 mg/kg increased weight gain during lactation. Food intake also increased during gestation. Pups: At 40 mg/kg/day: reduced body weights during lactation. Delayed development as evidenced by appearance of reflexes and incisors and opening of the auditory meatus and the palpebrae. The open-field test also revealed diminished defecation in the high-dose group.

Studies in rats showed reduced fertility in males treated with doxazosin at oral doses of 20 (but not 5 or 10) mg/kg/day, about 4x the AUC exposures obtained with a 12 mg/day human dose. This effect was reversible within 2 weeks of drug withdrawal.

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PART III: CONSUMER INFORMATION

PrCARDURA-1®
PrCARDURA-2®
PrCARDURA-4®
(Doxazosin mesylate tablets)

This leaflet is part III of a three-part "Product Monograph" published when CARDURA was approved for sale in Canada and is designed specifically for Consumers receiving CARDURA as a treatment for benign prostatic hyperplasia (BPH or for Hypertension. This leaflet is a summary and will not tell you everything about CARDURA. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Your doctor has prescribed CARDURA because you either have a medical condition called benign prostatic hyperplasia (BPH) or Hypertension. This leaflet describes CARDURA as a treatment for BPH.

What is BPH?
BPH is an enlargement of the prostate gland. After age 50, most men develop enlarged prostates. The prostate is located below the bladder and surrounds the urethra which is a tube that drains urine from the bladder. The symptoms of BPH, however, can be caused by an increase in the tightness of muscles in the prostate. If the muscles inside the prostate tighten, they can squeeze the urethra and slow the flow of urine. This can lead to symptoms such as:

- weak or interrupted urinary stream
- sensation that you cannot completely empty your bladder
- sensation of delay or hesitation when you start to urinate
- need to urinate often, especially at night, or
- sensation that you must urinate immediately.

Hypertension is the medical term for high blood pressure (HBP). When blood flows through the blood vessels, it pushes against their walls, almost like water pushing against the sides of a hose. Blood pressure is like that "push". When blood pressure is high (like the water pressure in a hose when the nozzle is partially shut), damage can occur to the heart and blood vessels.

Although you may not feel any symptoms for years, hypertension can lead to stroke, heart attack, kidney disease and other serious conditions.

What it does:
CARDURA blocks smooth muscle receptors of the bladder neck and the prostate called alpha1-adrenoceptors. This blockade causes the smooth muscles of the bladder neck and prostate to relax and decreases muscle tone. This can lead to a rapid improvement in urine flow and symptoms within 1 to 2 weeks period. However, not all patients respond in the same way, and since each case of BPH is different, you should keep in mind the following:

- Prior to treatment with CARDURA, you should have a thorough urological evaluation to determine the severity of your condition, and to exclude the need for immediate surgery or the possibility of carcinoma of the prostate.
- Even if taking CARDURA helps your condition, it is not known whether CARDURA reduces the need for surgery.
- CARDURA will not cure your benign prostatic hyperplasia (BPH). CARDURA will make your urine flow better and improve the symptoms of BPH. In some patients, bothersome adverse effects may occur as a result of the CARDURA therapy.

Similarly, CARDURA lowers blood pressure by relaxing the blood vessels so that blood can flow more easily through the body.

When it should not be used:
CARDURA should not be used if you have a known allergy to CARDURA (doxazosin mesylate) or any or the non-medicinal ingredients (see list below).

It is also contraindicated in patients with a known sensitivity to quinazoline (such as prazosin and tetrazosin)

What the medicinal ingredient is:
doxazosin mesylate

What the nonmedicinal ingredients are:
microcrystalline cellulose, lactose, sodium starch glycolate, magnesium stearate,sodium lauryl sulphate and colouring agents (Yellow Lake Blend for the 2 mg and FD&C Yellow #6 Aluminum Lake for the 4 mg).

What dosage forms it comes in:
Tablets: 1, 2, and 4 mg (doxazosin)

WARNINGS AND PRECAUTIONS

BEFORE you use CARDURA talk to your doctor or pharmacist if:

- You take phosphodiesterase (PDE-5)-inhibitor such as sildenafil, tadalafil or vardenafil, due to the risk of developing low blood pressure.
- you take other medications, including those you can buy without prescription and herbal products, or if you drink alcohol;
- you have or have had heart or blood vessel diseases;
- you have heart problems;
- you have or have had kidney and liver disease;
- you have or have had stomach or intestinal problems;
- you suffer from muscular dystrophy or other neuromuscular disorder;
- You are pregnant or plan to get pregnant;
- You are breastfeeding or plan to breastfeed.

CARDURA can cause a sudden drop in blood pressure after the first dose or first few doses. You may feel dizzy, faint, or "light-headed", particularly after you get up from bed or from a chair. This is more likely to occur after you have taken the first few doses, but can occur at any time while you are taking the drug. It can also occur if you stop taking the drug and then restart treatment. If you feel very dizzy, faint or "light-headed" you should contact your doctor. Your doctor will discuss with you how often you need to visit and how often your blood pressure should be checked.

In general, you should be cautious when using a phosphodiesterase (PDE-5) inhibitor such as sildenafil, tadalafil or vardenafil when taking CARDURA due to the risks of developing serious hypotension (low blood pressure).

Your doctor has prescribed CARDURA for symptomatic BPH or High blood pressure and not for prostatic cancer. It is possible for men to have both BPH and prostate cancer at the same time. Doctors usually recommend that men be checked for prostate cancer once a year when they turn 50 (or 40 if a family member has had prostate cancer). These checks should continue while you are taking CARDURA. CARDURA is not a treatment for prostate cancer.

About Prostate Specific Antigen (PSA). Your doctor may have done a blood test called PSA. Your doctor is aware that CARDURA does not affect PSA levels. You may want to ask your doctor more about this if you have a PSA test done.

You should see an effect on your symptoms in 1 to 2 weeks. While taking CARDURA, you must have regular check-ups to evaluate your progress regarding your BPH and to monitor your blood pressure. Follow your doctor's advice about when to have these check-ups.

If you drink alcohol the effects of the alcohol may be increased and prolonged. You should be aware of that and be more cautious with alcohol or you may wish to avoid alcohol altogether.

If you're seeing more than one doctor make sure that each one knows about all the medicines you are taking.

INTERACTIONS WITH THIS MEDICATION

The following list includes drugs that may interact with CARDURA:

- drugs to treat erectile dysfunction (sildenafil, tadalafil, vardenafil)
- drugs to treat hypertension, including diuretics ("water pills") and other classes of medications
- drugs to treat infections (clarithromycin, itraconazole, ketoconazole, telithromycin, voriconazole)
- drugs to treat HIV infections (indinavir, nelfinavir, ritonavir, saquinavir)
- drugs to treat depression (nefazodone)

Talk to your doctor or pharmacist if you drink alcohol.

PROPER USE OF THIS MEDICATION

Follow your doctor's instructions very carefully about how to take CARDURA.

For the treatment of Hypertension:
Usual Adult Dose: Start with 1 mg once daily.
Maximum recommended daily dose is 16 mg once daily.

For the treatment of Benign Prostatic Hyperplasia:
Usual Adult Dose: Start with 1 mg once daily.
Maximum recommended daily dose is 8 mg once daily.

Dose increase should be done gradually with caution due to consideration of possible dizziness/vertigo effect.

Do not share CARDURA with anyone else; it was prescribed only for you.

Notify your doctor about any illness which may develop during your treatment with CARDURA and about any new prescription or non-prescription medication you may take. If you require medical help for other reasons,

inform the attending physician that you are taking CARDURA.

You can take CARDURA either in the morning or at bedtime, with or without food. If you take CARDURA at bedtime but need to get up from bed to go to the bathroom, get up slowly and cautiously until you are sure how the medication affects you. It is important to get up slowly from a chair or bed at any time until you learn how you react to CARDURA. You should not drive or do any hazardous tasks until you are used to the effects of the medication. If you begin to feel dizzy, sit or lie down until you feel better.

If you miss a dose: Talk with your doctor if you don't take it for a few days for some reason; you may then need to restart the medication at a 1 mg dose, increase your dose gradually and again be cautious about possible dizziness.

How long to take CARDURA: You should take CARDURA as long as your doctor thinks it is necessary.

Overdose:

If you take too many tablets by accident, call a poison control center immediately.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medications, some patients may experience side effects with CARDURA.

Side effects you could have while taking CARDURA include drowsiness, fatigue (tiredness), swelling of the feet, shortness of breath, weight gain, headache, and a decrease in your white blood cell count.

You may also experience dry or reduced or other kinds of ejaculation disorders. This condition may be harmless but can lead to temporary infertility during the medication usage.

Most side effects are mild. Discuss any unexpected effects you notice with your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Extremely rarely, CARDURA and similar medications have caused painful erection of the penis, sustained for hours and unrelieved by sexual intercourse or masturbation. This condition is serious, and if untreated it can be followed by permanent inability to have an erection. If you have a prolonged abnormal erection, call your doctor, or go to an emergency room as soon as possible.

If you notice any of the following potentially serious side effects, please stop taking CARDURA and contact your doctor immediately:

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect	Talk with your doctor or pharmacist		Stop taking drug and seek medical assistance immediately
	Only if severe	In all cases	
Dizziness **Faint** **lightheaded**		√ √ √	
Painful erection/ sustained erection for hours			√
Chest pain			√
Rapid, pounding, or irregular heartbeat			√
Allergic Reaction: **Rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing.**			√

This is not a complete list of side effects. If you have any unexpected effects after receiving CARDURA*, contact your doctor or pharmacist.*

HOW TO STORE IT

Store your tablets in a dry place at room temperature (15°C – 30°C). Protect from light and moisture

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 1908C
    Ottawa, Ontario
    K1A 0K9

  Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

Keep out of sight and reach of children.

This document plus the full product monograph, prepared for health professionals can be found at: http://www.pfizer.ca

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