

This product is no longer marketed in New Zealand and this data sheet may not be up to date. A more up-to-date data sheet for a product with the same active ingredient may be available on the Medsafe website.

## DOSAN

### *Doxazosin Mesylate Tablets 2mg and 4mg*



## Presentation

Doxazosin Mesylate Tablets 2mg: white, capsule-shaped tablets debossed DX/2 on one side and plain on the other side.

Doxazosin Mesylate Tablets 4mg: white, capsule-shaped tablets debossed DX/4 on one side and plain on the other side.

## Uses

### Actions

Doxazosin is a potent and selective post-junctional alpha-1-adrenoceptor antagonist. This action results in a decrease in systemic blood pressure. Doxazosin is appropriate for oral administration in a once daily regimen in patients with essential hypertension.

Doxazosin has been shown to be free of adverse metabolic effects and is suitable for use in patients with coexistent diabetes mellitus, gout and insulin resistance.

Doxazosin is suitable for use in patients with co-existent asthma, left ventricular hypertrophy and in elderly patients. Treatment with doxazosin has been shown to result in regression of left ventricular hypertrophy, inhibition of platelet aggregation and enhanced activity of tissue plasminogen activator. Additionally, doxazosin improves insulin sensitivity in patients with impairment.

Doxazosin, in addition to its antihypertensive effect, has in long term studies produced a modest reduction in plasma total cholesterol, LDL-cholesterol and triglyceride concentrations and therefore may be of particular benefit to hypertensive patients with concomitant hyperlipidaemia.

Administration of doxazosin to patients with symptomatic BPH results in a significant improvement in urodynamics and symptoms. The effect in BPH is thought to result from selective blockade of the alpha-adrenoceptors located in the muscular stroma and capsule of the prostate, and in the bladder neck.

### Pharmacokinetics

**Absorption:** Following oral administration in humans (young male adults or the elderly of either sex), doxazosin is well absorbed and approximately two thirds of the dose is bioavailable.

**Biotransformation/Elimination:** Approximately 98% of doxazosin is protein-bound in plasma.

Doxazosin is extensively metabolised in man and in the animal species tested, with the faeces being the predominant route of excretion.

The mean plasma elimination half-life is 22 hours thus making the drug suitable for once daily administration.

After oral administration of doxazosin the plasma concentrations of the metabolites are low. The most active (6' hydroxy) metabolite is present in man at one fortieth of the plasma concentration of the parent compound, which suggests that the antihypertensive activity is in the main due to doxazosin.

There are only limited data in patients with liver impairment and on the effects of drugs known to influence hepatic metabolism (e.g. cimetidine). In a clinical study in 12 subjects with moderate hepatic impairment, single dose administration of doxazosin resulted in an increase in AUC of 43% and a

decrease in apparent oral clearance of 40%. As with any drug wholly metabolised by the liver, Doxazosin should be administered with caution to patients with impaired liver function (see: Warnings and Precautions).

## Indications

**Hypertension:** Doxazosin is indicated for the treatment of hypertension and can be used as the initial agent to control blood pressure in the majority of patients. In patients not adequately controlled on a single antihypertensive agent, doxazosin may be used in combination with another agent such as a thiazide diuretic, a beta-blocker, a calcium antagonist or an angiotensin-converting enzyme inhibitor.

**Benign Prostatic Hyperplasia:** Doxazosin is also indicated for the treatment of the urinary outflow obstruction and symptoms associated with benign prostatic hyperplasia (BPH). Doxazosin may be used in BPH patients who are either hypertensive or normotensive. While the blood pressure changes in normotensive patients with BPH are clinically insignificant, patients with hypertension and BPH have had both conditions effectively treated with doxazosin monotherapy.

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## Dosage and Administration

**Hypertension:** The full dosage range of doxazosin is 1 to 16mg daily. It is recommended that therapy be initiated at 1mg (half a 2mg tablet) given once daily for one or two weeks. The dosage may then be increased to 2mg once daily for an additional one or two weeks. If necessary, the daily dosage should then be increased gradually at similar intervals to 4mg, 8mg, and 16mg as determined by patient response to achieve the desired reduction in blood pressure. The usual dose is 2-4mg once daily.

**Benign Prostatic Hyperplasia:** The initial dosage of doxazosin is 1mg given once daily. Depending on the individual patient's urodynamics and BPH symptomatology, dosage may then be increased to 2mg and thereafter, to 4mg and up to the maximum recommended dose of 8mg. The recommended titration interval is 1-2 weeks. The usual recommended dose is 2-4mg once daily.

**Usage in renally impaired:** Since the pharmacokinetics of doxazosin are unchanged in patients with renal insufficiency, and there is no evidence that doxazosin aggravates existing renal dysfunction, the usual dosages may be used in these patients.

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## Contraindications

Doxazosin is contraindicated in

1. Patients with a known hypersensitivity to quinazolines (e.g. prazosin, terazosin, doxazosin), or any of the excipients
2. Patients with a history of orthostatic hypotension
3. Patients with benign prostatic hyperplasia and concomitant congestion of the upper urinary tract, chronic urinary tract infection or bladder stones
4. During lactation (see: Pregnancy and Lactation)
5. Patients with hypotension (for benign prostatic hyperplasia indication only).

Doxazosin is contraindicated as monotherapy in patients with either overflow bladder or anuria with or without progressive renal insufficiency.

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## Warnings and Precautions

**Postural hypotension/Syncope:**

Initiation of therapy – As with all alpha-blockers, a very small percentage of patients have experienced postural hypotension evidenced by dizziness and weakness, or rarely loss of consciousness (syncope), particularly with the commencement of therapy (see: Dosage and Administration). Therefore, it is prudent medical practice to monitor blood pressure on initiation of therapy to minimise the potential for postural effects.

When instituting therapy with any effective alpha-blocker, the patient should be advised how to avoid symptoms resulting from postural hypotension and what measures to take should they develop. The patient should be cautioned to avoid situations where injury could result, should dizziness or weakness occur during the initiation of doxazosin therapy.

**Use in patients with acute cardiac conditions:**

As with any other vasodilatory anti-hypertensive agent it is prudent medical practice to advise caution when administering doxazosin to patients with the following acute cardiac conditions:

- pulmonary oedema due to aortic or mitral stenosis
- high-output cardiac failure
- right-sided heart failure due to pulmonary embolism or pericardial effusion
- left ventricular heart failure with low filling pressure.

**Use in hepatically impaired patients:**

As with any drug wholly metabolised by the liver, doxazosin should be administered with particular caution to patients with evidence of impaired hepatic function (see: Dosage and Administration). Since there is no clinical experience in patients with severe hepatic impairment, use in these patients is not recommended.

**Use with PDE-5 Inhibitors:**

Concomitant administration of doxazosin with phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil and vardenafil) should be done with caution as both drugs have vasodilating effects and may lead to symptomatic hypotension in some patients. To reduce the risk of orthostatic hypotension it is recommended to initiate the treatment with phosphodiesterase-5-inhibitors only if the patient is haemodynamically stabilized on alpha-blocker therapy. Furthermore, it is recommended to initiate phosphodiesterase-5-inhibitor treatment with the lowest possible dose and to respect a 6-hour time interval from intake of doxazosin.

**Use in patients undergoing cataract surgery:**

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 tamsulosin. Isolated reports have also been received with other alpha-1 blockers and the possibility of a class effect cannot be excluded. As IFIS may lead to increased procedural complications during the cataract operation, current or past use of alpha-1 blockers should be made known to the ophthalmic surgeon in advance of surgery.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

**Effects on ability to drive and use machines**

The ability to drive or use machinery may be impaired, especially when initiating therapy.

**Pregnancy and Lactation**

(Applicable for the hypertension indication; this section is not applicable for the benign prostatic hyperplasia indication)

Use during pregnancy: As there are no adequate and well controlled studies in pregnant women, the safety of doxazosin during pregnancy has not yet been established. Accordingly, doxazosin should be

used only when in the opinion of the physician, potential benefit outweighs potential risk. Although no teratogenic effects were seen in animal testing, reduced foetal survival was observed in animals at extremely high doses. These doses were approximately 300 times the maximum recommended human dose.

Use during lactation: Doxazosin is contraindicated during lactation as animal studies have shown that doxazosin accumulates in milk of lactating rats, and there is no information about the excretion of the drug into the milk of lactating women. The clinical safety of doxazosin during lactation has not been established, consequently doxazosin is contraindicated in nursing mothers.

Alternatively, mothers should stop breast-feeding when treatment with doxazosin is necessary.

## Use in Children

No experience is available on the use of doxazosin in children.

## Adverse Effects

**Hypertension:** In clinical trials involving patients with hypertension, the most common reactions associated with doxazosin therapy were of the postural type (rarely associated with fainting) or non-specific.

**Benign Prostatic Hyperplasia:** Experience in controlled clinical trials in BPH indicates a similar adverse event profile to that seen in hypertension

Frequencies used are as follows: Very common  $\geq 1/10$ , Common  $\geq 1/100$  and  $< 1/10$ , Uncommon  $\geq 1/1,000$  and  $< 1/100$ , Rare  $\geq 1/10,000$  and  $< 1/1,000$ , Very rare  $< 1/10,000$ , Unknown (cannot be estimated from the available data).

MedDRA System Organ Class	Frequency	Undesirable Effects
<i>Infections and infestations</i>	Common	Respiratory tract infection, urinary tract infection
<i>Blood and lymphatic system disorders</i>	Very Rare	Leukopenia, thrombocytopenia
<i>Immune System Disorders</i>	Uncommon	Allergic drug reaction
<i>Metabolism and Nutrition Disorders</i>	Uncommon	Gout, increased appetite, anorexia
<i>Psychiatric Disorders</i>	Uncommon	Agitation, depression, anxiety, insomnia, nervousness
<i>Nervous System Disorders</i>	Common	Somnolence, dizziness, headache
	Uncommon	Cerebrovascular accident, hypoesthesia, syncope, tremor
	Very Rare	Postural dizziness, paresthesia,

<i>Eye Disorders</i>	Very Rare	Blurred vision
	Unknown	Intraoperative floppy iris syndrome (see: Warnings and Precautions )
<i>Ear and Labyrinth Disorders</i>	Common	Vertigo
	Uncommon	Tinnitus
<i>Cardiac Disorders</i>	Common	Palpitation, tachycardia
	Uncommon	Angina pectoris, myocardial infarction,
	Very Rare	Bradycardia, cardiac arrhythmias
<i>Vascular Disorders</i>	Common	Hypotension, postural hypotension
	Very Rare	Hot flushes
<i>Respiratory, Thoracic and Mediastinal Disorders</i>	Common	Bronchitis, cough, dyspnea, rhinitis
	Uncommon	Epistaxis
	Very Rare	Aggravated bronchospasm
<i>Gastrointestinal Disorders</i>	Common	Abdominal pain, dyspepsia, dry mouth, nausea,
	Uncommon	Constipation, flatulence, vomiting, gastroenteritis diarrhoea
<i>Hepatobiliary Disorders</i>	Uncommon	Abnormal liver function tests
	Very Rare	Cholestasis, hepatitis, jaundice
<i>Skin and Subcutaneous Tissue Disorders</i>	Common	Pruritus
	Uncommon	Skin rash
	Very Rare	Urticaria, alopecia, purpura
<i>Musculoskeletal and Connective Tissue Disorders</i>	Common	Back pain, myalgia

	Uncommon	Arthralgia,
	Rare	Muscle cramps, muscle weakness
<i>Renal and Urinary Disorders</i>	Common	Cystitis, urinary incontinence
	Uncommon	Dysuria, micturition frequency, hematuria
	Rare	Polyuria
	Very Rare	Increased diuresis, micturition disorder, nocturia
<i>Reproductive System and Breast Disorders</i>	Uncommon	Impotence
	Very Rare	Gynecomastia, priapism
	Unknown	Retrograde ejaculation
<i>General Disorders and Administration Site Conditions</i>	Common	Asthenia, chest pain, influenza-like symptoms, peripheral oedema,
	Uncommon	Pain, facial oedema
	Very Rare	Fatigue, malaise
<i>Investigations</i>	Uncommon	Weight increase

## Interactions

### Phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil)

Concomitant administration of doxazosin with a PDE-5 inhibitor may lead to symptomatic hypotension in some patients (see: Warnings and Precautions).

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

Conventional doxazosin has been administered without any adverse interaction in clinical experience with thiazide diuretics, frusemide, beta-blocking agents, non-steroidal anti-inflammatory agents, antibiotics, oral hypoglycaemic agents, uricosuric agents, or anticoagulants. However, data from formal drug/drug interaction studies are not present.

Doxazosin potentiates the blood pressure lowering activity of other alpha blockers and other antihypertensives.

In an open-label, randomized, placebo-controlled trial in 22 healthy male volunteers, the administration of a single 1 mg dose of doxazosin on day 1 or a four-day regimen of oral cimetidine (400 mg twice

daily) resulted in a 10% increase in mean AUC of doxazosin, and no statistically significant changes in mean C<sub>max</sub> and mean half-life of doxazosin. The 10% increase in the mean AUC for doxazosin with cimetidine is within intersubject variation (27%) of the mean AUC for doxazosin with placebo.

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## Overdosage

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Should overdosage lead to hypotension, the patient should be immediately placed in a supine, head down position. Other supportive measures may be appropriate in individual cases.

If this measure is inadequate, shock should first be treated with volume expanders. If necessary vasopressor should then be used. Renal function should be monitored and supported as needed.

Since doxazosin is highly protein bound, dialysis is not indicated.

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## Pharmaceutical Precautions

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Store in a dry place below 25°C.

Keep out of reach of children.

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## Medicine Classification

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Prescription Medicine.

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## Package Quantities

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2mg tablets: 30 tablets in calendar pack & 250 tablets in bottle pack.

4mg tablets: 30 tablets in calendar pack & 250 tablets in bottle pack.

Not all pack sizes and presentations may be marketed

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## Further Information

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Excipients: microcrystalline cellulose, lactose, magnesium stearate, sodium starch glycollate, sodium lauryl sulphate.

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## Name and Address

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## Date of Preparation

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5 November 2009