

APO-DOXAZOSIN

1. APO-DOXAZOSIN (1mg, 2mg and 4mg tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

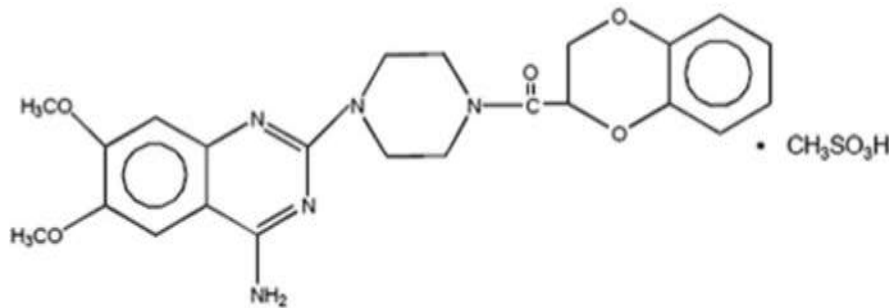
Name and strength of the active substance

Doxazosin mesylate is equivalent to Doxazosin 1mg

Doxazosin mesylate is equivalent to Doxazosin 2mg

Doxazosin mesylate is equivalent to Doxazosin 4mg

Chemical Structure:



The chemical name of doxazosin mesylate is 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(1,4-benzodioxan-2-ylcarbonyl)piperazine methanesulfonate.

The empirical formula is C₂₃H₂₅N₅O₅•CH₄O₃S

The molecular weight is 547.6.

Doxazosin mesylate is freely soluble in dimethylsulfoxide, soluble in dimethylformamide, slightly soluble in methanol, ethanol, and water and very slightly soluble in acetone and methylene chloride.

Excipient with known effect:

Gluten: Apo-Doxazosin is gluten free.

Lactose: Apo-Doxazosin contains Lactose. If you have been told by your doctor that you may have intolerance to some sugars, please contact your doctor before taking this medicinal product.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

APO-DOXAZOSIN 1mg tablets are white, round, biconvex tablets, 4.8mm in diameter, engraved APO on one side and D1 on the other side. Each tablet typically weighs 60mg and contains doxazosin mesylate equivalent to 1mg doxazosin.

APO-DOXAZOSIN 2mg tablets are white, capsule-shaped, biconvex tablets, 4.5mm x 9mm, engraved APO on one side and D2 and a partial bisect on the other side. Each tablet typically weighs 120mg and contains doxazosin mesylate equivalent to 2mg doxazosin.

APO-DOXAZOSIN 4mg tablets are white, diamond-shaped, biconvex tablets, 9mm x 12mm, engraved APO on one side and D4 and scored on the other side. Each tablet typically weighs 240mg and contains doxazosin mesylate equivalent to 4mg doxazosin.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension

APO-DOXAZOSIN is indicated for the treatment of hypertension and can be used as the initial agent to control pressure in the majority of patients. For patients who are not adequately controlled on a single antihypertensive agent, APO-DOXAZOSIN can be used in combination with another agent such as a thiazide diuretic, a beta-blocker, a calcium antagonist or and angiotensin-converting enzyme inhibitor.

Benign Prostatic Hyperplasia (BPH)

APO-DOXAZOSIN is also indicated for the treatment of the urinary outflow obstruction and symptoms associated with benign prostatic hyperplasia.

APO-DOXAZOSIN can be used in 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 APO-DOXAZOSIN monotherapy.

4.2 Dose and method of administration

Dose

Hypertension

The dosage range for APO-DOXAZOSIN is 1 – 16mg daily. It is recommended that the initial dose should be 1mg given once daily for one to two weeks. This starting dose is intended to minimize postural hypotensive effects. The dosage may then be increased to 2mg once daily for an additional two weeks. If necessary the daily dosage can 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 dosage range is 2 – 4mg once daily.

Benign Prostatic Hyperplasia

The initial dosage of APO-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 8mg once daily. The maximum recommended daily dose is 8mg. The recommended titration interval is 1 – 2 weeks. The usual recommended dose is 2 – 4mg once daily. Blood pressure should be evaluated routinely in these patients.

Usage in Renally Impaired:

The pharmacokinetics of APO-DOXAZOSIN is unchanged in patients with renal insufficiency and there is no evidence that APO-DOXAZOSIN aggravates existing renal dysfunction. Therefore the usual dosages may be used in these patients.

Method of administration

APO-DOXAZOSIN may be taken with or without food.

Maximum tolerated Daily Dose

Hypertension: Maximum 16mg daily.

Benign Prostatic Hyperplasia: Maximum 8mg daily

4.3 Contraindications

Known hypersensitivity to doxazosin or quinazolines.

4.4 Special warnings and precautions for use

APO-DOXAZOSIN has been shown to be free of adverse metabolic effects and is suitable for use in patients with diabetes, gout, asthma, elderly patients and in patients with left ventricular dysfunction.

Impaired hepatic function

Since APO-DOXAZOSIN is extensively metabolised and excreted by the liver this drug should be administered with caution to patients with evidence of impaired hepatic function.

Elderly patients

APO-DOXAZOSIN 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 patients treated with this drug.

Phosphodiesterase-5-inhibitors

Concomitant use of phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil) and doxazosin may lead to symptomatic hypotension in some patients. In order to minimise the risk of developing postural hypotension the patient should be stable on the alpha-blocker therapy before initiating use of phosphodiesterase-5-inhibitors.

Use in Children

The use of APO-DOXAZOSIN is not recommended in children as the safety and efficacy have not been established.

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic Interactions

Most (98%) of plasma doxazosin is protein bound. In vitro data in human plasma indicate the doxazosin has no effect on protein binding of digoxin, indomethacin, phenytoin or warfarin.

Doxazosin has been administered without any adverse interactions with thiazide diuretics, frusemide, beta-blocking agents, non-steroidal anti-inflammatory agents, antibiotics, oral hypoglycemic agents, uricosuric agents or anticoagulants.

Concomitant use of phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil) and doxazosin may lead to symptomatic hypotension in some patients.

Pharmacodynamic Interactions

Oral bioavailability is approximately 65% and is unaffected by food.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B3.

There are no adequate and well controlled studies in pregnant women therefore the safety of APO-DOXAZOSIN use during pregnancy have not yet been established. APO-DOXAZOSIN should only be used when in the opinion of the physician the potential benefit outweighs the potential risk. Doxazosin crosses the placental barrier. Although no teratogenic effects were seen in animal testing, reduced foetal survival was observed in animals at extremely high doses (82mg/kg/day).

Breast-feeding

There are no adequate and well controlled studies in nursing women therefore the safety of APO-DOXAZOSIN use during lactation has not yet been established. APO-DOXAZOSIN should only be used when in the opinion of the physician the potential benefit outweighs the potential risk.

Fertility

Nil information on mutagenicity or carcinogenicity. Please refer to section 4.3, 4.4 and 4.8 as appropriate.

4.7 Effects on ability to drive and use machines

Likely to produce minor or moderate adverse effects on the ability to drive or use machinery. Especially when therapy is being initiated, the patient's ability to drive or operate machinery may be impaired. Care should be taken until the effects of the therapy are known.

4.8 Undesirable effects

Controlled clinical hypertension and benign prostatic hyperplasia trials showed similar adverse effects.

Frequency	Adverse Effect
Common ($\geq 1\%$)	Asthenia Dizziness Postural dizziness Fatigue Headache Malaise Oedema Rhinitis Somnolence Vertigo
Rare ($\leq 0.1\%$)	Urinary incontinence

The most common adverse effects associated with doxazosin treatment were of the postural type (rarely associated with syncope). The urinary incontinence may be related to the pharmacological action of doxazosin.

Isolated cases of priapism have been reported to be associated with alpha-1-agonists, including doxazosin.

Cases of abnormal liver function tests have been reported.

Post-Marketing Experience

Cases of blurred vision, cholestatis, epistaxis, hematuria, jaundice, hepatitis, leukopenia, pruritis, purpura, skin rash and thrombocytopenia have been reported.

The following adverse effects have also been reported but in general, these are not distinguishable from symptoms that might have occurred in the absence of exposure to doxazosin: angina pectoris, cardiac arrhythmias, cerebrovascular accidents, chest pain, myocardial infarction, palpitation and tachycardia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professional are asked to report any suspected adverse reactions

<https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

No data is available regarding over-dosage with doxazosin in humans. Should over-dosage 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 a supine, head down position. If this is inadequate shock should first be treated with volume expanders and if necessary vasopressors used. As doxazosin is highly protein bound, dialysis may not be of benefit.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: antihypertensive

ATC code: C02CA04

Mechanism of Action

Doxazosin is in a group of medicines called antihypertensive medicines. It is a quinazoline derivative. It exerts a vasodilator effect via selective and competitive blockade of post-junctional alpha-1-adrenoceptors.

Administration of doxazosin results in a reduction of blood pressure as a result of a reduction in the systemic vascular resistance. This effect is thought to result from the selective blockade of the alpha-1-adrenoceptors located in the vasculature. With once daily dosing, there is a significant reduction in blood pressure, which is present throughout the day and at 24 hours post dose. Maximum reductions in blood pressure usually occur 2-6 hours after dosing and are associated with a small increase in standing heart rate. Doxazosin treatment in hypertensive patients showed similar blood pressures in the supine and standing positions. Unlike non-selective alpha adrenoceptor blocking agents the tolerance of doxazosin treatment for long term therapy has not been established. Elevations of plasma renin activity and tachycardia were seen infrequently in sustained therapy.

Doxazosin produces favourable effects on blood lipids, with significant increase in the HDL/total cholesterol ratio and tends to a favourable reduction in total triglycerides. Doxazosin therefore has advantages over other diuretic and beta adrenoceptor blocking agents, which adversely affect these parameters. Based on established association of hypertension and blood lipids with coronary heart disease, the favourable effects of doxazosin therapy on both blood pressure and lipids indicate a reduction in risk of developing coronary heart disease.

Treatment with doxazosin has been shown to result in regression of left ventricular hypertrophy, inhibition of platelet aggregation and enhanced tissue plasminogen activator capacity

Doxazosin improves insulin sensitivity in patients who have impairment.

Administration of Doxazosin to patients with symptomatic Benign Prostatic Hyperplasia (BPH) results in a significant improvement in urodynamics. The effect of doxazosin in BPH is thought to result from selective blockade of the alpha-1-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 studies in hypertensive patients, treatment with doxazosin was associated with improvement of erectile dysfunction (ED). Also, the patients who received doxazosin reported fewer new cases of ED than those who received other antihypertensive agents.

Doxazosin has been shown to be an effective blocker of the A1 subtype of the alpha-1-adrenoceptor which accounts for over 70% of the subtypes in the prostate. This accounts for the action in BPH patients.

Doxazosin has demonstrated sustained efficacy and safety for up to 4 years in the treatment of BPH.

An in vitro study has demonstrated the antioxidant properties of the 6'- and 7'- hydroxy metabolites of doxazosin at concentrations of 5 micromolar.

5.2 Pharmacokinetic properties

Doxazosin is well absorbed with peak blood levels occurring after about 2 hours. Oral bioavailability is approximately 65% and is unaffected by food.

Doxazosin is extensively metabolised in the liver, mainly by O-demethylation of the quinazoline nucleus or hydroxylation of the benzodioxan moiety.

Excretion is mainly in the faeces (approximately 65%) with less than 5% of the dose excreted as the unchanged drug and with 9% being excreted in the urine mainly as metabolites. Studies indicate that the antihypertensive effect of doxazosin is due almost exclusively to the parent compound. Approximately 98% is bound to plasma proteins. Plasma elimination is biphasic with a terminal elimination half-life of about 22 hours. This provides the basis for once daily dosing. There is accumulation of plasma levels of doxazosin following steady state dosing, consistent with the terminal elimination half-life.

Studies with elderly and patients with renal insufficiency have shown no significant alterations compared to younger patients with normal renal function.

There is only limited data on patients with liver impairment and on the effects of drugs known to influence hepatic metabolism e.g. cimetidine.

As with any drug wholly metabolised by the liver, use of doxazosin in patients with altered liver function should be undertaken with caution.

5.3 Preclinical safety data

Nil information.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Apo-Doxazosin acid 1mg, 2mg and 4mg tablet contains the following excipients:

- Microcrystalline cellulose
- Croscarmellose sodium
- Lactose
- Magnesium Stearate

Apo-Doxazosin 1mg, 2mg and 4mg are gluten free.

Apo-Doxazosin 1mg, 2mg and 4mg contain lactose.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

Apo-Doxazosin 1mg, 2mg and 4mg HDPE bottle has shelf life of 36 months from the date of manufacture

Apo-Doxazosin 1mg PVC/PE/PVdC blister pack has a shelf life of 24 months from the date of manufacture

Apo-Doxazosin 2mg and 4mg PVC/PVdC or PVC/PE/PVdC blister pack has a shelf life of 24 months from the date of manufacture

6.4 Special Precautions

Store at or below 25°C

Protect from heat, light and moisture. Keep the container tightly closed.

6.5 Nature and contents of container

APO-DOXAZOSIN 1mg: PVC/PE/PVdC blisters containing 30 tablets

APO-DOXAZOSIN 1mg tablets: HDPE Bottles of 100 tablets

APO-DOXAZOSIN 2mg: PVC/PVdC or PVC/PE/PVdC blisters containing 30 tablets

APO-DOXAZOSIN 2mg tablets: HDPE Bottles of 100 and 500 tablets



APO-DOXAZOSIN

APO-DOXAZOSIN 4mg PVC/PVdC or PVC/PE/PVdC blisters containing 30 tablets

APO-DOXAZOSIN 4mg tablets: HDPE Bottles of 500 tablets

Not all pack sizes and strengths maybe marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Apotex NZ Ltd.
32 Hillside Road
Glenfield
AUCKLAND 0627

Telephone: (09) 444 2073

Fax: (09) 444 2951

E-mail: NZcustomerservice@apotex.com

9. DATE OF FIRST APPROVAL

02 March 2006

10. DATE OF REVISION OF THE TEXT

14 February 2018



APO-DOXAZOSIN

Summary Table of Changes

Section changed	Summary of new information
Whole data sheet	Reformatted as per Medsafe new datasheet requirement.
6.1	Additional information as per Medsafe requirements Apo-Doxazosin 1mg, 2mg and 4mg are gluten free. Apo-Doxazosin 1mg, 2mg and 4mg contain lactose.