



New Zealand Data Sheet

APO-DOXAZOSIN

Doxazosin 2mg and 4mg Tablets

Doxazosin Mesylate equivalent to Doxazosin 2mg & 4mg Tablets

Presentation

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.

Uses

Actions

Doxazosin is a quinazoline derivative. It exerts its 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.



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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.

Pharmacokinetics

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.

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.



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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.

Dosage and Administration

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.

Contraindications

Known hypersensitivity to doxazosin or quinazolines.

Warnings and Precautions

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.

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.

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.



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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.

Driving/Use of Machinery

Especially when therapy is being initiated, the patients ability to drive or operate machinery may be impaired. Care should be taken until the effects of the therapy are known.

Use in Pregnancy and Lactation

Category B3

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). There are no adequate and well controlled studies in pregnant and nursing women therefore the safety of APO-DOXAZOSIN use during pregnancy or 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.

Use in Children

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

Adverse Effects

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

The most common adverse effects associated with doxazosin treatment were of the postural type (rarely associated with syncope) or were non-specific and included asthenia, dizziness, postural dizziness, fatigue, headache, malaise, nausea, oedema, rhinitis, somnolence and vertigo. Extremely rare cases of urinary incontinence were reported which may be related to the pharmacological action of doxazosin.

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

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

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.



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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.

Overdosage

No data is available regarding overdosage with doxazosin in humans.

Should overdosage 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.

Pharmaceutical Precautions

Store below 25°C.
Protect from heat, light and moisture.

Medicine Classification

Prescription Only Medicine

Package Quantities

Bottle packs containing 100 tablets.
Bottle packs containing 500 tablets.
Blister packs containing 30 tablets.

Further Information

Tablets contain lactose



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