



APO- PRAZOSIN

1. APO-PRAZOSIN (1mg, 2mg and 5mg Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Prazosin Hydrochloride 1mg, 2mg and 5mg tablets

Excipient(s) of known effect

APO-PRAZOSIN tablets contain lactose and gluten free.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

APO-PRAZOSIN 1 mg tablets are white, capsule shaped tablets, bevelled edge, 5.1 mm x 10.2 mm, identified APO above scoreline P1 on one side. Each tablet contains prazosin hydrochloride equivalent to 1mg prazosin and typically weighs 140 mg.

APO-PRAZOSIN 2 mg tablets are white, round, biconvex tablets, 7.9 mm in diameter, identified APO above scoreline P2 on one side. Each tablet contains prazosin hydrochloride equivalent to 2 mg prazosin and typically weighs 160 mg.

APO-PRAZOSIN 5 mg tablets are white, diamond-shaped, biconvex tablets, identified APO over P5 on one side. Each tablet contains prazosin hydrochloride equivalent to 5 mg of prazosin and typically weighs 400 mg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension:

Prazosin is effective in the management of primary hypertension, and also secondary hypertension from various causes. Prazosin may be used as the sole agent, but it is generally more effective if used in combination with a diuretic. Prazosin can be used successfully with other antihypertensive agents. Prazosin may be used safely by hypertensive patients with impaired renal function.

Congestive Cardiac Failure:

Prazosin may be added to the therapeutic regime of patients who have become refractory to conventional therapy with cardiac glycosides and diuretics.

Raynaud's phenomenon and Raynaud's disease

Benign prostatic hyperplasia:

An adjunct in the symptomatic treatment of urinary obstruction caused by BPH in patients waiting for prostatic surgery.

4.2 Dose and method of administration

Treatment should be initiated in low doses to ensure better tolerance of any potential adverse effects. Dosage should be adjusted on the basis of the patient's response. Response is usually seen within 1 to 14 days if it is to occur at a given dose. If a response is seen therapy should be continued at that dose until the degree of response has reached the optimum possible before adding the next increment.

Hypertension:

Initiating therapy: To reduce the risk of first-dose hypotension, APO-PRAZOSIN is usually started at a dose of 0.5 mg given 2 to 3 times daily for 3 to 7 days. The initial dose is best given in the evening 2 to 3 hours before going to bed. If tolerated, the dose may be increased to 1 mg given 2 to 3 times daily for a further 3 to 7 days, and then gradually increased if necessary, until the desired effect is achieved. The maximum daily dose is 20 mg in divided doses.

Maintenance therapy: The usual dose of APO-PRAZOSIN varies between 3 and 20 mg daily given in 2 or 3 divided doses. Smaller doses may be sufficient in patients taking diuretics or other antihypertensive agents.

Patients receiving diuretics or other antihypertensives, with inadequate control: The doses of these agents (especially beta-blockers) should be reduced before APO-PRAZOSIN is added at the low doses used for initiation of therapy (see above). The dosage of clonidine should be gradually reduced to prevent rebound hypertension.

There is evidence that adding prazosin to ACE, β -adrenergic antagonist or calcium antagonist therapy may bring about a substantial reduction in blood pressure. It is therefore recommended that therapy be initiated at 0.5 mg daily and that dose increases occur cautiously.

Congestive Heart Failure:

The recommended starting dose is 0.5 mg to 4 mg daily in divided doses. Dosage should be titrated to the patient's clinical response. Dosage increments may be prescribed every 2 to 3 days under close medical supervision or over 1 to 2 days in severely decompensated patients. Maintenance doses usually range from 4 mg to 20 mg in divided doses.

Raynaud's phenomenon and Raynaud's disease:

The recommended initial dose is 0.5 mg twice daily for 3 to 7 days. Dosage should be adjusted according to the patient's clinical response. The usual maintenance dose is 1 to 2 mg twice daily.

Benign prostatic hyperplasia:

The recommended initial dose is 0.5 mg twice daily for 3 to 7 days. Dosage should be adjusted according to the patient's clinical response. The recommended maintenance dose is 2 mg twice daily. The use of dosages greater than 4mg daily have not been studied and are not therefore recommended.

Children:

APO-PRAZOSIN is not recommended for children under 12 years old.

Use in renal insufficiency:

Prazosin does not appear to cause further impairment of renal function. However, some patients with moderate to severe renal insufficiency respond to smaller than usual doses of APO-PRAZOSIN. The recommended starting dose is 0.5 mg daily. Dosage increases should be small and very gradual.

4.3 Contraindications

Known sensitivity to quinazolines.

4.4 Special Warnings and Precautions for use

Prazosin may occasionally cause dizziness, weakness or syncope with sudden loss of consciousness 30 to 90 minutes after receiving a dose. In most cases this is due to excessive postural hypotension following the initial dose and may be preceded by rapid tachycardia. This can generally be avoided with a low starting dose that is gradually increased. Postural hypotension is usually self-limiting, and in most patients does not recur once a steady maintenance dose is initiated. Patients should be warned to avoid driving and other activities where injury could result in the event of syncope for the first 24 hours and following a dose increase. Patients should also be advised to minimise the possibility of postural hypotension occurring throughout treatment by standing up slowly, limiting alcohol intake and taking care during exercise, hot weather or if standing for long periods.

Hypotension may develop in patients given APO-PRAZOSIN who are also receiving a β -blocker or a diuretic.

Addition of a diuretic or other antihypertensive agent to APO-PRAZOSIN therapy causes an additive hypotensive effect. To minimise this effect APO-PRAZOSIN dose should be reduced to 1 to 2 mg twice daily, the additional antihypertensive agents added cautiously and the APO-PRAZOSIN retitrated based upon the clinical response.

Patients suffering from Raynaud's phenomenon or Raynaud's disease should have their blood pressure monitored during initial administration or during titration due to the decrease in peripheral vascular resistance that occurs.

APO-PRAZOSIN is not recommended in the treatment of congestive heart failure due to mechanical obstruction such as aortic valve stenosis, mitral valve stenosis, pulmonary embolism or restrictive pericardial disease. There is insufficient information on the effect of prazosin on the long-term prognosis when used to treat congestive heart failure following a recent myocardial infarction.

In patients with left ventricular failure who have undergone diuretic or vasodilator therapy, the decrease in left ventricular filling may be associated with a significant fall in cardiac output and systemic blood pressure. A low initial dose with gradual titration under close observation is recommended.

Patients with congestive heart failure should be carefully monitored to ensure sustained clinical improvement as rapid attenuation of improved cardiac performance may occur in some patients.

The clinical efficacy of prazosin may diminish after several months of treatment. There may be evidence of weight gain or peripheral oedema indicating fluid retention.

Adjustment of the diuretic dosage is required to prevent excessive fluid retention and recurrence of symptoms. In those patients who do not demonstrate the signs of fluid retention an increase in the dosage, temporary withdrawal of the product and/or addition of an aldosterone antagonist eg spironolactone to the treatment regime usually restores clinical efficacy.

Prazosin should be used cautiously in patients with ischaemic heart disease as angina may be exacerbated.

There is no information available on the use of prazosin in liver disease however as prazosin is primarily metabolised by the liver, patients with impaired liver function may require a lower dose. In long term studies testicular changes, necrosis and atrophy occurred in rats and dogs occurred at high doses. Studies to date have not indicated similar effects in man at the recommended dosage levels.

Concomitant use of phosphodiesterase-5-inhibitors (e.g. sildenafil, tadalafil, vardenafil) and prazosin 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.

4.5 Interactions with other medicines and other forms of interactions

Pharmacokinetics Interactions

There are few medicine interactions of clinical significance.

Inhibition Interactions

Beta-blockers: Addition of prazosin may result in severe hypotension.

Calcium channel blockers: There have been isolated reports of enhanced hypotensive effects with combined use of prazosin and verapamil or nifedipine.

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

Laboratory tests: Patients treated with prazosin may provide false positive results in screening tests for pheochromocytoma such as presenting urinary vanillylmandelic acid and methoxyhydroxyphenyl glycol - a urinary metabolite of noradrenaline.

Pharmacodynamic Interactions

Nil.

4.6 Fertility, pregnancy and lactation

Use in Pregnancy (Category B2)

Teratogenic effects have not been seen in animal testing, and prazosin has been used during pregnancy by a limited number of hypertensive women unresponsive to beta-blockers alone. However, the safety of prazosin during pregnancy (especially in the first trimester) has not been established and routine use is not recommended unless there is a favourable risk to benefit ratio.

Use in Lactation

Prazosin is excreted in small amounts into the breast milk. Caution is recommended when prazosin is administered to nursing mothers.

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.

4.8 Undesirable effects

The most common reactions associated with prazosin therapy are postural dizziness (11%), nausea (9.5%), drowsiness (8.7%), headache (8.4%), palpitations (6.6%), dry mouth (5.6%), weakness (4.6%) and fatigue/malaise (4.5%). IN most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dosage.

The following reactions have also been reported during use of prazosin at occurrence levels of 1-4%.

Gastrointestinal: Vomiting, diarrhoea, constipation, abdominal discomfort and/or pain, liver function abnormalities, pancreatitis.

Cardiovascular: syncope, oedema, dyspnoea, orthostatic hypotension, tachycardia.

Central Nervous System: nervousness, vertigo, depression, paresthesia, hallucinations.

Dermatologic: Rash, pruritus, alopecia, lichen planus.

Genitourinary: Urinary frequency, incontinence, impotence, priapism.

EENT: Blurred vision, reddened sclera, epistaxis, tinnitus, nasal congestion.

Other: Diaphoresis, fever, positive ANA titre, arthralgia.

Reports exist of pigmentary mottling, serous retinopathy and cataract development but the exact causal relationship has not been established.

Reports indicate that administration of prazosin increases the frequency of cataplectic attacks incases of pre-existing narcolepsy but a causal relationship has not been established in all cases.

Post-marketing Experience

Nil

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 professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

Overdosage of 120mg prazosin by a 72 year old man resulted in profound drowsiness and severely depressed blood pressure. Recovery was uneventful with supportive measures.

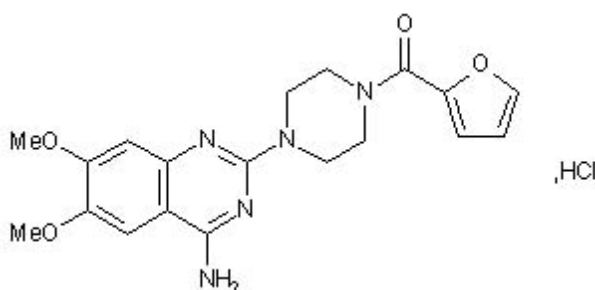
If overdosage leads to hypotension, the patient should be placed in the supine position with the head of the bed lowered if possible; this may facilitate restoration of blood pressure and normalisation of heart rate. If necessary, vasopressors and/or volume expanders may be used to treat shock. Renal function should be monitored and supportive measures instituted if needed. Prazosin is not removed by dialysis due to the high degree of protein binding.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics Properties

Prazosin Hydrochloride has the following chemical structure:



Prazosin decreases total peripheral resistance. Studies suggest that the vasodilator effect is related to blockade of postsynaptic α_1 -adrenoreceptors. The peripheral vasodilator effect is confined mainly to the resistance vessels (arterioles). The hypertensive effect of prazosin is usually not accompanied by reflex tachycardia. The usual therapeutic effect is a fall in blood pressure unaccompanied by a clinically significant change in cardiac output, heart rate, renal blood flow and glomerular filtration rate. There is no measurable negative chronotropic effect. There may be an increase in plasma renin activity in patients with congestive heart failure. Prazosin reduces both standing and supine blood pressure with a greater effect on the diastolic pressure. Tolerance to the antihypertensive effects of prazosin does not appear to develop and abrupt cessation has not resulted in rebound hypertension. Cardiovascular responses to exercise are not altered by prazosin.

Prazosin therapy is not associated with adverse changes in the serum lipid profile. The therapeutic effects in patients with congestive heart failure is due to a reduction in left ventricular filling pressure, reduction in cardiac impedance and an augmentation of

cardiac output. These effects are associated with a balanced vasodilator effect on both resistance vessels (arterioles) and capacitance vessels (veins). The use of prazosin in congestive heart failure does not provoke a reflex tachycardia.

Enucleated hyperplastic glandular tissue and hypertrophied muscular tissue removed from the enlarged prostate gland is rich in α_1 -adrenoreceptor content. Variations in the tone of the smooth muscle in the prostate will produce variations in the closure pressure exerted on the prostatic urethra. This finding has been used as the basis of a pharmacological treatment of benign prostatic hyperplasia (BPH) involving α_1 -adrenoreceptor antagonism. There is evidence of improved urinary flow, reduced volume of residual bladder urine and improvement of symptoms eg frequency of micturition following prazosin therapy in patients with BPH.

Raynaud's phenomenon and Raynaud's disease have been successfully treated with prazosin. The vasodilator action of the medication may increase blood flow to the affected parts reducing the severity of the sign and symptoms and the frequency and duration of the attacks.

5.2 Pharmacokinetics Properties

Prazosin is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring 1 to 3 hours after an oral dose. The bioavailability is variable and a range of 43-85% has been reported. Prazosin is highly bound to plasma protein (97%). The plasma half-life is 2-3 hours. In patients with congestive heart failure, most of whom had hepatic congestion, the peak plasma concentrations are reached in 2.5 hours and the plasma half-life is increased to 7 hours. The bioavailability of oral prazosin is also increased 2 to 3 times in patients with congestive heart failure but the time to reach peak is unchanged. The duration of action of prazosin is longer than predicted from the relatively short plasma half-life.

Prazosin is extensively metabolised in the liver primarily demethylation and conjugation and is excreted (primarily as glucuronide conjugates) mainly via bile and faeces. Between 5 and 11% unchanged prazosin may be excreted in the faeces with less than 10% being excreted in the urine. Four of the metabolites are reported to have antihypertensive activity.

5.3 Preclinical safety data

Nil

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

APO-PRAZOSIN tablets contain the following excipients:

- Lactose
- Polysorbate 80
- Microcrystalline cellulose
- Croscarmellose sodium
- Magnesium stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf-Life

Shelf life 24 months from date of manufacture.

6.4 Special precautions for storage

Store below 30°C.

Protect from heat, light and moisture.

6.5 Nature and contents of container

APO-PRAZOSIN 1mg, 2mg and 5mg:

Blister packs of 100, 500 and 1000 tablets.

Bottle of 100, 500 and 1000 tablets

Not all pack types and strengths may be 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 Medicine

8. SPONSOR

Apotex NZ Ltd

32 Hillside Road

Glenfield

Private Bag 102-995

North Shore Mail Centre

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Telephone: (09) 444 2073

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9. DATE OF FIRST APPROVAL

17 May 2001

10. DATE OF REVISION OF THE TEXT

31 January 2018

Summary Table of Changes

Section changed	Summary of new information
Entire datasheet	Reformatted to SMPc layout