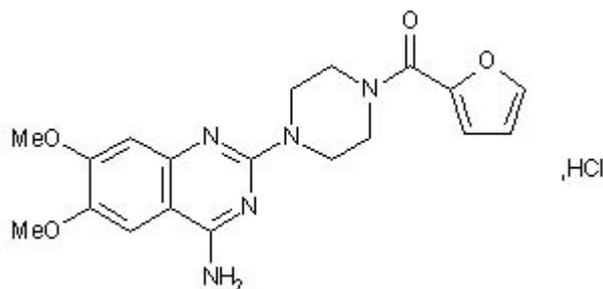


APO-PRAZOSIN TABLET**NAME OF THE MEDICINE**

Prazosin hydrochloride.

Chemical Name: 1-(4-amino-6,7-dimethoxy-2-quinazoliny)-4-(2-furoyl)piperazine hydrochloride

Structural Formula:



Molecular Formula: C₁₉H₂₁N₅O₄. HCl.

Molecular Weight: 419.87

CAS Registry Number: 19237-84-4

DESCRIPTION

Prazosin hydrochloride, a quinazoline derivative, is the first antihypertensive of its chemical class.

Prazosin hydrochloride is a white or almost white powder, which is very slightly soluble in water.

Each tablet contains prazosin hydrochloride equivalent to 1 mg, 2 mg or 5 mg prazosin base. In addition, each tablet contains the following inactive ingredients: lactose, polysorbate 80, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

PHARMACOLOGY**Pharmacological Actions**

Prazosin causes a decrease in total peripheral resistance. Animal studies suggest that the vasodilator effect of prazosin is related to blockade of post synaptic alpha adrenoreceptors. The results of dog forelimb experiments demonstrate that the peripheral vasodilator effect is confined mainly to the level of the resistance vessels (arterioles). Unlike conventional alpha blockers the antihypertensive action of prazosin is usually not accompanied by reflex tachycardia.

Haemodynamic studies have been carried out in hypertensive patients following acute single dose administration and during the course of long-term maintenance therapy. The results confirm that 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.

Prazosin may increase plasma renin activity in patients with congestive heart failure.

Clinically, the antihypertensive effect is believed to be a direct result of peripheral vasodilation. In man, blood pressure is lowered in both the supine and standing positions. This effect is more pronounced on the diastolic blood pressure. Tolerance does not appear to develop in long term clinical use in the treatment of hypertension.

Rebound elevation of blood pressure does not occur following abrupt cessation of prazosin therapy.

A variety of epidemiological, biochemical and experimental studies have suggested that an elevated level of low density lipoprotein (LDL) cholesterol may be associated with an increased risk of coronary heart disease. There is also evidence that reduced levels of high density lipoprotein (HDL) cholesterol may be associated with an increased risk of coronary heart disease. Clinical studies have shown that prazosin therapy is not associated with adverse changes in the serum lipid profile.

Haemodynamic studies carried out in patients with congestive heart failure following acute oral dosing and during the course of longer term maintenance therapy both at rest and during exercise indicate that the therapeutic effect in these patients is due to a reduction in left ventricular filling pressure, reduction in cardiac impedance, and an augmentation of cardiac output. These effects, as indicated in forearm plethysmographic studies in humans, 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 alpha adrenoceptor 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 provided the basis of a pharmacological treatment of benign prostatic hyperplasia (BPH) involving alpha adrenoceptor antagonism.

There is evidence of statistically significant improvement in urinary flow following prazosin therapy in patients with BPH. There is also evidence for a reduction in the volume of residual bladder urine and for improvement in symptoms of BPH such as frequency of micturition.

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

Pharmacokinetics

Absorption & Distribution

Following oral administration to normal volunteers and hypertensive patients, plasma concentrations reach a peak in one to two hours, with a plasma half life of two to three hours. Pharmacokinetic data in a limited number of patients with congestive cardiac failure, most of whom showed evidence of hepatic congestion, indicate that peak plasma concentrations are reached in 2.5 hours and plasma half life is approximately seven hours. The bioavailability of oral prazosin was also increased 2 - 3 times in patients with congestive cardiac failure but the time to reach the peak was not affected in patients compared to normal volunteers. The mechanism of increase in plasma half life and bioavailability of prazosin in congestive heart failure has not been satisfactorily explained.

Metabolism

The drug is highly bound to plasma protein. Animal studies indicate that prazosin is extensively metabolised primarily by demethylation and conjugation. Less extensive human studies suggest similar metabolism in man.

Excretion

Prazosin is excreted mainly via bile and faeces.

INDICATIONS

In Patients with Hypertension

Prazosin is indicated in the treatment of hypertension of varied aetiology and all grades of severity. It can be used as the initial and sole agent or it may be employed in a general treatment programme in conjunction with other antihypertensive agents.

Renal blood flow and glomerular filtration rate are not impaired by long term oral administration. Prazosin can be used with safety in hypertensive patients with impaired renal function.

In Patients with Congestive Heart Failure

Prazosin is indicated in the treatment of severe refractory congestive heart failure. Prazosin may be added to the therapeutic regimen in those patients who have become refractory to conventional therapy with cardiac glycosides and diuretics.

In Patients with Raynaud's Phenomenon & Raynaud's Disease

Prazosin is indicated in the treatment of Raynaud's phenomenon and Raynaud's disease.

Benign Prostatic Hyperplasia

Prazosin is indicated as an adjunct in the symptomatic treatment of urinary obstruction caused by benign prostatic hyperplasia in patients awaiting prostatic surgery.

CONTRAINDICATIONS

Prazosin is contraindicated in patients with a known sensitivity to quinazolines, prazosin or any of the inactive excipients.

PRECAUTIONS

General (All Patients)

Prazosin may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120-160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug: occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of prazosin. The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimised by limiting the initial dose of the drug to 0.5 mg, by subsequently increasing the dosage slowly and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see **DOSAGE AND ADMINISTRATION**). Hypotension may develop in patients given prazosin who are also receiving a beta blocker or a diuretic.

Addition of a diuretic or other antihypertensive agent to prazosin therapy has been shown to cause an additive hypotensive effect. This effect can be minimised by reducing the dose of prazosin to 1 mg or 2 mg twice daily, by introducing additional antihypertensive drugs cautiously and then re-titrating prazosin based on clinical response.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started at a dose of 0.5 mg of prazosin. The 2 and 5 mg tablets are not indicated for initial therapy. Both lying and standing blood pressure should be measured.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and light-headedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of prazosin therapy.

Priapism

Prolonged erections and priapism have been reported with alpha-1 blockers, including prazosin, in post-marketing experience. In the event of an erection that persists longer than 4 hours, the patient should seek immediate medical assistance. If priapism is not treated immediately, penile tissue damage and permanent loss of potency could result.

Patients with Raynaud's Phenomenon or Raynaud's Disease

Because prazosin decreases peripheral vascular resistance, careful monitoring of blood pressure during initial administration and titration of prazosin is suggested (see **PRECAUTIONS** – General [All Patients]).

Patients with Congestive Heart Failure

In patients with acute or chronic left ventricular failure who have undergone vigorous diuretic and vasodilator treatment, the resultant decrease in left ventricular filling may be associated with a significant fall in cardiac output and systemic blood pressure when prazosin is administered. In such patients, a low initial dose of prazosin and gradual titration with close observation is recommended. (see **DOSAGE AND ADMINISTRATION**).

The haemodynamic response to prazosin in patients with congestive heart failure should be carefully monitored to ensure sustained clinical improvement as rapid attenuation of improved cardiac performance might occur in some patients.

In occasional patients with congestive heart failure, the clinical efficacy of prazosin has been reported to diminish due to complete or partial tolerance to haemodynamic effects of prazosin. Evidence of efficacy for periods exceeding 6 months is lacking. In these patients there is usually evidence of weight gain or peripheral oedema indicating fluid retention. Since spontaneous deterioration may occur in such severely ill patients a causal relationship to prazosin therapy has not been established. Thus, as with all patients with congestive heart failure, careful adjustment of diuretic dosage according to the patient's clinical condition is required to prevent excessive fluid retention and consequent recurrence of symptoms. In those patients without evidence of fluid retention, when clinical improvement has diminished, an increase in the dosage of prazosin, temporary withdrawal of the drug and/or addition of an aldosterone antagonist (e.g. spironolactone) to the treatment regimen will usually restore clinical efficacy.

Use in Patients with Congestive Heart Failure

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 and restrictive pericardial disease. Adequate data are not yet available to establish efficacy in patients with congestive heart failure due to recent myocardial infarction.

Patients with Benign Prostatic Hyperplasia

Prazosin decreases peripheral vascular resistance and since many patients with this disorder are elderly, standing and lying blood pressure should be carefully monitored during initial administration and during adjustment of the dose of prazosin (refer to **PRECAUTIONS** – General [All Patients]). Close observation is especially recommended for patients taking medications that are known to lower blood pressure.

Patients with Angina

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

Patients with Impaired Liver Function

There is no data available on the use of prazosin in liver disease. However, as the drug is primarily metabolised by the liver and excreted in the bile and faeces, patients with impaired hepatic function may require a lower dose.

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.

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

Effects on Fertility

In long-term studies for one year or more, testicular changes, necrosis and atrophy have occurred at 25 mg/kg/day in rats and dogs. This is 60 times the usual maximum recommended dose of 20 mg per day in humans. Testicular weight was marginally depressed but no morphological testicular changes were seen in dogs at a daily dose of 10 mg/kg which is 24 times the usual maximum recommended dose of 20 mg per day in humans.

In view of the testicular changes observed in animals, 105 patients on long term therapy with prazosin were monitored for 17-ketosteroid excretion. No changes indicating a drug effect were observed. In addition no changes in sperm morphology suggestive of drug effect were seen in 27 males given prazosin alone for up to 51 months.

Use in Pregnancy (Category B2)

When both male and female rats were treated with prazosin at a dose of 75 mg/kg/day and then mated, there was a significant impairment of fertility. There is no information available as to whether prazosin crosses the placenta. No teratogenic effects were seen in animal testing. However the safety of prazosin used during pregnancy has not been established. Accordingly, it should be used only when, in the opinion of the physician, expected benefit to the pregnant patient outweighs any potential risk.

Australian Categorisation Definition of Category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of foetal damage.

Use in Lactation

Prazosin has been shown to appear in breast milk. Prazosin should be administered to a nursing mother only when, in the opinion of the physician, the expected benefit outweighs any potential risk. Consideration should be given to not breast feeding the baby.

Paediatric Use

Prazosin is not recommended for the treatment of children under the age of twelve years since safe conditions for its use have not been established.

Carcinogenicity, Genotoxicity, Impairment of Fertility

In long-term studies for one year or more, testicular changes, necrosis and atrophy have occurred at 25 mg/kg/day in rats and dogs. This is 60 times the usual maximum recommended dose of 20 mg/day in humans. Testicular weight was marginally depressed but no morphological testicular changes were seen in dogs at a daily dose of 10 mg/kg which is 24 times the usual maximum recommended dose of 20 mg/day in humans.

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Effect on Ability to Drive and Use Machines

Patients should be cautioned that their ability to drive or operate machinery may be impaired, especially when initiating prazosin therapy.

Effect on Laboratory tests

False positive results may occur in screening tests for phaeochromocytoma (urinary vanillylmandelic acid, VMA, and methoxy hydroxyphenyl glycol, MHPG, a urinary metabolite of noradrenaline) in patients who are being treated with prazosin.

INTERACTIONS WITH OTHER MEDICINES

Patients Taking PDE-5 Inhibitors

As with other alpha-1 blockers, concomitant administration of prazosin hydrochloride with a PDE-5 inhibitor should be used with caution as it may lead to symptomatic hypotension in a few susceptible individuals. No studies have been conducted with prazosin hydrochloride.

ADVERSE EFFECTS

During clinical trials and subsequent marketing experience with prazosin the following reactions have been observed. The percentages are derived from reports of clinical trials but it should be noted that the dosages used in some of these trials were higher than the current recommendations.

More Common Reactions

Cardiovascular

Postural hypotension (14%), palpitations (5%), oedema (4%).

Gastrointestinal

Nausea (5%), dry mouth (4%).

General

Lack of energy (7%), weakness, asthenia (7%).

Nervous System

Headaches (8%), drowsiness (8%), dizziness (faintness).

Ocular

Blurred vision (4%).

Respiratory

Nasal congestion (4%).

Less Common Reactions

Body as a Whole

Allergic reaction, malaise, pain.

Cardiovascular

Tachycardia (1%), syncope (1%) bradycardia, angina pectoris, hypotension, vasculitis.

Endocrine

Gynaecomastia.

Dermatological

Rash and pruritus (1%); alopecia; lichen planus; urticaria.

Gastrointestinal

Vomiting (3%), constipation (3%), diarrhoea (2%); liver function abnormalities; pancreatitis, abdominal discomfort and/or pain.

Genitourinary

Urinary incontinence, priapism, impotence, urinary frequency.

Musculoskeletal

Central Nervous System

Nervousness (2%), depression (2%), paraesthesiae, hallucinations, reddened sclera, tinnitus, worsening of pre-existing narcolepsy, vertigo, insomnia.

Respiratory

Dyspnoea (2%), epistaxis.

Ocular

During cataract surgery, a variant of small pupil syndrome known as Intraoperative Floppy Iris Syndrome (IFIS) has been reported in association with tamsulosin and alpha-1 blocker therapy (see **PRECAUTIONS**).

General

Fever, diaphoresis, positive ANA titre, arthralgia, flushing, eye pain.

Serious or Life-Threatening Reactions

Postural hypotension, especially in elderly patients with cerebrovascular disease, may be dangerous. Exacerbation of pre existing angina, new onset angina and myocardial infarction have been associated with prazosin, although a causal relationship has not been established.

DOSAGE AND ADMINISTRATION

General Comment

There is evidence that patient toleration is best when therapy is initiated with a low starting dose. The dose is to be adjusted on the basis of the patient's individual blood pressure response.

Response is usually seen early (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.

Specific Recommendations

In Patients with Hypertension

Suggested initial dose range: 0.5 mg twice daily (b.d.) increasing to 1.0 mg b.d. or three times daily (t.i.d.)

Usual maintenance dose: 3.0 mg to 20 mg daily in divided doses.

The following are given as guides to administration.

Patients Receiving No Antihypertensive Therapy:

It is recommended that therapy be initiated at 0.5 mg b.d. for three days. Unless the patient is unusually sensitive, this dose should be increased to 1.0 mg b.d. or t.i.d. for a further three days and then to 2.0 mg two or three times daily. Thereafter, as determined by the patient's response to the blood pressure lowering effect, the daily dose should be increased gradually to 20 mg. The optimal response may take up to six weeks. After initial titration some patients can be maintained on a twice daily dosage regimen.

A diuretic may be added to enhance the efficacy. It is recommended that this addition be considered when the prazosin dose is at 2 mg b.d. or t.i.d.

Patients Receiving Diuretic Therapy with Inadequate Control of Blood Pressure:

The diuretic should be reduced to a maintenance dose level for the particular agent and prazosin initiated at 0.5 mg twice or three times daily.

After the initial period of observation, the dose of prazosin should be gradually increased as determined by the patient's response.

Patients Receiving Other Anti-Hypertensive Agents but with Inadequate Control:

Because some additive effect is anticipated, the other agent (e.g. beta adrenergic blocking agent, alpha methyl dopa, reserpine, clonidine* etc.) should be reduced and prazosin initiated at 0.5 mg b.d. Subsequent dosage increase should be made depending upon the patient's response.

Though experience is limited, there is evidence that adding prazosin to beta adrenergic blocking agents, calcium channel blockers, or ACE inhibitors may bring about a substantial reduction in blood pressure. Thus, the low initial dose regimen is strongly recommended.

*Termination of oral therapy should be gradual (e.g. over more than 7 days). Sudden cessation of antihypertensive therapy is known to be associated with rebound hypertension which in some cases may be severe. This may occur with clonidine particularly in patients receiving more than 900 micrograms per day.

In Patients with Congestive Heart Failure

Suggested initial daily dose range: 0.5 mg increasing to 4.0 mg in divided doses.

Usual daily maintenance dose: 4.0 mg to 20 mg in divided doses.

In recumbent patients the recommended starting dose is 0.5 mg three or four times a day. Dosage should be titrated according to the patient's clinical response, based on careful monitoring of cardiopulmonary signs and symptoms or haemodynamic studies when indicated. Dosage titration steps may be performed as often as every two to three days in patients under close medical supervision. In severely ill, decompensated patients, rapid dose titration over one or two days may be indicated and is best done when haemodynamic monitoring is available. In clinical studies to date the mean optimal daily dose during the initial treatment period was 11.5 mg, with therapeutic dosages ranging from 4 mg to 20 mg daily in divided doses. Re-titration may be required in some patients to maintain optimal clinical improvement.

Raynaud's Phenomenon And Raynaud's Disease

Suggested starting dosage: 0.5 mg b.d.

Usual daily maintenance dosage: 1 mg or 2 mg b.d.

The recommended starting dosage is 0.5 mg b.d. given for a period of three to seven days. Dosage should be adjusted according to the patient's clinical response.

Benign Prostatic Hyperplasia

The recommended starting dose is 0.5 mg twice daily, given for a period of 3 to 7 days and then adjusted according to clinical response. The recommended maintenance dosage is 2 mg twice daily. The use of doses over 4 mg daily has not been studied, and cannot be recommended at present. Doses up to 4 mg daily have produced amelioration of symptoms for periods of up to 4 weeks but currently longer term data are not available. Postural hypotension may occur (refer to **PRECAUTIONS** – General [All Patients]).

Dosage Adjustment for Renal Impairment

For patients with moderate to severe grades of renal impairment, evidence to date shows that prazosin does not further compromise renal function when used in patients with renal impairment. Because some patients in this category have responded to small doses of prazosin, it is recommended that therapy be initiated at 0.5 mg daily and that dose increases be instituted cautiously.

OVERDOSAGE

Symptoms

Accidental ingestion of at least 50 mg of prazosin in a two year old child resulted in profound drowsiness and depressed reflexes. No decrease in blood pressure was noted. Recovery was uneventful.

Treatment

Should overdose lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalisation 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 then be used. Renal function should be monitored and supported as needed. Laboratory data indicate prazosin is not dialysable because it is protein bound.

Contact the Poison Information Centre on 13 11 26 (Australia) for advice on the management of overdose.

PRESENTATION AND STORAGE CONDITIONS

APO-Prazosin tablets are intended for oral administration.

Each tablet contains prazosin hydrochloride equivalent to 1 mg, 2 mg or 5 mg prazosin base.

APO-Prazosin 1 mg tablets

Capsule-shaped, white, flat-faced, bevelled-edged tablets scored and engraved "APO P1" on one side, other side plain.

Cartons containing 100 tablets in clear PVC/PVDC/Aluminium blister packs.
AUST R 73858.

APO-Prazosin 2 mg tablets

Round, white, biconvex tablets, scored and engraved "APO" over "P2" on one side, other side plain.
Cartons containing 100 tablets in clear PVC/PVDC/Aluminium blister packs.

AUST R 73862.

APO-Prazosin 5 mg tablets

Diamond-shaped, white, biconvex tablets, scored and engraved "APO" over "P5" on one side, other side plain.

Cartons containing 100 tablets in clear PVC/PVDC/Aluminium blister packs.

AUST R 73866.

Storage

Store below 25°C. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Apotex Pty Ltd
16 Giffnock Ave
Macquarie Park NSW 2113
Australia

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POISON SCHEDULE OF THE MEDICINE:

S4: Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG): 19 June 2000

DATE OF MOST RECENT AMENDMENT: 21 December 2015