

AUSTRALIAN PRODUCT INFORMATION – MINIPRESS® (PRAZOSIN HYDROCHLORIDE)

1. NAME OF THE MEDICINE

Prazosin hydrochloride

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Prazosin hydrochloride equivalent to 1 mg, 2 mg and 5 mg prazosin base.

3. PHARMACEUTICAL FORM

Tablet.

MINIPRESS 1 mg tablets: orange, capsule-shaped with MNP 1 on one side and scored on the other.

MINIPRESS 2 mg tablets: white, round, scored, marked with MNP 2 on the scored side.

MINIPRESS 5 mg tablets: white, diamond-shaped, scored on both sides, marked with MNP 5 on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In Patients with Hypertension

MINIPRESS (prazosin hydrochloride) 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 treatment programme in conjunction with other antihypertensive agents.

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

In Patients with Congestive Heart Failure

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

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

MINIPRESS is indicated in the treatment of Raynaud's phenomenon and Raynaud's Disease.

Benign Prostatic Hyperplasia

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

4.2 Dose and method of administration

General Comments

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 the dose until the degree of response has reached the optimum possible before adding the next increment.

Specific Recommendations

Hypertension

Suggested initial dose range: 0.5 mg twice daily increasing to 1.0 mg twice daily or three times daily.

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 twice daily for 3 days. Unless the patient is unusually sensitive, this dose should be increased to 1.0 mg twice daily or three times daily for a further 3 days and thence to 2.0 mg twice daily 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 6 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 twice daily or three times daily.

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 daily 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 Antihypertensive Agents but with Inadequate Control

Because some additive effect is anticipated, the dosage level of other agents (e.g. beta-adrenergic blocking agent, alpha methyl dopa, reserpine, clonidine* etc.) should be reduced and prazosin initiated at 0.5 mg twice daily. 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 angiotensin-converting enzyme (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 µg/day.

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 daily. 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 2 to 3 days in patients under close medical supervision. In severely ill, decompensated patients, rapid dose titration over 1 or 2 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. Retitration may be required in some patients to maintain optimal clinical improvement.

Raynaud's Phenomenon and Raynaud's Disease

Suggested starting dosage: 0.5 mg twice daily.

Usual daily maintenance dosage: 1 mg or 2 mg twice daily.

The recommended starting dosage is 0.5 mg twice daily given for a period of 3 to 7 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 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 (see Section 4.4 Special warnings and precautions for use - General (All Patients)).

Dosage adjustment in 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 with caution.

4.3 Contraindications

MINIPRESS is contraindicated in patients with a known sensitivity to quinazolines, prazosin or any other component of the tablets.

4.4 Special warnings and precautions for use

General (All Patients)

Syncope

MINIPRESS 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 MINIPRESS. 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 Section 4.2 Dose and method of administration). Hypotension may develop in patients given MINIPRESS who are also receiving a beta-blocker or a diuretic.

Addition of a diuretic or other antihypertensive agent to MINIPRESS therapy has been shown to cause an additive hypotensive effect. This effect can be minimised by reducing the dose of MINIPRESS to 1 mg or 2 mg twice daily, by introducing additional antihypertensive drugs cautiously and then retitrating MINIPRESS 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 MINIPRESS. The 2 mg 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 lightheadedness. 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 MINIPRESS 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 MINIPRESS is suggested (see Section 4.4 Special warnings and precautions for use - 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 MINIPRESS is administered. In such patients, a low initial dose of MINIPRESS and gradual titration with close observation is recommended (see Section 4.2 Dose and method of administration).

The haemodynamic response to MINIPRESS 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, the clinical efficacy of MINIPRESS 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 MINIPRESS therapy has not been established. Thus, as with all patients with congestive cardiac 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 MINIPRESS, 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

MINIPRESS 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 is not yet available to establish efficacy in patients with congestive cardiac failure due to a recent myocardial infarction.

Patients with Benign Prostatic Hyperplasia

MINIPRESS 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 MINIPRESS (see Section 4.4 Special warnings and precautions for use - General (All Patients)). Close observation is especially recommended for patients taking medications that are known to lower blood pressure.

Patients with Angina

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

Use in hepatic impairment

There are no data available on the use of MINIPRESS 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.

Use in renal impairment

See Section 4.2 Dose and method of administration - Dosage Adjustment in Renal Impairment.

Use in the elderly

See Section 4.4 Special warnings and precautions for use - Patients with Benign Prostatic Hyperplasia, and section 4.8 Adverse effects - Serious or Life-threatening Reactions.

Paediatric use

MINIPRESS is not recommended for the treatment of children under the age of 12 years, since safe conditions for its use have not been established.

Effects on laboratory tests

False-positive results may occur in screening tests for phaeochromocytoma (urinary vanillylmandelic acid [VMA] and methoxyhydroxyphenylglycol [MHPG], urinary metabolites of noradrenaline) in patients who are being treated with MINIPRESS.

4.5 Interactions with other medicines and other forms of interactions

Patients taking Phosphodiesterase Type-5 Inhibitors

As with other alpha-1 blockers, concomitant administration of prazosin hydrochloride with a phosphodiesterase type-5 (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.

4.6 Fertility, pregnancy and lactation

Effects on fertility

In long-term studies for 1 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 MINIPRESS were monitored for 17-ketosteroid excretion and 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 MINIPRESS alone for up to 51 months.

Use in pregnancy – 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 MINIPRESS used during pregnancy has not been established. Accordingly, it should be used only when, in the opinion of the physician, potential benefit to the pregnant patient outweighs potential risk.

Use in lactation

Prazosin has been shown to appear in breast milk. MINIPRESS 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.

4.7 Effects 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.

4.8 Adverse effects (undesirable effects)

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, hypotension, vasculitis, angina pectoris.
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.
Nervous System	Nervousness (2%), depression (2%), paraesthesiae, hallucinations, reddened sclera, tinnitus, worsening of pre-existing narcolepsy, vertigo, insomnia.
Respiratory	Dyspnoea (2%), epistaxis.
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.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

Accidental ingestion of at least 50 mg of prazosin in a 2-year old child resulted in profound drowsiness and depressed reflexes. No decrease in blood pressure was noted. Recovery was uneventful.

Should overdosage 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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

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-adrenoceptors. 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 humans, 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 MINIPRESS therapy.

A variety of epidemiologic, 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 MINIPRESS 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 on 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 MINIPRESS in the treatment of 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 smooth muscle in the prostate will produce variations in the closure pressure exerted on the prostatic urethra. This finding has provided the basis of pharmacological treatment of benign prostatic hyperplasia (BPH) involving alpha-adrenoceptor antagonism.

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

Raynaud's phenomenon and Raynaud's disease have been successfully treated with MINIPRESS. 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.

Clinical trials

No data available.

5.2 Pharmacokinetic properties

Absorption

Following oral administration to normal volunteers and hypertensive patients, plasma concentrations reach a peak in 1 to 2 hours, with a plasma half-life of 2 to 3 hours. Pharmacokinetic data in a limited number of patients with congestive heart 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 7 hours. The bioavailability of oral

prazosin was also increased 2-3 times in patients with congestive heart 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 the bile and faeces.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

calcium hydrogen phosphate
maize starch
microcrystalline cellulose
magnesium stearate
sodium lauryl sulfate

The 1 mg tablet also contains sunset yellow FCF.

6.2 Incompatibilities

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

PVC/Al blister packs of 100 tablets.

6.6 Special precautions for disposal

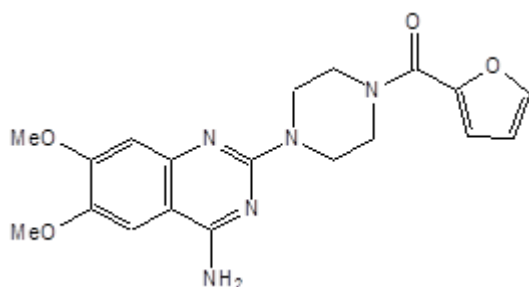
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

Prazosin hydrochloride is a white or almost white powder, very slightly soluble in water, slightly soluble in alcohol and in methanol, practically insoluble in acetone.

Chemical structure

MINIPRESS (prazosin hydrochloride), a quinazoline derivative, was the first antihypertensive of its chemical class. It is the hydrochloride salt of 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furoyl) piperazine and its structural formula is:



Molecular weight is 419.87

CAS number

19237-84-4

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
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9. DATE OF FIRST APPROVAL

19 July 1991

10. DATE OF REVISION

25 November 2019

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Summary Table of Changes

Section changed	Summary of new information
All	All sections reformatted in line with the new form.
2; 4; 5; & 6	Editorial
8	Sponsor details updated