MINIPRESS*
Prazosin Hydrochloride

1. NAME OF THE MEDICINAL PRODUCT

MINIPRESS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prazosin hydrochloride tablet contains the equivalent of 1 mg, 2 mg or 5 mg of prazosin-free base.

3. PHARMACEUTICAL FORM

Tablets

Minipress 1 mg Tablet:
Orange, round, biconvex tablet with 'K' breakline 'K' on one side and Pfizer logo on the other.

Minipress 2 mg Tablet:
White, round, biconvex tablet with 'K' breakline 'K' on one side and Pfizer logo on the other.

Minipress 5 mg Tablet:
White, diamond shaped tablet with 'K' breakline 'K' on one side and 'MNP' breakline '5' on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypertension

Prazosin hydrochloride is indicated in the treatment of all grades of essential (primary) hypertension and all grades of secondary hypertension of varied etiology. It can be used as the initial and sole agent or it may be employed in a treatment program in conjunction with a diuretic and/or other antihypertensive drugs, as needed, for proper patient response.

Left Ventricular Failure

Prazosin hydrochloride is indicated in the treatment of left ventricular failure. Prazosin hydrochloride may be added to the therapeutic regimen in patients who have not shown a

satisfactory response or who have become refractory to conventional therapy with diuretics, with or without cardiac glycosides.

Benign Prostatic Hyperplasia

Prazosin hydrochloride is indicated as an adjunct in the symptomatic treatment of urinary obstruction caused by benign prostatic hyperplasia (BPH). It is also of value in patients awaiting prostatic surgery.

Raynaud's Phenomenon and Raynaud's Disease

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

4.2 Posology and method of administration

There is evidence that toleration is best when therapy is initiated with a low starting dose of prazosin hydrochloride (see section 4.4 Special warnings and precautions for use).

During the first week, the dosage of prazosin hydrochloride should be adjusted according to the patient's individual toleration. Thereafter, the daily dosage is to 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 any particular dose. When a response is seen, therapy should be continued at that dosage until the degree of response has reached the optimum before the next dose increment is added.

Hypertension

For maximum benefit, small increases should be continued until the desired effect is achieved or a total daily dosage of 20 mg is reached. A diuretic or beta-adrenergic blocking agent may be added to enhance efficacy. The maintenance dosage of prazosin hydrochloride may be given as a twice-or three-times daily regimen.

A. Patients Receiving No Antihypertensive Therapy

It is recommended that therapy be initiated with 0.5 mg given at bedtime, then 0.5 mg two or three times daily for 3 to 7 days. Unless poor toleration suggests that the patient is unusually sensitive, this dosage should be increased to 1 mg given two or three times daily for a further 3 to 7 days. Thereafter, as determined by the patient's response to the blood pressure lowering effect, the dosage should be increased gradually to a maximum total daily dosage of 20 mg given in divided doses.

B. Patients Receiving Diuretic Therapy with Inadequate Control of Blood Pressure

The diuretic should be reduced to a maintenance dosage level for the particular agent, and prazosin hydrochloride should be initiated with 0.5 mg at bedtime, then proceeding to 0.5 mg two or three times daily.

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

C. Patients Receiving Other Antihypertensives but with Inadequate Control

Because some additive effect is anticipated, the dosage level of other agents (e.g., beta-adrenergic blocking agents, methyldopa, reserpine, clonidine, etc.) should be reduced and prazosin hydrochloride initiated at 0.5 mg at bedtime, then proceeding to 0.5 mg two or three times daily. Subsequent dosage increase should be made depending upon the patient's response.

There is evidence that adding prazosin hydrochloride to a beta-adrenergic blocking agent, calcium antagonists or angiotensin-converting enzyme (ACE) inhibitors may bring about a substantial reduction in blood pressure. Thus, the low initial dosage regimen is strongly recommended.

D. Patients with Moderate to Severe Grades of Renal Impairment

Evidence to date shows that prazosin hydrochloride 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 hydrochloride, it is recommended that therapy be initiated at 0.5 mg daily and that dosage increases be instituted with caution.

Left Ventricular Failure

The recommended starting dose is 0.5 mg prazosin hydrochloride two, 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, and when indicated, hemodynamic studies. Dosage titration steps may be performed as often as every 2 or 3 days in patients under close medical supervision.

In severely ill, decompensated patients, rapid dosage titration over 1 to 2 days may be indicated, and is best done when hemodynamic monitoring is available. In clinical studies, the therapeutic dosages ranged from 4 mg to 20 mg daily in divided doses. Adjustment of dosage may be required in the course of prazosin hydrochloride therapy in some patients to maintain optimal clinical improvement.

Benign Prostatic Hyperplasia

The recommended starting dose is 0.5 mg twice daily given for a period of 3 to 7 days and should then be adjusted according to the patient's clinical response.

The usual maintenance dose is 2 mg twice daily. The safety and efficacy of a total daily dosage greater than 4 mg has not been established. Therefore, total daily dosages greater than 4 mg should be used with caution.

Raynaud's Phenomenon and Raynaud's Disease

The recommended starting dosage is 0.5 mg twice daily given for a period of 3 to 7 days and should be adjusted according to the patient's clinical response. The usual daily maintenance dosage is 1 mg or 2 mg twice daily. Doses up to 2 mg three times a day may be required for some patients.

Use in Children

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

4.3 Contraindications

Prazosin hydrochloride is contraindicated in patients with known sensitivity to quinazolines, prazosin hydrochloride, or any of the inert ingredients.

4.4 Special warnings and precautions for use

Left Ventricular Failure

Prazosin hydrochloride is not recommended in the treatment of left ventricular 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 left ventricular failure due to a recent myocardial infarction.

When prazosin hydrochloride is initially administered to patients with left ventricular failure who have undergone vigorous diuretic or other vasodilator treatment, particularly in higher than the recommended starting dose, the resultant decrease in left ventricular filling pressure may be associated with a significant fall in cardiac output and systemic blood pressure. In such patients, observance of the recommended starting dose of prazosin hydrochloride followed by gradual titration is particularly important (see section 4.2 Posology and method of administration: *Left Ventricular Failure*).

Occasionally, in patients with left ventricular failure, the clinical efficacy of prazosin hydrochloride has been reported to diminish after several months of treatment. In these

patients, there is usually evidence of weight gain or peripheral edema, indicating fluid retention. Since spontaneous deterioration may occur in such severely ill patients, a causal relationship to prazosin hydrochloride therapy has not been established. Thus, as with all patients with left ventricular failure, careful adjustment of diuretic dosage according to the patient's clinical condition is required to prevent excessive fluid retention and consequent relief of symptoms. In those patients without evidence of fluid retention, when clinical improvement has diminished, an increase in the dosage of prazosin hydrochloride will usually restore clinical efficacy.

Hypertension

A very small percentage of patients have responded in an abrupt and exaggerated manner to the initial dose of prazosin hydrochloride. Postural hypotension evidenced by dizziness and weakness, or rarely loss of consciousness, has been reported, particularly with the commencement of therapy, but this effect is readily avoided by initiating treatment with a low dose of prazosin hydrochloride and with small increases in dosage during the first 1 to 2 weeks of therapy. The effect, when observed, is not related to the severity of hypertension is self-limiting and in most patients does not recur after the initial period of therapy or during subsequent dose-titration steps.

When instituting therapy with any effective antihypertensive agent, the patient should be advised how to avoid symptoms resulting from postural hypotension and what measures to take should they develop. The patient should be cautioned to avoid situations where injury could result, should dizziness or weakness occur during the initiation of prazosin hydrochloride therapy.

Benign Prostatic Hyperplasia

Prazosin hydrochloride decreases peripheral vascular resistance, and since many patients with this disorder are elderly, careful monitoring of blood pressure during initial administration and during adjustment of the dose of prazosin hydrochloride is suggested. Close observation is especially recommended for patients taking medications that are known to lower blood pressure.

Raynaud's Phenomenon and Raynaud's Disease

Because prazosin hydrochloride decreases peripheral vascular resistance, careful monitoring of blood pressure during initial administration and titration of prazosin hydrochloride is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure.

Use with 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 some patients. No studies have been conducted with prazosin hydrochloride.

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.

4.5 Interaction with other medicinal products and other forms of interaction

Prazosin hydrochloride has been administered without any adverse drug interaction in clinical experience to date with the following: (1) cardiac glycosides -- digitalis and digoxin; (2) hypoglycemic agents -- insulin, chlorpropamide, phenformin, tolazamide, and tolbutamide; (3) tranquilizers and sedatives -- chlordiazepoxide, diazepam, and phenobarbital; (4) agents for the treatment of gout -- allopurinol, colchicine, and probenecid; (5) antiarrhythmic agents -- procainamide, propranolol and quinidine; and (6) analgesics, antipyretics and anti-inflammatory agents -- propoxyphene, aspirin, indomethacin, and phenylbutazone type.

Addition of a diuretic or other antihypertensive agent to prazosin hydrochloride has been shown to cause an additive hypotensive effect. This effect can be minimized by reducing the dose of prazosin hydrochloride to 1 mg to 2 mg three times a day, by introducing additional antihypertensive drugs cautiously and then by retitrating prazosin hydrochloride based on clinical response.

Concomitant Administration of Prazosin Hydrochloride with PDE-5 Inhibitors (see section 4.4 Special warnings and precautions for use: *Use with Phosphodiesterase Type-5 Inhibitors*).

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

In clinical studies in which lipid profiles were followed, there were generally no adverse changes noted between pre- and post-treatment lipid levels.

4.6 Fertility, pregnancy and lactation

Fertility

In a reproductive toxicology study conducted in rats with prazosin hydrochloride, a decrease in fertility occurred in both males and females at a dose of 75 mg/kg/day (225 times the usual maximum recommended human dose), while animals given 25 mg/kg/day (75 times the usual maximum recommended human dose) were unaffected.

Pregnancy

Prazosin hydrochloride was not teratogenic in rats and rabbits up to the highest dose tested of 75 mg/kg (225 times the usual maximum recommended human dose).

Although no teratogenic effects were seen in animal testing, the safety of prazosin hydrochloride during pregnancy has not yet been established. The use of prazosin hydrochloride and a beta-blocker for the control of severe hypertension in 44 pregnant women revealed no drug-related fetal abnormalities or adverse effects. Therapy with prazosin hydrochloride was continued for as long as 14 weeks. No fetal or neonatal abnormalities have been reported with the use of prazosin hydrochloride.

Prazosin hydrochloride has also been used alone or in combination with other hypotensive agents in severe hypertension of pregnancy.

Prazosin hydrochloride should be used during pregnancy only if in the opinion of the physician the potential benefit justifies the potential risk to the mother and fetus.

Lactation

Prazosin hydrochloride has been shown to be excreted in small amounts in human milk. Caution should be exercised when prazosin hydrochloride is administered to nursing mothers.

4.7 Effects on ability to drive and use machines

The ability to engage in activities, such as operating machinery or operating a motor vehicle may be impaired, especially when initiating prazosin hydrochloride therapy.

4.8 Undesirable effects

The most common reactions associated with prazosin hydrochloride therapy are:

Body as a Whole: lack of energy, weakness (asthenia).

Central & Peripheral Nervous: dizziness (faintness), headache.

Gastrointestinal: nausea.

Heart Rate/Rhythm: palpitations.

Psychiatric: drowsiness.

In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dosage of the drug.

In addition, the following reactions have been associated with prazosin hydrochloride therapy:

Autonomic Nervous: diaphoresis, dry mouth, flushing, priapism.

Body as a Whole: allergic reaction, asthenia (weakness), fever, malaise, pain.

Cardiovascular, General: angina pectoris, edema, hypotension, orthostatic hypotension, syncope.

Central & Peripheral Nervous: faintness (dizziness), paresthesia, vertigo.

Collagen: positive ANA titer.

Endocrine: gynecomastia.

Gastrointestinal: abdominal discomfort and/or pain, constipation, diarrhea, pancreatitis, vomiting.

Hearing/Vestibular: tinnitus.

Heart Rate/Rhythm: bradycardia, tachycardia.

Liver/Biliary: liver function abnormalities.

Musculoskeletal: arthralgia.

Psychiatric: depression, hallucinations, impotence, insomnia, nervousness.

Respiratory: dyspnea, epistaxis, nasal congestion.

Skin & Appendages: alopecia, pruritus, rash, lichen planus, urticaria.

Urinary: incontinence, urinary frequency.

Vascular (Extracardiac): vasculitis.

Vision: blurred vision, reddened sclera, eye pain.

Some of these reactions have occurred rarely, and in many instances the exact causal relationships have not been established.

Literature reports exist associating prazosin hydrochloride therapy with a worsening of pre-existing narcolepsy. A causal relationship is uncertain in these cases.

The following have been observed in patients being managed for left ventricular failure with prazosin hydrochloride when used in conjunction with cardiac glycosides and diuretics:

Autonomic Nervous: dry mouth.

Cardiovascular, General: edema, postural hypotension.

Central & Peripheral Nervous: dizziness, headache.

Gastrointestinal: diarrhea, nausea.

Heart Rate/Rhythm: palpitations.

Psychiatric: drowsiness, impotence.

Respiratory: nasal congestion.

Vision: blurred vision.

In most instances these occurrences have been mild to moderate in severity and have resolved with continued therapy or have been tolerated with no decrease in drug dosage.

The most commonly although infrequently reported side effect in the treatment of Raynaud's Phenomenon/Disease was mild dizziness.

4.9 Overdose

Accidental ingestion of at least 50 mg of prazosin hydrochloride in a 2-year 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 normalization 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 hydrochloride is not dialyzable because it is protein bound.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Clinical pharmacology studies have demonstrated that prazosin hydrochloride has bronchodilator activity in normal and asthmatic human volunteers.

Hypertension

Prazosin hydrochloride causes a decrease in total peripheral vascular resistance. Animal studies suggest that the vasodilator effect of prazosin hydrochloride is related to blockade of post-synaptic alpha-1-adrenoceptors. The results of forearm plethysmographic studies in humans demonstrate that the peripheral vasodilation is a balanced effect on both resistance vessels (arterioles) and capacitance vessels (veins).

Unlike non-selective alpha-adrenergic blocking agents, the antihypertensive action of prazosin hydrochloride is usually not accompanied by reflex tachycardia.

Most studies indicate that chronic therapy with prazosin hydrochloride has little effect on plasma renin activity. One report suggests a transient increase in plasma renin activity following the initial dose, as well as an attenuated, transient increase with subsequent doses.

Hemodynamic studies have been carried out in hypertensive patients following 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, or glomerular filtration rate.

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 has not been observed in long-term clinical use. Rebound elevation of blood pressure does not occur following abrupt cessation of therapy with prazosin hydrochloride.

A variety of epidemiologic, biochemical and experimental studies have established that an elevated level of low-density lipoprotein (LDL) cholesterol is associated with an increased risk of coronary heart disease. There is an even stronger relationship between reduced levels of high-density lipoprotein (HDL) cholesterol and an increased risk of coronary heart disease. Clinical studies have shown that prazosin hydrochloride lowers LDL levels and either has no effect or increases HDL levels.

Left Ventricular Failure

Hemodynamic studies carried out in patients with left ventricular failure following initial oral therapy and during the course of longer term maintenance therapy, both at rest and at 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 without any increase in myocardial oxygen consumption. These effects are associated with a balanced vasodilator effect on both arterioles and veins. The use of prazosin hydrochloride in the treatment of left ventricular failure does not provoke a reflex tachycardia, and blood pressure reduction is absent or minimal in normotensive patients.

Benign Prostatic Hyperplasia

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 a pharmacological treatment of BPH involving alpha-adrenoceptor antagonism.

There is evidence of statistically significant improvement in urinary flow following therapy with prazosin hydrochloride 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

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

5.2 Pharmacokinetic properties

Following oral administration in 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 left ventricular 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 drug is highly bound to plasma protein. Animal studies indicate that prazosin hydrochloride is extensively metabolized, primarily by demethylation and conjugation, and excreted mainly via the bile and feces. Similar metabolism and excretion have been documented in human studies.

5.3 Preclinical Safety Data

Prazosin hydrochloride was not mutagenic in genetic toxicology testing, and was not carcinogenic in an 18-month study conducted in rats. In chronic studies (1 year or more) conducted with prazosin hydrochloride in rats and dogs, testicular changes consisting of atrophy and necrosis occurred at 25 mg/kg/day (75 times the usual maximum recommended human dose), while no such changes were observed in either species at a dose of 10 mg/kg/day (30 times the usual maximum recommended human dose).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1 mg tablet
Prazosin hydrochloride, microcrystalline cellulose, FD and C Yellow No 6 Lake, dibasic calcium phosphate, maize starch, magnesium stearate, sodium lauryl sulphate.

2 mg tablet
Prazosin hydrochloride, microcrystalline cellulose, dibasic calcium phosphate, maize starch, magnesium stearate, sodium lauryl sulphate.

5 mg tablet
Prazosin hydrochloride, microcrystalline cellulose, dibasic calcium phosphate, maize starch, magnesium stearate, sodium lauryl sulphate.

6.2 Incompatibilities

None known

6.3 Shelf-life

Please refer to carton for shelf-life.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Blister Packs
1 mg (100's)
2 mg (100's)
5 mg (100's)

Some product strengths or pack sizes may not be available in your market.

6.6 Special precautions for disposal and other handling

Prazosin hydrochloride tablets are for oral administration only.

6.7 Manufacturer

Pharmaniaga Manufacturing Berhad
11A Jalan P/1,
Kawasan Perusahaan Bangi,
43650 Bandar Baru Bangi,
Selangor Darul Ehsan, Malaysia

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