PRESCRIBING INFORMATION
PRODUCT MONOGRAPH

[Pr]MINIPRESS

Prazosin Hydrochloride Tablets BP

TABLETS 1.0, 2.0 and 5.0 mg

Antihypertensive

Date of Revision:
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Control No. 248447

PrMINIPRESS

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Prazosin Hydrochloride Tablets BP

THERAPEUTIC CLASSIFICATION

Antihypertensive

ACTIONS AND CLINICAL PHARMACOLOGY

MINIPRESS is a formulation of prazosin hydrochloride and is a conventional release formulation. Prazosin causes a decrease in total peripheral resistance. Animal studies suggest that the vasodilator effect of prazosin is related to selective blockade of post-synaptic alpha$_1$- adrenoceptors. The results of dog forelimb experiments demonstrate that the peripheral vasodilator effect is confined mainly to the level of the resistance vessels (arterioles). Hemodynamic studies have been carried out in man following acute single dose administration and during the course of long term maintenance therapy. The results confirm that the therapeutic effect is a fall in blood pressure unaccompanied by a clinically significant change in heart rate, renal blood flow and glomerular filtration rate. In patients with hypertension there is little change in cardiac output. In addition, clinical pharmacology studies have shown that both prazosin and prazosin GITS antagonize the vasopressor effect of intravenous phenylephrine, an alpha$_1$-agonist.

In man blood pressure is lowered in both the supine and standing positions. The hypotensive effect of prazosin hydrochloride is greater when the patient is standing, and a mild reflex tachycardia can result. Tolerance has not been observed to develop in long term hypertensive therapy. Rebound elevation of blood pressure does not seem to occur following abrupt cessation of therapy with **MINIPRESS**.

Following oral administration of **MINIPRESS** in normal volunteers and hypertensive patients, plasma concentrations reach a peak at about 3 hours with a plasma half-life of 2-3 hours. The drug is highly bound to plasma protein (97 percent). After chronic administration, no apparent drug accumulation was observed nor were any obvious decreases in plasma concentrations noted. Secondary plasma drug peaks and shoulders suggested probable enterohepatic circulation. Animal studies indicate that prazosin hydrochloride is extensively metabolized, primarily by demethylation and conjugation, and excreted (primarily as glucuronide conjugates) mainly via bile and feces. Similar metabolism and excretion has been documented in human studies.

Most clinical studies indicate that chronic therapy with **MINIPRESS** has little effect on plasma renin activity. However one report suggests a transient increase in plasma renin activity following the initial dose, as well as attenuated transient increase with subsequent doses.

INDICATIONS AND CLINICAL USE

MINIPRESS (prazosin hydrochloride) is indicated in the treatment of mild to moderate essential hypertension. It is employed in a general treatment program in association with a thiazide diuretic and/or other antihypertensive agents as needed for proper patient response. **MINIPRESS** may be tried as a sole therapy in those patients in whom treatment with other agents caused adverse effects or is inappropriate.

CONTRAINDICATIONS

MINIPRESS (prazosin hydrochloride) are contraindicated in patients with a known sensitivity to quinazolines.

WARNINGS

MINIPRESS (PRAZOSIN HYDROCHLORIDE) MAY CAUSE SYNCOPE AND/OR EXCESSIVE HYPOTENSION 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 ASSOCIATED WITH ABOUT OF SEVERE TACHYCARDIA WITH HEART RATES OF 120-160 BEATS PER MINUTE. THE INCIDENCE OF SYNCOPAL EPISODES IS APPROXIMATELY 0.8% WHEN THE GRADUAL DOSE BUILD UP DESCRIBED UNDER DOSAGE AND ADMINISTRATION IS FOLLOWED. THE INCIDENCE IS HIGHER IF THE INITIAL DOSE EXCEEDS 0.5 MG. SYNCOPAL EPISODES HAVE OCCURRED WITHIN 30 TO 90 MINUTES OF THE INITIAL DOSE OF THE DRUG. THEY HAVE ALSO BEEN REPORTED IN ASSOCIATION WITH DOSAGE INCREASES OR THE INTRODUCTION OF **MINIPRESS** INTO THE REGIMEN OF A PATIENT TAKING ANOTHER ANTIHYPERTENSIVE AGENT OR A DIURETIC. PHYSICIANS ARE THEREFORE ADVISED TO LIMIT THE INITIAL DOSE OF THE DRUG TO 0.5 MG B.I.D. OR T.I.D., TO SUBSEQUENTLY INCREASE THE DOSAGE SLOWLY, AND TO INTRODUCE ANY ADDITIONAL ANTIHYPERTENSIVE DRUGS INTO THE PATIENT'S REGIMEN WITH CAUTION.

PATIENTS WHOSE BLOOD PRESSURE IS NOT ADEQUATELY CONTROLLED BY HIGH DOSES OF A BETA-ADRENERGIC BLOCKING AGENT SUCH AS PROPRANOLOL MAY DEVELOP ACUTE HYPOTENSION WHEN **MINIPRESS** IS ADDED. TO MINIMIZE THE INCIDENCE OF ACUTE HYPOTENSION IN SUCH PATIENTS, THE DOSE OF BETA- ADRENERGIC BLOCKING AGENT SHOULD BE REDUCED BEFORE **MINIPRESS** IS ADMINISTERED. A LOW INITIAL DOSE OF **MINIPRESS** IS ALSO STRONGLY RECOMMENDED (SEE DOSAGE AND ADMINISTRATION).

If syncope occurs, the patient should be placed in the recumbent position and supportive measures instituted. This adverse effect is self-limiting and in most cases does not recur once a steady maintenance level is initiated. Patients should be cautioned to avoid situations where injury could result should syncope occur during **MINIPRESS** therapy especially in the initial dose adjustment period.

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.

Use During Pregnancy

Although no teratogenic effects were seen in animal testing, there are no adequate and well controlled studies which establish the safety of **MINIPRESS** in pregnant women. Limited uncontrolled use in the management of hypertension in the later stages of pregnancy suggests that prazosin hydrochloride in combination with a beta-blocker can lower blood pressure in pregnant patients. The drug appears to be less effective in patients with proteinuria in whom the addition of i.v. hydralazine was usually required. Accordingly **MINIPRESS** should be used during pregnancy only if in the opinion of the physician the potential benefit outweighs potential risk to mother and child.

Use During Lactation

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

Use For Children

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

PRECAUTIONS

Use in Patients with Moderate to Severe Grades of Renal Impairment

Because some patients with moderate to severe grades of renal impairment have responded to

smaller than usual doses of prazosin hydrochloride, it is recommended that therapy be initiated with **MINIPRESS (prazosin hydrochloride)** at 0.5 mg and that dose increases be instituted cautiously.

Drug Interactions

MINIPRESS has been administered without any adverse drug interaction in limited clinical experience to date with the following: (1) cardiac glycosides - digitalis and digoxin; (2) hypoglycemics - insulin, chlorpropamide, tolazamide and tolbutamide; (3) tranquilizers and sedatives - chlordiazepoxide, diazepam and phenobarbital; (4) antigout - allopurinol, colchicine and probenecid; (5) antiarrhythmics - procainamide, propranolol (see WARNINGS however), and quinidine; and (6) analgesics, antipyretics and anti-inflammatories - propoxyphene, ASA, indomethacin and phenylbutazone.

Addition of a diuretic or other antihypertensive agent to **MINIPRESS** has been shown to cause an additive hypotensive effect. (See **WARNINGS** and **DOSAGE & ADMINISTRATION** sections.) An exaggerated hypotensive response has also been observed.

Drug/Laboratory Test Interactions

False positive results may occur in screening tests for pheochromocytoma (urinary vanillylmandelic acid [VMA] and methoxyhydroxyphenyl glysol (MHPG) urinary metabolites of norepinephrine in patients who are being treated with (prazosin hydrochloride). If an elevated VMA is found, **MINIPRESS** should be discontinued and the patient retested after a month.

ADVERSE REACTIONS

MINIPRESS

The most common reactions associated with **MINIPRESS (prazosin hydrochloride)** 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 dose of drug. The following reactions have also been observed during **MINIPRESS (prazosin hydrochloride)** administration.

Gastrointestinal:	vomiting, diarrhea, constipation, abdominal discomfort and/or pain.
Cardiovascular:	syncope (See **WARNINGS**), orthostatic hypotension, edema, dyspnea, tachycardia, faintness.
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.
Hepatic:	liver function abnormalities, pancreatitis.
Hematologic:	decreased hematocrit/hemoglobin.
Other:	diaphoresis, fever, arthralgia, positive ANA titer.

Single reports of pigmentary mottling and serous retinopathy have been reported. In these instances, the exact causal relationship has not been established because the baseline observations were frequently inadequate.

In more specific slit-lamp and funduscopic studies, which included adequate baseline examinations, no drug-related abnormal ophthalmological findings have been reported.

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

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

A few reports of prazosin hydrochloride overdose have been documented with **MINIPRESS (prazosin hydrochloride)**. The most frequently observed symptoms of overdose include hypotension and somnolence.

Accidental ingestion of at least 50 mg of **MINIPRESS** 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 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 necessary, vasopressors should be used. If this measure is

inadequate, shock should then be treated with volume expanders. Renal function should be monitored and supported as needed. Laboratory data indicate **MINIPRESS** is not dialysable because it is protein bound.

DOSAGE AND ADMINISTRATION

MINIPRESS CONVENTIONAL RELEASE TABLETS (prazosin hydrochloride)

NOTE: When titration is to be undertaken using the tablet formulation it will be necessary to split the 1 mg scored tablet to obtain the 0.5 mg starting dose.

It is recommended that the starting dose of 0.5 mg be given with food preferably with the evening meal, at least two or three hours before retiring. The dose should be built up gradually with 0.5 mg being given b.i.d. or t.i.d. for at least three days. Unless adverse effects occur and subject to the blood pressure lowering effect this dose should be increased to 1 mg given b.i.d. or t.i.d. for at least a further three days.

Thereafter, as determined by the patient's response to the blood pressure lowering effect, the dose should be increased gradually. Response to **MINIPRESS** is usually seen within one to fourteen days if it is to occur at any particular dose. When a response is seen, therapy should be continued at that dose until the degree of response has reached the optimum before the next dose increment is added.

Incremental increases should be continued until a desired effect is achieved or a maximum daily dose of 20 mg is reached.

The maintenance dose of **MINIPRESS** may be given as a twice or three times daily dosage regimen.

In patients with moderate to severe grades of renal impairment, it is recommended that therapy be initiated at 0.5 mg daily and that dose increases be instituted gradually.

Use With Other Drugs

Patients Receiving Diuretic Therapy

The diuretic should be reduced to a maintenance dose level for the particular agent and **MINIPRESS** initiated at 0.5 mg h.s. then proceeding to 0.5 mg b.i.d. or t.i.d. After the initial period of observation, the dose of **MINIPRESS** should be gradually increased as determined by the patient's response.

Patients Receiving Other Antihypertensive Agents

Because some additive effect is anticipated, the other agent (e.g., propranolol* or other beta-adrenergic blocking agents*, alpha methyldopa, reserpine, clonidine*, etc.) should be reduced and **MINIPRESS** initiated at 0.5 mg h.s. then proceeding to 0.5 mg b.i.d. or t.i.d. Subsequent dosage

increase should be made depending upon the patients response.

Patients on **MINIPRESS** to Whom Other Antihypertensive Agents Are Added

When adding a diuretic or other antihypertensive agent, the dose of **MINIPRESS** should be reduced to 1 mg or 2 mg b.i.d. or t.i.d. and retitration then carried out.

*Appropriate precautions should be observed when the dosage of these other antihypertensive agents is reduced.

PHARMACEUTICAL INFORMATION

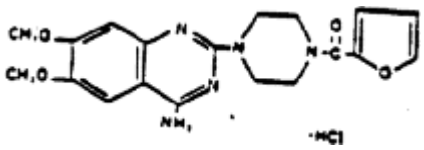
CHEMISTRY

Trade Name: **MINIPRESS**

Proper Name: Prazosin hydrochloride

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

Structural Formula:



Molecular Formula: $C_{19}H_{21}N_5O_4HCl$

Molecular Weight: 419.9

Description: Prazosin hydrochloride is a white, crystalline substance, slightly soluble in water and isotonic saline.

Composition: **MINIPRESS** Tablets contain prazosin hydrochloride equivalent to 1.0, 2.0 and 5.0 mg of prazosin. Also contains calcium phosphate, microcrystalline cellulose, corn starch (gluten), magnesium stearate/sodium lauryl sulfate and FD & C yellow #6 in 1 mg tablets only.

Inactive ingredients in the formulation are: cellulose acetate; hydroxypropyl methylcellulose; magnesium stearate; polyethylene glycol; polyetheylene oxide; red ferric oxide; sodium chloride; coating material and synthetic black iron oxide.

DOSAGE FORMS

AVAILABILITY

MINIPRESS Tablets: available as scored tablets containing prazosin hydrochloride equivalent to 1.0 (orange), 2.0 (white, round) and 5.0 (white, diamond) mg of prazosin in bottles (HDPE) of 100 (all tablet strengths) and 500 (1 and 2 mg).

Available in bottles and unit dose packages of 100 tablets.

MINIPRESS should be stored between 15-30°C.

PHARMACOLOGY

Hypotensive Action

The nature of the hypotensive action of prazosin hydrochloride was studied both by in vitro and in vivo methodology. Intravenously administered prazosin hydrochloride in dogs caused prolonged hypotension and reduction in total peripheral resistance. Cardiac output, heart rate, and blood flow in the femoral, renal, and splanchnic vascular beds were increased transiently. Cardiac responses to electrical stimulation of cardioaccelerator nerves were not depressed, nor was there sympathetic ganglion or adrenergic neurone blockade. Although prazosin hydrochloride reversed the epinephrine pressor response in intact animals, vasodilator activity was only slightly diminished when the vessels were deprived of sympathetic tone by ganglionic blockade.

Physiologic and direct radioligand binding data from studies in experimental animals indicates that the hypotensive effect of prazosin hydrochloride ascribed to peripheral vasodilation is achieved primarily by competitive blockade of the vascular postsynaptic $alpha_1$-adrenergic receptors. As prazosin acts preferentially on postsynaptic $alpha_1$-adrenergic receptors, the feedback control of neuronal norepinephrine release by presynaptic $alpha_2$-receptors remains unchanged.

In the dog, the hypotensive effect of prazosin hydrochloride intravenously was reversed by metaraminol and norephinephrine given by intravenous infusion.

Miscellaneous Actions

At doses considerably higher than those required for antihypertensive activity, prazosin hydrochloride has mild CNS depressant activity, decreases heart norepinephrine and adrenal epinephrine in rats, causes diuresis in anesthetized dogs, but fluid retention in conscious dogs and mice, and is hyperglycemic in rats.

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

TOXICOLOGY

Acute Toxicity

The results of single-dose acute toxicity studies on prazosin hydrochloride are presented in Table 1.

TABLE 1

Acute Toxicity of Prazosin Hydrochloride

SPECIES	SEX	ORAL	INTRAPERITONEAL
		LD_{50} mg/kg	LD_{50} (95% Confidence limits)mg/kg
Mouse	M & F	>5000	84 (62-113)
Rat	M & F	>2000	141 (121-165)

The signs of toxicity observed following the administration of this compound were, for the most part, common to both mice and rats by both routes and included blanching, depression, decreased respiration, ptosis, writhing, ataxia, tremors and convulsions.

Mongrel dogs given 250 and 500 mg/kg as a single oral dose showed ataxia, depression, occasional diarrhea, relaxed nictitating membrane, ptosis, and occasional tremors. Tachycardia was also noted in the three dogs at 250 mg/kg. Anorexia was noted 48 hours post dose in one dog receiving 500 mg/kg.

Chronic Toxicity

Prazosin hydrochloride was administered to dogs in doses of 2, 10 and 25 mg/kg/day seven days per week for one year. Testicular atrophy and degeneration accompanied by prostatic atrophy and fibrosis occurred in male dogs receiving doses of 25 mg/kg/day.

(Urinary 17-ketosteroid excretion in human clinical studies was monitored in 105 patients for any possible effect on testicular function for periods ranging from 3 to 33 months. A trend analysis of the 17-ketosteroid data disclosed a seasonal variation, but did not suggest a drug effect. Routine semen analysis in 27 male patients on prazosin hydrochloride alone for up to 51 months revealed no semen abnormalities.)

Rats received prazosin hydrochloride in doses of 5, 25, 75 and 150 mg/kg/day for 18 months. During the first 18 weeks of study, drug-induced hepatocellular degeneration and/or necrosis and renal corticomedullary necrosis occurred at the dose level of 150 mg/kg; mild hepatocellular degenerative

changes and/or necrosis were found at the dose level of 75 mg/kg.

Between 19 and 53 weeks, the following pathologic changes were observed at dose levels of 150 and 75 mg/kg: testicular necrosis with accompanying inguinal and/or scrotal adhesions; chronic nephrotoxic nephritis; degenerative folding and contracture of the retina (retinitis proliferans); adrenal plethora; gastric necrosis and hepatic necrosis. At the dose level of 25 mg/kg, there was a low percent incidence of testicular, renal and gastric alterations; since these same changes occurred in larger numbers of animals at the two higher dose levels, they appear drug-related.

Between 54 weeks and 18 months, the following changes occurred at dose levels of 150, 75 and 25 mg/kg: testicular atrophy and/or degeneration with accompanying inguinal and/or scrotal adhesions; retinitis proliferans (150 and 75 mg/kg levels only) and hepatic degeneration and/or necrosis. Additionally, bilateral cataracts (not observed previously) occurred at the dose levels of 150 and 75 mg/kg. Chronic nephritis and adrenal plethora (cystic degeneration) which previously (19-53 weeks) had a higher percent incidence at the dose levels of 150, 75 and 25 mg/kg, and 150 and 75 mg/kg respectively, appeared with approximately the same frequency at all dose levels including the controls.

Carcinogenicity

In a chronic study with rats, prazosin hydrochloride fed at levels up to 75 mg/kg/day for 18 months showed no evidence of carcinogenicity.

Reproductive and Teratologic Studies

Reproductive and teratologic studies were carried out at dose levels of 25 and 75 mg/kg/day in rats and rabbits. No drug-induced changes were observed.

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