MINIPRESS

(prazosin hydrochloride)

TABLETS 1.0, 2.0 and 5.0 mg

Antihypertensive

DATE OF PREPARATION: August 10, 2005

DATE OF REVISION:

Control No. 100295
NAME OF DRUG
MINIPRESS TABLETS 1.0, 2.0 and 5.0 mg
AND
MINIPRESS XL EXTENDED RELEASE TABLETS 2.5 and 5.0 mg
(prazosin hydrochloride)

THERAPEUTIC CLASSIFICATION

Antihypertensive

ACTIONS AND CLINICAL PHARMACOLOGY

MINIPRESS and MINIPRESS XL are two formulations of prazosin hydrochloride. MINIPRESS is the conventional release formulation and MINIPRESS XL is the extended release formulation of prazosin hydrochloride GITS (gastrointestinal therapeutic system). 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 alpha₁-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 alpha₁-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.

Plasma prazosin concentrations, after a 2 to 4 hour lag, rise at a controlled rate after initial dosing with **MINIPRESS XL** and reach a plateau at approximately six to ten hours after the first dose.

For subsequent doses, relatively constant plasma concentrations are maintained at this plateau with minimal fluctuations over the 24-hour dosing interval. Less peak-to-through fluctuations was observed in the plasma prazosin concentrations of individual patients after **MINIPRESS XL** than after conventional immediate release **MINIPRESS**.

Steady state plasma concentration occurs within one week after initiating a once daily dosing regimen. At steady-state, the bioavailability of the **MINIPRESS XL** tablet is 60-86% relative to **MINIPRESS**. The mean accumulation index for **MINIPRESS XL** is 1.4.

The pharmacokinetics of **MINIPRESS XL** tablets are linear over the 2.5 to 20 mg dose range in that plasma prazosin concentrations are proportional to dose administered and the multi-dose profile can be predicted from the single-dose profile. Bioavailability was not significantly influenced by morning versus evening administration nor by concurrent high fat food ingestion. There was no evidence of dose-dumping either in the presence or absence of food in over 100 subjects who participated in pharmacokinetic studies.
However, in patients with markedly reduced GI retention time over prolonged periods (e.g. short bowel syndrome, conditions resulting in chronic rapid transit time), lower plasma prazosin concentrations may result with administration of MINIPRESS XL.

**INDICATIONS AND CLINICAL USE**

MINIPRESS or MINIPRESS XL (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 and MINIPRESS XL (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 A BOUT 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).

MINIPRESS XL: To decrease the likelihood of syncope or excessive hypotension (see WARNINGS, MINIPRESS above), treatment should always be initiated with the 2.5 mg dose of MINIPRESS XL. The 5 mg tablet is not indicated as initial therapy (see DOSAGE AND ADMINISTRATION). In an early, placebo-controlled single dose study designed to elicit postural effects, postural dizziness was reported in 5 of 19 patients (26%) administered 2.5 mg of MINIPRESS XL. Postural hypotension was documented in only 2 of these MINIPRESS XL patients occurring between 16 and 24 hours after dosing, with no episodes of syncope reported. In controlled clinical trials involving 689 patients receiving MINIPRESS XL for periods as long as one month, syncope occurred in one patient (0.15%) on the fourth day of dosing. Other less severe symptoms of lowered blood pressure, such as dizziness and palpitations, have been reported (see MINIPRESS XL ADVERSE REACTIONS).

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 or MINIPRESS XL 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 or MINIPRESS XL 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 or MINIPRESS XL 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 or MINIPRESS XL is administered to nursing mothers.

Use For Children
MINIPRESS or MINIPRESS XL 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 daily or with MINIPRESS XL (prazosin hydrochloride) at 2.5 mg daily and that dose increases be instituted cautiously.

Altered GI Retention Time
In patients with markedly reduced GI retention time, the pharmacokinetic profile of the MINIPRESS XL extended release system (i.e. GITS) may be altered, potentially diminishing its antihypertensive effectiveness.
Patients with Pre-Existing Gastrointestinal Narrowing

In patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic), caution should be used when administering MINIPRESS XL because of the non-deformable nature of the tablet materials. There have been rare reports of GI obstruction in patients with known strictures in association with the use of this dosage form for drug delivery (i.e. GITS).

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.

Interaction studies have not been performed with MINIPRESS XL.

Addition of a diuretic or other antihypertensive agent to MINIPRESS or MINIPRESS XL 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 or MINIPRESS XL should be discontinued and the patient retested after a month.

INFORMATION FOR PATIENTS

MINIPRESS XL Extended Release Tablets:

Patients should be made aware of the possibility of occurrence of symptoms associated with lowering of blood pressure e.g. orthostatic symptoms, especially at the initiation of therapy and to avoid driving or hazardous tasks for 24 hours after the first dose, after a dosage increase, and after interruption of therapy when treatment is resumed. Dizziness, lightheadedness or fainting may occur, especially when rising from a supine or sitting position. If such an event occurs, patients should be advised to lie down. Getting up slowly and going from a supine to a
sitting position before standing up may help reduce the problem. As with most other antihypertensive agents, while taking **MINIPRESS XL** patients should be careful of their alcohol intake, use extra care during exercise or hot weather, and avoid standing for long periods, all of which can contribute to the occurrence of orthostatic symptoms. If dizziness, lightheadedness, or palpitations are bothersome they should be reported to the physician.

**MINIPRESS XL** Extended Release Tablets should be swallowed whole. Patients should be advised not to chew, divide or crush tablets and not to be concerned if they occasionally notice something that looks like a tablet in their stool. With **MINIPRESS XL** Extended Release Tablets, the medication is contained within a non-absorbable shell that has been specially designed to slowly release the drug for intestinal absorption. When this process is completed the empty or nearly empty tablet is eliminated from the body in the feces as an insoluble flaccid shell.

**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.

**MINIPRESS XL**

Four hundred and eighty one (481) hypertensive patients from placebo controlled multiple-dose trials treated with MINIPRESS XL Extended Release Tablets were included in the evaluation of adverse effects. Adverse reactions requiring discontinuation of therapy occurred in 2.9% of patients. In controlled clinical trials in 689 patients, the most serious adverse reaction was syncope which occurred in one patient (0.1%) on the fourth day of dosing with MINIPRESS XL. (See **WARNINGS** section) The most common adverse effects reported with MINIPRESS XL were headache (11.6%), dizziness (10.0%), fatigue (5.8%), edema (5.4%), and palpitations (3.7%).

All adverse reactions found to occur with MINIPRESS can potentially occur with MINIPRESS XL.

The following adverse reactions were reported in **1 to 3%** of patients receiving MINIPRESS XL Extended Release Tablets (n=481):

Cardiovascular: chest pain, dyspnea.
In addition, less than 1% of patients have reported the following (in some instances, exact causal relationships have not been established):

**Cardiovascular:** flushing, syncope, tachycardia.

**Central Nervous System:** anxiety, depression, hypoesthesia, impotence, leg cramps, increased sweating, paresthesia, vertigo.

**EENT:** conjunctivitis, dry mouth, deafness, earache, epistaxis, tinnitus.

**Gastrointestinal:** abdominal pain, dysphagia, irritation/bleeding, vomiting.

**Genitourinary:** incontinence, polyuria.

**Respiratory:** bronchospasm, cough.

**Other:** arthralgia, back pain, diaphoresis, fever, malaise, myalgia, pruritus, weight increase.

**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. In addition, before gastric lavage is attempted, the diameters of the MINIPRESS XL Extended Release Tablet should be considered relative to the size of the tubes intended for use: 2.5 mg (7.4 mm); 5 mg (8.9 mm).

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.

**MINIPRESS XL EXTENDED RELEASE TABLETS (prazosin hydrochloride)**
Dosage should be individualized depending on patient tolerance and response.

**MINIPRESS XL** Extended Release Tablets must be swallowed whole and should not be bitten or divided.

Therapy for hypertension with **MINIPRESS XL** must be initiated at 2.5 mg once daily. The 5 mg dosage form of **MINIPRESS XL** is not for initial dosing. Dosage may be increased slowly, in general over a 7 to 14 day period, depending on the response to each dose level. Doses above 20 mg once daily have not been studied.

**Maintenance dose:** dosage may be increased as clinically indicated to 20 mg given in once-daily doses.
Hypertensive patients controlled on MINIPRESS Tablets alone or in combination with other antihypertensive medications may be switched to MINIPRESS XL Extended Release Tablets at the equivalent or nearest higher total daily dose, e.g. MINIPRESS Tablets 4 mg daily equivalent to MINIPRESS XL Extended Release Tablets 5 mg once daily. Blood pressure measurements should be taken at the end of the dosing interval to assure adequate blood pressure control is maintained throughout the 24 hour period. Further titration may be necessary in some patients.

Addition of a diuretic or other antihypertensive agent to prazosin has been shown to cause an additive hypotensive effect (see also DOSAGE & ADMINISTRATION for MINIPRESS Tablets, Use With Other Drugs).

Care should be taken when dispensing MINIPRESS XL to ensure that the extended release dosage form has been prescribed.
PHARMACEUTICAL INFORMATION

CHEMISTRY

Trade Name: MINIPRESS
MINIPRESS XL

MINIPRESS XL is a trademark for prazosin Gastrointestinal Therapeutic System (GITS).

Proper Name: Prazosin hydrochloride

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

Structural Formula:

Molecular Formula: C₁₉H₂₁N₅O₄HCl

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.

MINIPRESS XL Extended Release Tablets is formulated as a controlled-release bilayer tablet designed to deliver prazosin hydrochloride equivalent to 2.5 and 5.0 mg of prazosin. MINIPRESS XL is similar in appearance to a conventional tablet. It consists however, of a semipermeable membrane surrounding an osmotically active drug core. The core itself is divided into two layers: an “active”
core layer containing the drug, and “push” core layer containing pharmacologically inert (but osmotically active) components.

Inactive ingredients in the formulation are: cellulose acetate; hydroxypropyl methylcellulose; magnesium stearate; polyethylene glycol; polyethylene 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).

**MINIPRESS XL Extended Release Tablets:** contain prazosin hydrochloride equivalent to 2.5 and 5.0 mg prazosin.

**MINIPRESS XL 2.5 mg** is a round, biconvex, rose and white coated bi-layered tablet imprinted in black with "2.5" on one side.

**MINIPRESS XL 5.0 mg** is a round, biconvex, rose and white coated bi-layered tablet imprinted in black with "5.0" on one side.

Available in bottles and unit dose packages of 100 tablets.

**MINIPRESS XL Extended Release Tablets** should be protected from moisture and humidity and 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\textsubscript{1}-adrenergic receptors. As prazosin acts preferentially on postsynaptic alpha\textsubscript{1}-adrenergic receptors, the feedback control of neuronal norepinephrine release by presynaptic alpha\textsubscript{2}-receptors remains unchanged.

In the dog, the hypotensive effect of prazosin hydrochloride intravenously was reversed by metaraminol and norepinephrine 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**

<table>
<thead>
<tr>
<th>SPECIES</th>
<th>SEX</th>
<th>ORAL</th>
<th>INTRAPERITONEAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>LD$_{50}$ mg/kg</td>
<td>LD$_{50}$ (95% Confidence limits) mg/kg</td>
</tr>
<tr>
<td>Mouse</td>
<td>M &amp; F</td>
<td>&gt;5000</td>
<td>84 (62-113)</td>
</tr>
<tr>
<td>Rat</td>
<td>M &amp; F</td>
<td>&gt;2000</td>
<td>141 (121-165)</td>
</tr>
</tbody>
</table>

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.

Esophageal Adherence and Mucosal Irritation Potential
The esophageal adherence of **MINIPRESS XL 10 mg** was evaluated in isolated dog esophagus using the method described by Marvola et al. The irritation potential was assessed on colonic mucosa in New Zealand White rabbits using the modified method of Alphin & Dropplemen. No microscopic changes were associated within these findings. The extended release formulation of prazosin hydrochloride presented minimal risk for esophageal adherence or intestinal irritation.
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.
REFERENCES


