PRODUCT MONOGRAPH

PrTEVA-PRAZOSIN

(Prazosin Hydrochloride)

1.0, 2.0 and 5.0 mg Tablets

Teva Standard

Antihypertensive

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THERAPEUTIC CLASSIFICATION

Antihypertensive

ACTION AND CLINICAL PHARMACOLOGY

TEVA-PRAZOSIN (prazosin hydrochloride) is a sympatholytic antihypertensive agent. Its primary mechanism of action is the competitive blockade of the vascular postsynaptic alpha-adrenoceptors. Prazosin acts preferentially on post-synaptic $alpha_1$-receptors, thereby blocking the contractile response of vascular smooth muscle to norepinephrine without interfering with its activity at $alpha_2$-receptors. Abrupt termination of prazosin treatment does not appear to cause a rebound elevation in blood pressure. Tolerance to prazosin does not appear to develop.

Hemodynamic studies have shown that the decrease in blood pressure is not accompanied by any significant changes in renal blood flow or glomerular filtration rate.

A comparative three-way bioavailability study was conducted in order to compare TEVA-PRAZOSIN 1 mg and 2 mg Tablets with MINIPRESS® 2 mg Tablets. The pharmacokinetic data (mean ± standard deviation) calculated for TEVA-PRAZOSIN and MINIPRESS® are tabulated below:

Geometric Mean Arithmetic Mean (C.V.)					
	Minipress 1 x 2 mg	**TEVA-PRAZOSIN 2 x 1 mg**	**% of Minipress®**	**TEVA-PRAZOSIN 1 x 2 mg**	**% of Minipress®**
AUC_T (ng·h/mL)	67 70 (28)	71 74 (28)	106	69 72 (25)	103
AUC_I (ng·h/mL)	72 74 (27)	75 78 (28)	104	74 76 (24)	103
C_{max} (ng/mL)	18 19 (30)	21 22 (26)	117	21 22	117
T_{max}* (h)	1.15 (0.58)	0.81 (0.44)	-	0.90 (0.49)	-
$T_{½}$* (h)	2.58 (0.79)	2.73 (0.73)	-	2.91 (0.88)	-

* For the T_{max} and $T_{1/2}$ parameters these are the arithmetic means (standard deviation).

A comparative, two-way bioavailability study was conducted to compare TEVA-PRAZOSIN 5 mg Tablets and MINIPRESS® 5 mg Tablets. The pharmacokinetic data (mean ± standard deviation) calculated for TEVA-PRAZOSIN and MINIPRESS® are tabulated below:

Geometric Mean Arithmetic Mean (C.V.)			
	TEVA-PRAZOSIN 1 x 5 mg	**MINIPRESS® 1 x 5 mg**	**% of Minipress®**
AUC_T (ng·h/mL)	200 205 (22)	200 207 (28)	100
AUC_I (ng·h/mL)	206 211 (22)	206 214 (28)	100
C_{max} (ng/mL)	44 45 (27)	41 43 (31)	107
T_{max}* (h)	2.04 (0.58)	2.52 (1.05)	-
$T_{½}$* (h)	2.65 (0.40)	2.76 (0.45)	-

* For the T_{max} and $T_{1/2}$ parameters these are the arithmetic means (standard deviation).

Following oral administration of prazosin hydrochloride, plasma concentrations of the drug reach a peak in 1 to 3 hours in most fasting patients. Blood pressure begins to decrease within 2 hours after oral dosing with the maximal decrease occurring in 2 to 4 hours. A period of 4 to 6 weeks at a maintenance dose level may be required before the full effect of the drug is achieved.

INDICATIONS AND CLINICAL USE

TEVA-PRAZOSIN (prazosin hydrochloride) is indicated in the treatment of hypertension. It has mild to moderate antihypertensive activity. Prazosin is employed in a general treatment program in conjunction with other antihypertensive agents and/or diuretic drugs, depending on the needs of the patient. In cases of mild hypertension, TEVA-PRAZOSIN can be employed as the initial treatment if the physician feels that treatment should be initiated with a sympatholytic rather than a diuretic agent.

CONTRAINDICATIONS

TEVA-PRAZOSIN (prazosin hydrochloride) is contraindicated in patients with a known hypersensitivity to the drug.

WARNINGS

TEVA-PRAZOSIN (prazosin hydrochloride) can cause syncope with a sudden loss of consciousness. This is believed to be the result of an excessive postural hypotensive effect in most cases. Occasionally, however, syncopal episodes have been associated with a bout of severe tachycardia with heart rates between 120 and 160 beats per minute. When the dose is increased gradually, as described under dosage and administration, the occurrence of syncope is rare. If the initial dose exceeds 0.5 mg, however, the risk of syncope is increased. Syncope episodes have occurred with 30 to 90 minutes of the initial dose. Syncope has also been reported in association with the introduction of prazosin hydrochloride into the treatment regimen of patients already taking a diuretic or another antihypertensive agent, as well as

with dosage increases. It is therefore advisable to limit the initial dosage to 0.5 mg bid or tid and to make gradual increases. Caution should also be exercised when any additional hypertensive drugs are added to the treatment regimen.

The addition of TEVA-PRAZOSIN into the regimen of patients whose blood pressure is not adequately controlled by large doses of beta-adrenergic blocking agents, such as propranolol, may result in acute hypotension. The dose of the beta-adrenergic blocking agent should, therefore, be reduced prior to the administration of TEVA-PRAZOSIN in order to minimize the risk of acute hypotension in these patients. It is also strongly recommended that TEVA-PRAZOSIN administration be initiated at a low dosage (see DOSAGE AND ADMINISTRATION).

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

The symptoms associated with a decrease in blood pressure, namely dizziness and lightheadedness, are more common than loss of consciousness. Patients should be warned about the possible adverse effects and advised on what measures to take should these develop.

Use During Pregnancy

TEVA-PRAZOSIN (prazosin hydrochloride) is not recommended for use in pregnant women or nursing mothers unless the potential benefit out weighs the possible risk to the mother and child. Although animal studies have not revealed any teratogenic effects; the safety of prazosin hydrochloride has not been established in this patient group.

Use for Children

The safety of TEVA-PRAZOSIN (prazosin hydrochloride) has not been established in pediatric patients, therefore, it is not recommended for use in children under 12 years of age,

PRECAUTIONS

Use in Patients with Moderate to Severe Grades of Renal Impairment:

Patients with moderate to severe grades of renal impairment have, in some cases, responded to smaller than usual doses of prazosin hydrochloride. It is recommended, therefore, that treatment with TEVA-PRAZOSIN (prazosin hydrochloride) be initiated at 0.5 mg daily and that any increases in dose be instituted with caution.

Drug Interactions:

When prazosin is used with diuretics or other hypotensive agents, particularly beta-adrenergic blocking agents, the hypotensive effect of prazosin may be increased. Careful adjustment of dosage is, therefore, necessary when these drugs are used concomitantly. (See DOSAGE AND ADMINISTRATION: Use with Other Drugs)

Prazosin hydrochloride has been administered without any adverse drug interaction in the limited 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 and quinidine; and (6) analgesic, antipyretic and anti-inflammatory agents - propoxyphene, aspirin, indomethacin and phenylbutazone.

ADVERSE REACTIONS

The most common reactions associated with prazosin hydrochloride are: postural dizziness (10.3%), nausea (4.9%); drowsiness (7.6%), headache (7.8%), palpitations (5.3%), weakness (6.5%) and fatigue/malaise (6.9%). In most cases, the side effects disappear with continued therapy, or can be tolerated without a decrease in dosage. The following reactions have also been observed during prazosin hydrochloride administration, some of them rarely:

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

Cardiovascular: syncope (see WARNINGS), edema, dyspnea, tachycardia.

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, dry mouth, nasal congestion.

Other: diaphoresis, fever.

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

No drug related abnormal ophthalmological findings were reported in slit-lamp and fundoscopic studies which included adequate baseline examinations.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms:

A 2-year old child accidentally ingested at least 50 mg of prazosin hydrochloride. The resulting symptoms were profound drowsiness and depressed reflexes. No decrease in blood pressure was noted and recovery was uneventful.

Treatment:

If hypotension occurs as a result of the overdose, support of the cardiovascular system is of primary importance. By placing the patient in the supine position, the heart rate may be normalized and normal blood pressure can be restored. Vasopressors should be used if required and if necessary, volume expanders should be used to treat shock. Renal function should be monitored and supported if necessary. Laboratory data indicates that since prazosin is protein bound, it is not dialyzable.

DOSAGE AND ADMINISTRATION

Note: When TEVA-PRAZOSIN (prazosin hydrochloride) tablets are used for titration, it is necessary to split the 1.0 mg scored tablet in order to obtain the 0.5 mg starting dose.

The initial dose of 0.5 mg should be taken with food, preferably with the evening meal, and at least 2 to 3 hours before retiring. The dose should be increased gradually, with 0.5 mg, taken bid or tid, for at least 3 days. Depending on the blood pressure lowering effect, and the occurrence of adverse effects, the dose should be increased to 1.0 mg b.i.d or tid for at least another 3 days.

The dose should then be increased gradually, depending on the patient's response to the blood pressure lowering effect. If a response is to occur at any particular dose, it will usually be seen within 1 to 14 days. Once a response is seen, therapy should be continued at that dose until the response has reached the optimum. The dosage can then be increased gradually until the desired effect is obtained, or until a maximum dose of 20 mg/day is reached.

The maintenance dose may be given as a twice daily dosage regimen.

It is recommended that for patients with moderate to severe renal impairment, therapy be initiated at 0.5 mg daily, and that dosage increases be made gradually.

USE WITH OTHER DRUGS

Patients Receiving Diuretic Therapy:

TEVA-PRAZOSIN (prazosin hydrochloride) should be initiated at 0.5 mg bid or tid after the diuretic has been reduced to a maintenance dose level. After an initial period of observation, the TEVA-PRAZOSIN dose should be increased gradually, according to the patient's response.

Patients Receiving Other Antihypertensive Agents:

Some additive effect is anticipated, therefore; the dose of the other agent (for example, propranolol* or other beta-adrenergic blocking agents*, alpha methyldopa, reserpine, clonidine*, etc.) should be reduced and TEVA-PRAZOSIN (prazosin hydrochloride) should be initiated at 0.5 mg bid or tid. Any dosage increase should be made depending on the response of the patient.

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

Patients on TEVA-PRAZOSIN to Whom Other Antihypertensive Agents Are Added:

TEVA-PRAZOSIN (prazosin hydrochloride) should be reduced to 1 or 2 mg bid or tid before adding another antihypertensive agent or a diuretic drug. The patient should then be re-titrated.

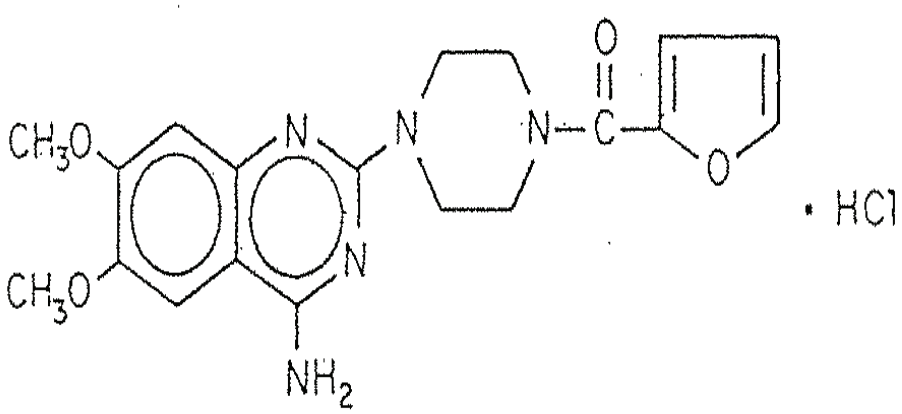
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Proper Name: Prazosin Hydrochloride

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

Structural Formula:



Molecular Formula: $C_{19}H_{21}N_5O_4$•HCI Molecular Weight: 419.87

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

STABILITY AND STORAGE RECOMMENDATIONS:

Store between 15°-30°C and protect from light. Unit dose strips should be stored between 15°-25°C and protected from light and high humidity.

AVAILABILITY OF DOSAGE FORMS

TEVA-PRAZOSIN is available as:

1.0 mg - Orange coloured, capsule-shaped, bi-convex, compressed tablets engraved no|vo on one side and '1' on the reverse, containing prazosin hydrochloride equivalent to 1 mg prazosin.

2.0 mg - White, round, biconvex, compressed tablets engraved novo on one side and 2 between broken vertical scorelines on the reverse, containing prazosin hydrochloride equivalent to 2.0 mg prazosin.

5.0 mg - White, diamond-shaped, biconvex, compressed tablets; engraved no|vo on one side and 5 on the reverse, containing prazosin hydrochloride equivalent to 5 mg prazosin.

Supplied: Bottles of 100 and 500 and boxes of 100 as unit dose strips.

PHARMACOLOGY

Hypotensive Action:

The hypotensive action of prazosin hydrochloride has been studied using both in vitro and in vivo methodology. Prolonged hypotension and a reduction in the total peripheral resistance resulted when prazosin was administered intravenously in dogs. There was also a transient increase in cardiac output, heart rate and blood flow in the femoral, renal and splanchnic vascular beds. When electrical stimulation was applied to the cardioaccelerator nerves, no depression of cardiac responses was seen, nor was there any blockade of the sympathetic ganglion or adrenergic neurons. Prazosin hydrochloride reversed the epinephrine pressor response in intact animals, but when the vessels were deprived of sympathetic tone, through ganglionic blockade, the vasodilator activity was only slightly diminished.

It is believed that the hypotensive effect of prazosin hydrochloride is the result of vasodilation, which is dependent on both direct reaction of vascular smooth muscle, and peripheral sympatholytic activity. in vitro analysis of sympatholytic activity shows that prazosin hydrochloride modulates the function of alpha-adrenergic receptors in a manner which does not involve occupancy blockade. It has been suggested that prazosin hydrochloride acts at a site distal to the alpha-adrenergic receptors in a manner which preserves compensatory reflexes.

The hypotensive effect of prazosin hydrochloride, administered intravenously in the dog, can be reversed through intravenous infusion of metaraminol and norepinephrine.

Other Effects:

Prazosin hydrochloride has mild CNS depressant activity, when administered to rats at doses which are considerably higher than those required for antihypertensive activity. At these elevated doses it also decreases heart norepinephrine and is hyperglycemic in rats. Prazosin caused diuresis when administered to dogs, but resulted in fluid retention when the same dose was given orally to dogs and mice.

Clinical studies to date, indicate that plasma renin activity is not increased by prazosin hydrochloride.

Metabolism

In humans, the maximum drug levels attained, following oral administration of prazosin hydrochloride, are generally low and variable. Peak serum concentrations of approximately 23 ± 10.5 ng/mL have been reported 1 to 3 hours after a single 2 mg oral dose.

Prazosin hydrochloride is highly protein bound in human plasma (97%), yet disappears rapidly with a plasma half-life of 1.77 to 4.55 hours. There is no apparent drug accumulation after chronic administration, nor is there any decreases in plasma concentrations.

There was no correlation between maximum plasma drug levels and decrease in blood pressure, between rates of use and fail in drug levels and the mean arterial pressure response, or between the total plasma drug concentration and the biological effect. The relationship between plasma drug concentrations and biological response is somewhat obscure, and drug activity persists for approximately 10 hours which is longer than would be expected from the short plasma half-life.

Urinary excretion, measured by chemical assay, was low since not all of the drug related metabolites can be detected. Also, the preferred biliary elimination, noted in rats and dogs, probably occurs in man as well. Rats, dogs and man all appear to excrete similar metabolites. Routes of prazosin hydrochloride metabolism involve 0-demethylation, hydrolysis of the amide linkage glucuronide formation and, to a lesser extent, piperazine opening and N-dealkylation. It appears that 0-dealkylation and glucuronide formation occur more readily and that the metabolism of the piperazine moiety is of minor importance. Free 6 -0-demethyl prazosin and its glucuronide conjugate are the major excretion products along with smaller amounts of 7-0-demethyl prazosin and its glucuronide conjugate.

TOXICOLOGY

Acute Toxicity:

The results of single-dose acute toxicity studies on prazosin hydrochloride are as follows:

Species	Sex	Oral LD50 mg/kg	Intraperitoneal LD50 (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 prazosin hydrochloride included depression, decreased respiration, ptosis, writhing, ataxia, tremors and convulsions. These were, for the most part, common to both mice and rats by both routes of administration.

A 30 day oral toxicity study employing prazosin doses of 2, 10 and 40 mg/kg 7 days per week was conducted in beagles. All of the animals survived. Dose related ptosis, ataxia and relaxation of the nictitating membrane were observed in the mid and high dose groups. Emesis, diarrhea and decreased activity were also observed in all of the treated animals and all dosed animals showed spiked EKG T-waves. The pupillary reflex was decreased in the mid and high dose animals and there was a dose dependent decrease in the thymus weight and an increase in spleen weight. Gross and histological examinations revealed that the spleens of the mid and high dose animals were congested with dilated vessels containing blood. The hepatic vessels were dilated and pericentral hepatocellular degenerative changes were seen in the high dose animals.

Chronic Toxicity:

A chronic toxicity study was conducted in beagle dogs of both sexes with oral doses of prazosin 2, 10 and 25 mg/kg administered 7 days per week for 1 year. Testicular atrophy and degeneration were observed in all of the male animals in the high dose group and this was accompanied by prostatic atrophy and fibrosis in 2 of the 4 animals. In addition, splenic enlargement which was probably drug related was observed in all of the treated animals.

(In human clinical studies, urinary 17-ketosteroid excretion was monitored in 105 patients for any possible effect on testicular function. No drug effects were observed. No semen abnormalities were revealed by routine semen analysis in 27 male patients receiving prazosin hydrochloride alone for up to 51 months).

An 18 month oral toxicity study was conducted in rats during which prazosin was administered in the diet at doses of 5, 25, 75 and 150 mg/kg/day. Drug related toxic effects included testicular atrophy and/or degeneration with accompanying inguinal and/or scrotal adhesions; bilateral cataracts and retinitis proliferans; and hepatic degeneration and/or necrosis. The effects on the testes were dose related and were evident at all dose levels except 5 mg/kg. Ocular toxicity occurred only at the 75 and 150 mg/kg dosage level. Retinitis proliferans showed a drug, but not dose relationship, and cataracts showed a dose

response. Significant degrees of hepatic degeneration and or necrosis occurred only at 75 and 150 mg/kg and this effect was dose related.

Reproductive Studies:

Male rats received prazosin 0, 25 and 75 mg/kg/day in the diet for 7 months and females were given the same dosages for 14 days prior to mating and to day 13 of gestation. Another group of females received 0, 5, 25 and 75 mg/kg/day to day 21 of gestation. Fertility was decreased in the high dose group (30% compared to 80% in the controls) and the number of pups per litter on days 1, 4 and 21 after birth was slightly decreased in the dosed groups. No gross, visceral or skeletal anomalies were noted in the pups that died; however, pup weight 21 days after birth was decreased in the prazosin groups compared to controls.

Teralology:

Rats were given oral doses of 0, 25 and 75 mg/kg from days 5 through 15 of gestation and rabbits were given oral doses of 0, 25 and 75 mg/kg on days 5 through 18 of gestation. No gross external visceral or stained skeletal abnormalities were observed except for one low dose rabbit pup that had craniochiasis.

REFERENCES

1. Bolli P, Simpson FO. A preliminary clinical trial of prazosin; a new oral antihypertensive agent. N Zealand Med J 1974; 79:969-72.

2. Brogden RN, Heel RC, Speight TM, Avery GS. Prazosin: A review of its pharmacological properties and therapeutic efficacy in hypertension. Drugs 1977; 14:163-97.

3. Cavero I, Roach AG. The pharmacology of prazosin, a novel antihypertensive agent. Life Sci 1980; 27:1525-40.

4. Cohen BM. Prazosin hydrochloride (CP-12, 229-1), an oral antihypertensive agent: Preliminary clinical observations in ambulatory patients. J Clin Pharmacol 1970; 10:408-17.

5. Jaillon P. Clinical pharmacokinetics of prazosin. Clin Pharmacokinet 1980; 5:365-76.

6. Kincaid-Smith P. Alpha blockade. An overview of efficacy data, Am J Med 1987; 82:21-5.

7. Kincaid-Smith P. Vasdilators in the treatment of hypertension. Med J Aust. 1975; 1:7-9.

8. Kincaid-Smith P, MacDonald IM, Hua A, Laver MC, Fang P. Changing concepts in the management of hypertension. Med J Aust 1975; 1:327-32.

9. Koch-Weser J, Graham RM, Pettinger WA, Prazosin. N Engl J Med 1979; 300:232-6.

10. Morrison B, Prazosin hydrochloride: A vasodilating agent for use in lowering left ventricular end diastolic pressure, Drug Intell Clin Pharm 1979; 13:212-5.

11. Mroczek WJ, Fotiu S, Davidov ME, Finnerty FA Jr. Prazosin in hypertension: A double-blind evaluation with methyldopa and placebo. Curr Ther Res 1974; 16:769-77.

12. Okun R. Effectiveness of prazosin as an initial antihypertensive therapy. Am J Cardiol 1983; 51:644-50.

13. Reid JL, Vincent J. Clinical pharmacology and therapeutic role of prazosin and related alpha-adrenoceptor agonists. Cardiology 1986; 73:164-74.

14. Stanaszek WF, Kellerman D, Brogden RN, Romankiewicz JA. Prazosin update. A review of its pharmacological properties and therapeutic use in hypertension and congestive heart failure. Drugs 1983; 25:339-84.

15. Stokes GS, Mennie BA, Marwood JF. Ketanserin and prazosin: A comparison of antihypertensive and biochemical effects, Clin Pharmacol Ther 1986; 40:56-63.

16. Taylor JA, Twomey TM, Schach Von Vittenau M. The metabolic fate of prazosin. Xenobiotica 1977; 357-64.

17. Weber MA, Stokes GS. Treatment of hypertension with an antihypertensive agent possessing vasodilator activity. Med J Aust, Special Supplement 1975;1:9-11.

18. A comparative bioavailability study of TEVA-PRAZOSIN (prazosin hydrochloride) 1 and 2 mg tablets, December 11, 1987. Data on file at Teva Canada Limited.

19. U.S.F.D.A. Summary basis of approval document for Minipress (prazosin hydrochloride) including medical and toxicology reviews, NDA #17-442, F.O.I. Services Inc., Rockville, Maryland.

20. Physicians' Desk Reference, 40th edition, Medical Economics Company Inc., Oradell, N.J. 1986;142'0-21.