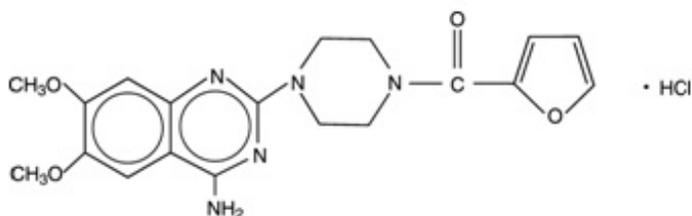


PRAZOSIN HYDROCHLORIDE- prazosin hydrochloride capsule
Aphena Pharma Solutions - Tennessee, LLC

DESCRIPTION

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



Prazosin hydrochloride, USP is a white to tan powder, slightly soluble in water and methanol, very slightly soluble in alcohol, practically insoluble in chloroform and acetone and has a molecular weight of 419.87. Its molecular formula is $C_{19}H_{21}N_5O_4 \cdot HCl$. Each capsule, for oral administration, contains prazosin hydrochloride equivalent (as the polyhydrate) to 1 mg, 2 mg or 5 mg of prazosin.

Each capsule for oral administration contains the following inactive ingredients: colloidal silicon dioxide, lactose monohydrate, magnesium stearate and microcrystalline cellulose. The empty gelatin capsules contain black iron oxide, gelatin, red iron oxide, titanium dioxide and yellow iron oxide. In addition, the 1 mg empty gelatin capsules contain D&C Yellow No. 10 and FD&C Green No. 3; the 2 mg empty gelatin capsules contain D&C Red No. 28, D&C Yellow No. 10, FD&C Blue No. 1 and FD&C Red No. 40; and the 5 mg empty gelatin capsules contain FD&C Blue No. 1.

The imprinting ink also contains ammonium hydroxide, propylene glycol, shellac glaze, simethicone and titanium dioxide.

CLINICAL PHARMACOLOGY

The exact mechanism of the hypotensive action of prazosin is unknown. Prazosin causes a decrease in total peripheral resistance and was originally thought to have a direct relaxant action on vascular smooth muscle. Recent animal studies, however, have suggested that the vasodilator effect of prazosin is also related to blockade of postsynaptic alpha-adrenoceptors. The results of dog forelimb experiments demonstrate that the peripheral vasodilator effect of prazosin is confined mainly to the level of the resistance vessels (arterioles). Unlike conventional alpha-blockers, the antihypertensive action of prazosin is usually not accompanied by a reflex tachycardia. Tolerance has not been observed to develop in long-term therapy.

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 cardiac output, heart rate, renal blood flow and glomerular filtration rate. There is no measurable negative chronotropic effect.

In clinical studies to date, prazosin has not increased plasma renin activity.

In man, blood pressure is lowered in both the supine and standing positions. This effect is most pronounced on the diastolic blood pressure.

Following oral administration, human plasma concentrations reach a peak at about 3 hours with a plasma

half-life of 2 to 3 hours. The drug is highly bound to plasma protein. Bioavailability studies have demonstrated that the total absorption relative to the drug in a 20% alcoholic solution is 90%, resulting in peak levels approximately 65% of that of the drug in solution. Animal studies indicate that prazosin is extensively metabolized, primarily by demethylation and conjugation, and excreted mainly via bile and feces. Less extensive human studies suggest similar metabolism and excretion in man.

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

INDICATIONS AND USAGE

Prazosin hydrochloride capsules are indicated in the treatment of hypertension. It can be used alone or in combination with other antihypertensive drugs such as diuretics or beta-adrenergic blocking agents.

CONTRAINDICATIONS

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

WARNINGS

As with all alpha-blockers, prazosin hydrochloride may cause syncope with sudden loss of consciousness. In most cases this is believed to be due to an excessive postural hypotensive effect, although occasionally the syncopal episode has been preceded by a bout of severe tachycardia with heart rates of 120 to 160 beats per minute. Syncopal episodes have usually occurred within 30 to 90 minutes of the initial dose of the drug; occasionally they have been reported in association with rapid dosage increases or the introduction of another antihypertensive drug into the regimen of a patient taking high doses of prazosin. The incidence of syncopal episodes is approximately 1% in patients given an initial dose of 2 mg or greater. Clinical trials conducted during the investigational phase of this drug suggest that syncopal episodes can be minimized by limiting the initial dose of the drug to 1 mg, by subsequently increasing the dosage slowly, and by introducing any additional antihypertensive drugs into the patient's regimen with caution (see DOSAGE AND ADMINISTRATION). Hypotension may develop in patients given prazosin who are also receiving a beta-blocker such as propranolol.

If syncope occurs, the patient should be placed in the recumbent position and treated supportively as necessary. This adverse effect is self limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

Patients should always be started on the 1 mg capsules of prazosin hydrochloride. The 2 mg and 5 mg capsules are not indicated for initial therapy.

More common than loss of consciousness are the symptoms often associated with lowering of the blood pressure, namely, dizziness and lightheadedness. The patient should be cautioned about these possible adverse effects and advised what measures to take should they develop. The patient should also be cautioned to avoid situations where injury could result should syncope occur during the initiation of prazosin therapy.

PRECAUTIONS

General

Intraoperative Floppy Iris Syndrome (IFIS) has been observed during cataract surgery in some patients treated with alpha-1 blockers. This variant of small pupil syndrome is characterized by the combination of a flaccid iris that billows in response to intraoperative irrigation currents, progressive intraoperative

miosis despite preoperative dilation with standard mydriatic drugs, and potential prolapse of the iris toward the phacoemulsification incisions. The patient's ophthalmologist should be prepared for possible modifications to the surgical technique, such as the utilization of iris hooks, iris dilator rings, or viscoelastic substances. There does not appear to be a benefit of stopping alpha-1 blocker therapy prior to cataract surgery.

Information for Patients

Dizziness or drowsiness may occur after the first dose of this medicine. Avoid driving or performing hazardous tasks for the first 24 hours after taking this medicine or when the dose is increased. Dizziness, lightheadedness or fainting may occur, especially when rising from a lying or sitting position. Getting up slowly may help lessen the problem. These effects may also occur if you drink alcohol, stand for long periods of time, exercise, or if the weather is hot. While taking prazosin hydrochloride, be careful in the amount of alcohol you drink. Also, use extra care during exercise or hot weather, or if standing for long periods. Check with your physician if you have any questions.

Drug Interactions

Prazosin hydrochloride 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, phenformin, 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, aspirin, indomethacin, and phenylbutazone.

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

Concomitant administration of prazosin hydrochloride with a phosphodiesterase-5 (PDE-5) inhibitor can result in additive blood pressure lowering effects and symptomatic hypotension (see DOSAGE AND ADMINISTRATION).

Drug/Laboratory Test Interactions

In a study on five patients given from 12 mg to 24 mg of prazosin per day for 10 to 14 days, there was an average increase of 42% in the urinary metabolite of norepinephrine and an average increase in urinary VMA of 17%. Therefore, false positive results may occur in screening tests for pheochromocytoma in patients who are being treated with prazosin. If an elevated VMA is found, prazosin should be discontinued and the patient retested after a month.

Laboratory Tests

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenic potential was demonstrated in an 18-month study in rats with prazosin hydrochloride at dose levels more than 225 times the usual maximum recommended human dose of 20 mg per day. Prazosin was not mutagenic in *in vivo* genetic toxicology studies. In a fertility and general reproductive performance study in rats, both males and females, treated with 75 mg/kg (225 times the usual maximum recommended human dose), demonstrated decreased fertility while those treated with 25 mg/kg (75 times the usual maximum recommended human dose) did not.

In chronic studies (one year or more) of 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). No testicular changes were seen in rats or dogs at 10 mg/kg/day (30 times the usual maximum recommended human dose). In view of the testicular changes observed in animals, 105 patients on long-term prazosin therapy were monitored for 17-ketosteroid excretion and no changes indicating a drug effect were observed. In addition, 27 males on prazosin for up to 51 months did not have changes in sperm morphology suggestive of drug effect.

Usage in Pregnancy

Teratogenic Effects. Pregnancy Category C

Prazosin has been shown to be associated with decreased litter size at birth, 1, 4, and 21 days of age in rats when given doses more than 225 times the usual maximum recommended human dose. No evidence of drug-related external, visceral, or skeletal fetal abnormalities were observed. No drug-related external, visceral, or skeletal abnormalities were observed in fetuses of pregnant rabbits and pregnant monkeys at doses more than 225 times and 12 times the usual maximum recommended human dose respectively.

The use of prazosin 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 was continued for as long as 14 weeks.¹

Prazosin has also been used alone or in combination with other hypotensive agents in severe hypertension of pregnancy by other investigators. No fetal or neonatal abnormalities have been reported with the use of prazosin.²

There are no adequate and well controlled studies which establish the safety of prazosin in pregnant women. Prazosin should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus.

Nursing Mothers

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

Usage in Children

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Clinical trials were conducted on more than 900 patients. During these trials and subsequent marketing experience, the most frequent reactions associated with prazosin hydrochloride therapy are: dizziness 10.3%, headache 7.8%, drowsiness 7.6%, lack of energy 6.9%, weakness 6.5%, palpitations 5.3%, and nausea 4.9%. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrease in dose of drug.

Less frequent adverse reactions which are reported to occur in 1% to 4% of patients are:

Gastrointestinal: vomiting, diarrhea, constipation.

Cardiovascular: edema, orthostatic hypotension, dyspnea, syncope.

Central Nervous System: vertigo, depression, nervousness.

Dermatologic: rash.

Genitourinary: urinary frequency.

EENT: blurred vision, reddened sclera, epistaxis, dry mouth, nasal congestion.

In addition, fewer than 1% of patients have reported the following (in some instances, exact causal relationships have not been established):

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

Cardiovascular: tachycardia.

Central Nervous System: paresthesia, hallucinations.

Dermatologic: pruritus, alopecia, lichen planus.

Genitourinary: incontinence, impotence, priapism.

EENT: tinnitus.

Other: diaphoresis, fever, positive ANA titer, arthralgia.

Single reports of pigmentary mottling and serous retinopathy, and a few reports of cataract development or disappearance 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 prazosin therapy with a worsening of preexisting narcolepsy. A causal relationship is uncertain in these cases.

In post-marketing experience, the following adverse events have been reported:

Autonomic Nervous System: flushing.

Body as a Whole: allergic reaction, asthenia, malaise, pain.

Cardiovascular:General: angina pectoris, hypertension.

Endocrine: gynecomastia.

Heart Rate/Rhythm: bradycardia.

Psychiatric: insomnia.

Skin/Appendages: urticaria.

Vascular (Extracardiac): vasculitis.

Vision: eye pain.

Special Senses: During cataract surgery, a variant of small pupil syndrome known as Intraoperative Floppy Iris Syndrome (IFIS) has been reported in association with alpha-1 blocker therapy (see PRECAUTIONS).

OVERDOSAGE

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

Should overdose 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 is not dialysable because it is protein bound.

DOSAGE AND ADMINISTRATION

The dose of prazosin hydrochloride capsules should be adjusted according to the patient's individual blood pressure response. The following is a guide to its administration:

Initial Dose

1 mg two or three times a day (see WARNINGS).

Maintenance Dose

Dosage may be slowly increased to a total daily dose of 20 mg given in divided doses. The therapeutic dosages most commonly employed have ranged from 6 mg to 15 mg daily given in divided doses. Doses higher than 20 mg usually do not increase efficacy, however a few patients may benefit from further increases up to a daily dose of 40 mg given in divided doses. After initial titration some patients can be maintained adequately on a twice daily dosage regimen.

Use With Other Drugs

When adding a diuretic or other antihypertensive agent, the dose of prazosin hydrochloride capsules should be reduced to 1 mg or 2 mg three times a day and retitration then carried out.

Concomitant administration of prazosin hydrochloride capsules with a PDE-5 inhibitor can result in additive blood pressure lowering effects and symptomatic hypotension; therefore, PDE-5 inhibitor therapy should be initiated at the lowest dose in patients taking prazosin hydrochloride capsules.

HOW SUPPLIED

Repackaged by Aphenia Pharma Solutions - TN.
See **Repackaging Information** for available configurations.



Prazosin Hydrochloride Capsules, USP are available containing 1 mg, 2 mg, or 5 mg of prazosin as the hydrochloride.

The 1 mg capsule is a hard-shell gelatin capsule with a dark green opaque cap and a light brown opaque body axially printed with **MYLAN** over **1101** in white ink on both the cap and body. The capsule is filled with a white to off-white powder blend. They are available as follows:

NDC 0378-1101-01

bottles of 100 capsules

NDC 0378-1101-10

bottles of 1000 capsules

The 2 mg capsule is a hard-shell gelatin capsule with a brown opaque cap and a light brown opaque body axially printed with **MYLAN** over **2302** in white ink on both the cap and body. The capsule is filled with a white to off-white powder blend. They are available as follows:

NDC 0378-2302-01

bottles of 100 capsules

NDC 0378-2302-10

bottles of 1000 capsules

The 5 mg capsule is a hard-shell gelatin capsule with a light blue opaque cap and a light brown opaque body axially printed with **MYLAN** over **3205** in white ink on both the cap and body. The capsule is filled with a white to off-white powder blend. They are available as follows:

NDC 0378-3205-01

bottles of 100 capsules

NDC 0378-3205-25

bottles of 250 capsules

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]

Protect from moisture and light.

Dispense in a tight, light-resistant container as defined by the USP using a child-resistant closure.

REFERENCES

1. Lubbe, WF, Hodge, JV: *New Zealand Med J* 94 (691) 169-172,1981.
2. Davey, DA, and Dommissee, J: *SA. Med J*, Oct.4, 1980 (551-556).

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

REVISED JANUARY 2010
PRSN:R13

Repackaging Information

Please reference the **How Supplied** section listed above for a description of individual tablets or capsules. This drug product has been received by Aphenia Pharma - TN in a manufacturer or distributor packaged configuration and repackaged in full compliance with all applicable cGMP regulations. The package configurations available from Aphenia are listed below:

Count	2mg
90	43353-868-60
180	43353-868-80

Store between 20°-25°C (68°-77°F). See USP Controlled Room Temperature. Dispense in a tight light-resistant container as defined by USP. Keep this and all drugs out of the reach of children.

Repackaged by:



Cookeville, TN 38506

20140403SC

PRINCIPAL DISPLAY PANEL - 2mg

NDC 43353-868 - **Prazosin HCl** 2mg - Rx Only

PRAZOSIN HYDROCHLORIDE

prazosin hydrochloride capsule

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:43353-868(NDC:0378-2302)
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
PRAZOSIN HYDROCHLORIDE (UNII: X0Z7454B90) (PRAZOSIN - UNII:XM03YJ541D)	PRAZOSIN	2 mg

Inactive Ingredients

Ingredient Name	Strength
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
FERROSFERRIC OXIDE (UNII: XM0M87F357)	
GELATIN (UNII: 2G86QN327L)	
FERRIC OXIDE RED (UNII: 1K09F3G675)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	
FERRIC OXIDE YELLOW (UNII: EX438O2MRT)	
D&C RED NO. 28 (UNII: 767IP0Y5NH)	
D&C YELLOW NO. 10 (UNII: 35SW5USQ3G)	
FD&C BLUE NO. 1 (UNII: HBR47K3TBD)	
FD&C RED NO. 40 (UNII: WZB9127XOA)	
AMMONIA (UNII: 5138Q19F1X)	

PROPYLENE GLYCOL (UNI: 6DC9Q167V3)	
SHELLAC (UNI: 46N107B71O)	

Product Characteristics

Color	BROWN (brown opaque) , BROWN (light brown opaque)	Score	no score
Shape	CAPSULE	Size	18mm
Flavor		Imprint Code	MYLAN;2302
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:43353-868-60	90 in 1 BOTTLE, PLASTIC		
2	NDC:43353-868-80	180 in 1 BOTTLE, PLASTIC		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA072575	05/17/2013	

Labeler - Aphenia Pharma Solutions - Tennessee, LLC (128385585)

Establishment

Name	Address	ID/FEI	Business Operations
Aphenia Pharma Solutions - Tennessee, LLC		128385585	Repack(43353-868)

Revised: 4/2014

Aphenia Pharma Solutions - Tennessee, LLC