Alphapress®

(Prazosin Hydrochloride USP)
Tablets for oral use

Description : ALPHAPRESS brand of prazosin hydrochloride, a quinazoline derivative, is the first of a new chemical class of antihypertensive. It is the Hydrochloride salt of 1-(4 amino-6, 7-dimethoxy-2 quinazolinyl)-4-(2-furoyl) piperazine.
Prazosin hydrochloride is a white, crystalline substance, slightly soluble in water and isotonic saline, with a molecular weight of 419.87.
Each Prazosin hydrochloride tablet contains the equivalent of 1 and 2mg of prazosin free base.
Actions : ALPHAPRESS causes a decrease in total peripheral vascular resistance. Animal studies suggest that the vasodilator effect of ALPHAPRESS related to-blockade of pesisyoaptic alpha-1 adrenoceptors. The results of forearm plethysmographic studies in humans demonstrate that the peripheral vasodilation is a balanced effect on both resistance vessels (arterioles) and capacitance vessels (veins). Unlike non-selective alpha-adrenergic blocking agents, the antihypertensive action of ALPHAPRESS is usually not accompanied by reflex tachycardia.
Most studies indicate that chronic therapy with ALPHAPRESS has little effect on plasma renin activity. One report suggests a transient increase in plasma renin activity following the initial dose, as well as an attenuated, transient increase with subsequent doses.
Hemodynamic studies have been carried out in hypertensive patients following single dose adminsitration and during the course of long-term maintenance therapy. The results confirm that the usual therapeutic effect is a fall in blood pressure unaccompanied by a clinically singificant change in cardiac output, heart rate, renal blood flow, or glomerular filtration rate.
Clinically, the antihypertensive effect is believed to be a direct result of peripheral vasodilation. In man, blood pressure is lowered in both the supine and standing positions. This effect is more pronounced on the diastolic blood pressure. Tolerance has not been observed in long-term clinical use. Rebound elevation of blood pressure does not occur following abrupt cessation of therapy with Alphapress. A variety of epidemiologic, biochemical and experimental studies have established that an elevated level of low density lipoprotein (LDL) cholesterol is associated with an increased risk of coronary heart disease. There is an even stronger relationship between reduced levels of high density lipoprotein (HDL) chotostetet-and anc increased risk of coronay heart disease.Clinical studies have shown that .Alphapress lowers LDL levels and either has no effect or increase levels of HDL. Hemodynamic studies carried out in patients with left ventricular failure following initial oral therapy and during the course of longer term maintenance therapy both at rest and at exercise indicate that the therapeutic effect in these patients is due to a reduction in left ventricular filling pressure, reduction in cardiac impedance, and an augmentation of cardiac output without any increase in myocardial oxygen consumption. These effects are associated with a balanced vasodilator effect on both arterioles and veins. The use of ALPHAPRESS in treatment of left ventricular failure does not provoke a reflex tachycardia and blood pressure reduction is absent or minimal in normotensive patients.
Raynaud's phenomenon and Raynaud's disease have been successfully treated with ALPHAPRESS. The vasodilator action of the drug increases blood flow to affected parts to reduce the severity of the signs and symptoms and the frequency and duration of attacks.
Enucleated hyperplastic glandular tissue and hypertrophied muscular tissue removed from the enlarged prostate gland is rich in alpha-adrenoceptor content. Variations in the tone of the smooth muscle in the prostate will produce variations in the closure pressure exerted on the prostatic urethra. This finding has provided the basis of pharmacological treatment of benign prostatic hyperplasia (BPH) invloMng alpha-adrenoceptor antagonism.
There is evidence of statistically significant improvement in urinary flow following therapy with ALPHAPRESS patients with BPH. There is also evidence for a reduction in the volume of residual bladder urine and for improvement symptoms of BPH such as frequency of micturition.
Following oral administration in normal volunteers and hypertensive patients, plasma concentrations reach a peak in one to two hours, with a plasma half-life of two to three hours. Pharmacokinetic data in a limited number of patients with left ventricular failure, most of whom showed evidence of hepatic congestion, indicates that peak plasma concentrations are reached in 2.5 hours and plasma half-life is approximately seven hours. The drug is highly bound to plasma protein. Animal studies indicate that Alphapress is extensively metabolized, primarily by demethylation and conjugation and excreted mainly via bile and feces. Similar metabolism and excretion has been documanted in human studies. Clinical Pharmacology studies have demonstrated that ALPHAPRESS has bronchodilator activity in normal and asthmatic human volunteers.

INDICATIONS

Hypertension

ALPHAPRESS is indicated in the treatment of all grades of essential (primary) hypertensicfh and of all grades of secondary hypertension of variec etiology. It can be used as the initial and sole agent or it may be employed in a treatment program in cofiouctionrwith a diuretic and/or other antihypertensive drugs as needed for proper patient response.
Renal blood flow and glomerular filtration rate are not impaired by long-term oral administration and thus ALPHAPRESS can be used with safety in hypertensive patients with impaired renal function
Left Ventricular Failure : ALPHAPRESS is indicated in the treatment of left ventricular failure. ALPHAPRESS may be added to the therapeutic regimen in those patients who have not shown a satisfactory response or who have become refractory to conventional therapy with diuretics, with or without cardiac glycosides.
Raynaud's Phenomenon And Raynaud's Disease : ALPHAPRESS indicated in the treatment of Raynaud's phenomenon and Raynaud's disease.
Benign Prostatic Hyperplasia : ALPHAPRESS is indicated as an adjunct in the symptomatic treatment of urinary obstruction caused by benign prostatic hyperplasia. It is also of value in patients awaiting prostatic surgery.
CONTRAINDICATIONS : ALPHAPRESS is contracindicated in patients with a known sensitivity to quinazolines.

WARNINGS

Pregnancy or Lactation

Although no teratogenic effects were seen in animal testing; the safety of ALPHAPRESS use during. pregnancy has not yet been established. The use of prazosin and a beta-blocker for the control of sever hypertension of 44 pregnant women revealed no drug-related fetal adnormalities or adverse effects. Therapy with prazosin was continued for as long as 14 weeks.
ALPHAPRESS has also been used alone or in combination with other hypotensive agents in severe hypertension or pregnancy. No fetal or neonatal abnormalities have been reported with the use of ALPHAPRESS.
There are no adequate and well controlled studies which establish the safety of ALPHAPRESS in pregnant women. ALPHAPRESS should be used during pregnancy only if in the opinion of the physician the potential benefit justifies the potential risk to the mother and fetus. ALPHAPRESS has been shown to be excreted in small amounts in human milk. Caution shold be exercised when ALPHAPRESS is adminsitered to nursing mothers.
Children : ALPHAPRESS is not recommended for the treatmet of children under the age of 12 years since safe conditions for its use have not been established.
Left Ventricular Failure : ALPHAPRESS is not recommended in the treatment of left ventricular failure due to mechanical obstrcution such as aortic valve stenosis, mitral valve stenosis, pulmonary embolism and restrictive pericardial disease. Adequate data are not yet available to establish efficacy in patients with left ventricular failure due to a recent myocardial infarction.

PRECAUTIONS

Hypertension

A very small percentage of patients have responded in an abrupt and exaggerated manner to the initial dose of ALPHAPRESS. Postural hypotension evidenced by dizziness and weakness, or rarely loss of consciousness, has been reported, particularly with the commencement of therapy, but this effect is readily avoided by initiating treatment with a low dose of ALPHAPRESS and with small increases in dosage during the first one to two weeks of therapy. The effect when observed is not related to the severity of hypertension, is self-limiting and in most patients does not recur after the initial period of therapy or during subsequent dose titration steps.
When instituting therapy with any effective antihypertensive agent, the patient should be advised how to avoid symptoms resulting from postural hypotension and what measures to take should they develop. The patient should be cautioned to avoid situations where injury could result should dizzines or weakness occur during the initiation of ALPHAPRESS therapy.
Left Ventricular Failure : When prazosin is initialy adminstered to patients with left ventricular failure who have undergone vigorours diuretic or other vasodilator treatment, particularly in higher than the recommended starting dose, the resultant decrease in left ventricular filling pressure may be associated with a significant fall in cardiac output and systemic blood pressure. In such patients, observance of the recommended starting dose of prazosin followed by gradual titration is particularly important. (See dosage and admininstration).
Occasional patients with left ventricular failure the clinical efficacy of ALPHAPRESS has been reported to diminish after several months of tratment. In these patients there is usually evidence of weight gain or peripheral edema indicating fluid retention. Since spontaneous deterioration may occur in such severely ill patients a causal relationship to prazosin therapy has not been established. Thus, as with all patients with left ventricular failure, careful adjustment of diuretic dosage according to the patient's clinical condition is required to prevent excessive fluid retention and consequent relief of symptoms.
In those patients without evidence of fluid retention, when clinical improvement has diminished; an ircrease in the dosage, of ALPHAPRESS will usually restore clinical efficacy.
Raynaud's Phenomenon and Raynaud's Disease: Because ALPHAPRESS decreases periphereai vascular resistance, careful monitoring of blood pressure during initial adminstration and titration of ALPHAPRESS is suggested. Close observation is especially recommended for patients already taking medication that are known the lower blood presssure.
Benign Prostatic Hyperplasia : ALPHAPRESS decreases peripheral vasular resistance and since many patients with this disorder are elderly, careful monitoring of blood preassure during initial administration and during adujstment of the dose of ALPHAPRESS is suggested. Close obervation is especially recommended for patients taking medications that are known to lower blood pressure.
Drug Interactions : ALPHAPRESS has been administered without any adverse drug interaction in clinical experience to date with the following .: (1) cardiae-glycosides-digitails and digoxin; (2) hypoglycemic agents-insulin, chlorpropamide, phenformin, tolazamide, and tolbutamide, (3) tranquilizers and sedatives-chlordiazepoxide, diazepam, and phenobarbital; (5) antiarrhytmic agents-procanamide, propranolol and quinidine; and (6) analgesic, antipyretic, and anti-inflammatory agents-propxyphene, aspirin, indomethacin, and phenylbutazone type.
Addition of a diuretic or other antihypertensive agnet to'ALPHAPRESS to 1 to 2 mg three times a day, by introducting additional antihypertensive drugs cautiously and then by retitrating ALPHAPRESS based on clincial response.
Drug/Laboratory Test Interactions : False positive results may occure in screening tests for pheochromocytoma (urinary vanillylmandelic acid (VMA) and methoxyhydroxyphenyl glyson (MHPG), urinary metabolites of norepinephrine) in patients who are being treated with Alphapress.
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.
ADVERSE REACTIONS : The most common reactions associated with ALPHAPRESS therapy are dizziness, headache, drowsiness, lack of energy, weakness, palpitations and nausea. In most instances side effects have disappeared with continued therapy or have been tolerated with no decrese in dosage of the drug. In addition, the following reactions have been associated with ALPHAPRESS therapy; vomiting diarrhea, constipation, abdominal discomfort and/or pain, liver function abnormalities, pancreatitis, edema, orthostatic hypotension, dyspnea, faintness, tachycardia, nervousness, vertigo, hallucinations, depression, parestnesia, rash, pruritus alopecia, lichen planus, urinary frequency, impotence, incontinece, priapism, blurred vision, reddened solera, epistaxis, tinnitus, dry mouth, nasal congestion, diaphoresis, fever, positve ANA liter, and arthralgia.
Some of these reactions have occurred rarely, and in many instances the exact causal relationships have not been eastblished.
Literature reports exist associating ALPHAPRESS, therapy with a worsening of pre-existing narcolepsy. A causal relationship is uncertain in these casses.
The following have been observed in parients being managed for left ventricular failure with ALPHAPRESS when used in conjuction with cardiac glycosides and diuretics; drowsiness, dizziness, postural hypotension, blurred vision, edema, dry mouth, palpitations, nausea, diarrhea, impotences, headache, and nasal congestion. In most instances these occurrences have been mild to moderate in severity and have resolved with continued therapy or have been tolerated with no decrease in drug dosage.
The most commonly although infrequently reported side effect in the treatment of Raynaud's Phenomenon/Disease was mild dizziness.
OVERDOSAGE: Accdental ingestion of at least 50 mg of ALPHAPRESS Jn a two year child resulted in profound drowsiness and depressed reflexes, No decrease in blood pressure was noted. Recovery was uneventful.
Should overdosage lead to hypotension, support of the cardiovascular system is of first importance. Restoration of blood pressure and normalization of heart rate may be accomplished by keeping the patient in the supine position. If this measure is inadequate, shock should first be treated with volume expanders. If necessary, vasopressors should then be used. Renal function should be monitored and supported as needed. Laboratory data indicate ALPHAPRESS is not dialyzable because it is protein bound.
DOSAGE AND ADMINISTRATRATION : There is evidence that toleration is best when therapy is initiated with a low starting dose.
During the first week, the dosage of ALPHAPRESS should be adjusted according to the patient's individual toleration. Thereafter the daily dosage is to be ajdusted on the basis of the patient's response. Response is usually seen within one to 14 days if it is to occur at any particular dose.
When a response is seen, therapy should be continued at that dosage until the degree of response has reaehedJt!e_optimurn before the next dose increment is added.
Hypertension : For maximum benefit, small increases should be continued until the desired effect is achieved or a total daily dosage of 20 mg is reached. A diuretic or adrenergic beta blocking agent may be added to enhance efficacy. The maintenance dosage of ALPHAPRESS may be given as a twice or three times daily regimen.

A. Patients Receiving No Antihypertensive Therapy
It is recommended that therapy be initiated with 0.5 mg given in the evening at bedtime then 0.5 mg b.i.d. or t.i.d for three to seven days. Unless poor toleration suggests the patients is unusually sensitive, this dosage should be increased to 1 mg given b.i.d. or t.i.d. for a further three to seven days. Thereafter, as determined by the patient's response to the blood pressure lowering effect, the dosage should be increased gradually to a total daily dosage of 20 mg given in divided doses.

B. Patients Receiving Diuretic Therapy With inadequate Control of Blood Pressure.
The diuretic should be reduced to a maintenance dosage level for the particular agent and ALPHAPRESS initiated with O.Smg h.s then proceeding to 0.5mg b.i.d or t.i.d. After the initial period of observation, the dosage of ALPHPRESS should be gradually increased as determined by the patient's response.

C. Patients Receiving Other Antihypertensives But With Inadequate Control
Because some additive effect is anticipated, the other agent dosage level (e.g. beta-adrenergic blocking agents, methyldopa. reserpine, «lsnidine etc.) should be reduced and ALPHAPRESS initiated at 0.5 mg h.s. then proceeding to O.Smg b.i.d, or t.i.d. Subsequent dosage increase, should be made depending upon the patient's response.
There is evidence that adding ALPHAPRESS to beta-adrenergic blocking agent, calicium antagonists or ACE inhibitors may bring about a substantial reduction in blood pressure. Thus, to low initial dosage regimen is strongly, recommended.

D. Patients With Moderate to Severe Gredes of Renal Impairment
Evidence to date shows that ALPHAPRESS dees not further compromise renal function when used in patients with renal impairment. Because some patients in this category have responded to small doses of ALPHAPRESS, it is recommended that therapy be initiated at O.Smg daily and that dosage increases be instituted cautiously.

Left Ventricular Failure : The recommended starting dose is O.Smg two, three or four times a day, Dosage should be titrated according to the patent's clinical response, based on careful monitoring of cardiopulmonary signs and symptoms, and when indicated, hemodynamic studies. Dosage titration steps may be performed as often as every two or three days in patients under close medical supervision. In severely ill, decompensated patients, rapid dosage titiration over one to two days may be indicated and is best done when hemodynamic_ monitoring is available In dininai studies, the therapeutic dosages ranged from 4 mg to 20mg daily in divided doses. Adjustment of dosage may be-required in the course of ALPHAPRESS therapy in some patients to maintain optimal clinical improvement.
Suggested Starting Dosage :
0.5 mg b.i.d., t.i.d. or q.i.d. increasing to 4 mg in divided doses
Usal Daily Maintenance Dosage
4 mg once daily to 20 mg in divided doses
Raynaud's Phenomenon And Raynaud's Disease
The recommended starting dosage is O.Smg b.i.d. given for a period of three to seven days. Dosage should be adjusted according to the patient's clinical response.
Suggested Starting Dosage
0.5mg b.i.d.
Usual Daily Maintenance Dosage
1mg or 2 mg b.i.d
Doses up to 2mg t.i.d. may be required for some patients.
Benign Prostatic Hyperplasia
The recommended starting dose is 0.5 mg twice daily given for a period of 3 to 7 days and should then be adjusted according to patient's clinical respones. The usual maintenance dose is 2mg twice daily. The safety and efficacy of a total daily dosage greater than 4 mg has not been established. Therefore, total daily dosages greater than 4mg should be used with caution.
SUPPLY : ALPHAPRESS tablets 1 and 2mg in blister packs of 10 x 10.
ALPHAPRESS tablets of 1mg in plastic container of 1000 tablets.

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